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DEDICATION

The CSI Update Book 2022 is dedicated to my parents, wife, children, teachers, CSI members, world cardiology fraternity, students, and patients.

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Despite improvements in care of acute coronary syndromes, heart failure, valvular heart disease, and cardiac arrhythmias, the number of people worldwide living with, and dying from, cardiovascular disease (CVD) continues to increase year to year. In addition to the global epidemic of obesity and resulting cardiometabolic disorders, a paradoxical result of improved acute care within an aging population is the rapid rise in the number of patients living with chronic CVD. This has placed great pressures on global and local health systems, governments, economies, as well as healthcare professionals themselves and has threatened the wellbeing, productivity, and functional status of individuals and communities around the world. These trends are of particular concern in low- and middle-income countries, which bear by far the disproportionate burden of CVD events globally.

Mortality from CVD, which had declined over the past few decades, is starting to rise in both developed and emerging parts of the world, threatening the advances of the recent past. This trend and acceleration predates the coronavirus disease 2019 (COVID-19) pandemic but has certainly been accelerated by it as a result of delayed and deferred care, limitations in health access and equity, and perhaps by COVID itself. However, longitudinally, the increase in the prevalence of obesity, diabetes, and environmental stresses are suspected of being most responsible. Insights from epidemiologic, clinical, and basic scientific investigations make it clear that the onset of many chronic CV illnesses, such as atherosclerotic vascular disease, go unrecognized and begin very early in life, long before becoming clinically manifest.

Growing awareness of noncommunicable diseases (NCDs), comprised in large part by CVD, as the greatest threat to mortality and morbidity globally voiced by many major medical societies and by agencies such as the United Nations, the World Health Organization, and the World Heart Federation has been a clarion call to action for all public health officials and CV clinicians.

Fortunately, although challenging, many of the factors that place individuals at risk for CVD are modifiable. These include hypertension, obesity, inactivity, poor quality diet, caloric excess, hyperglycemia/diabetes, nicotine use, hyperlipidemia, and inadequate sleep. The impact of each modifiable risk factor is influenced, in turn, by the upstream and surrounding social determinants of health: economic stability, physical environment, education, food security, health system access, as well as social and community context. Other prevailing social factors such as racism, gender inequity, political instability, agism, and income disparity may magnify the adverse impact of certain social determinants on overall health and wellbeing.

Solutions to address these modifiable risks will need to be multifaceted, including medical, educational, social, health policy, and environmental interventions. In addition to scientific and technologic advances, a focus on access to screening, preventive care, and basic healthcare services that promote diversity, inclusion, and equity will be a prerequisite to effectively "bending the CVD curve". Such interventions require broad-based efforts in population health to tilt the playing field toward health default choices that promote the health of communities and countries, and healthcare system approaches that must be implemented and considered one person at a time in an individualized and personalized manner.

To address the basics of prevention and access as well as to effectively treat the complexities of advanced CVD, we are indeed fortunate to live in an era of exploding biomedical science and basic discovery that are unlocking the secrets of disease and health. Advances at the individual and population health level will necessitate continued leverage of personalized medicine, data and information science, the "internet of things" (the "internet of health"), predictive analytics, artificial (or collaborative) intelligence, implementation and operational science, as well as various "-omics" (genomics, proteomics, imagenomics, etc.).

Today's cardiovascular specialists must be equipped with both the most advanced and the most basic tools to address the increased prevalence and complexity of CVD in an ever-changing world. It is in this context that the CSI Update Book 2022 brings together the latest advances in all areas of modern CV practice, from the bench top to the bedside in a comprehensive manner and emphasizes the perspective that we must simultaneously look upstream to the pervasive risks and underlying causes of acute and chronic CVD today while imaging, developing, and operationalizing the innovations, technologies, and discoveries of tomorrow.

The current volume brings together the very latest thinking on the mechanisms, determinants, and outcomes of all aspects of cardiometabolic health and disease, and, importantly, the state-of-the-art in treatment and management of cardiovascular disease from birth throughout the life course. The tremendous contributions of hundreds of expert authors, co-editors, and Editor-in-Chief Professor Dr Vijay Bang are to be celebrated—the CSI Update Book 2022 truly is a tour de force with countless enriching and clarifying figures and tables, and reliance on the very latest science and evidence to improve care for our patients. The inclusion of newer aspects of cardiovascular practice, such as cardio-oncology and cardio-obstetrics, is a laudable and important update as well. We congratulate all of the authors and editors for this important contribution to the practice of cardiology for a global audience.

PREFACE

Editor-in-Chief

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The editors are pleased to present CSI Cardiology Update Book 2022, a unique learning platform that aims to provide critical knowledge to keep abreast of the rapidly changing and advancing cardiovascular science in the 21st century. This edition of the CSI Cardiology Update Book will provide readers with the latest updates in the field in real time. The book extensively encompasses important clinical updates in preventive, general and interventional cardiology covering all dimensions of cardiovascular science with tips and tricks. We all are aware that since the early part of the 20th century clinical cardiology has had a strong foundation in clinical evaluation and diagnosis, understanding this aspect, a dedicated section on bedside cardiology has been included.

There is particular emphasis on cardiac biomarkers, reperfusion injury, LV remodelling, echocardiography, non-invasive testing for evaluation of myocardial ischemia, and interventional cardiology covering coronary and structural interventions including a chapter on Bench Testing to Cath Lab Practice, Intracoronary Imaging, CHIP Interventions, Mitral Transcatheter Edge-to-edge Repair (TEER), TAVI, Tricuspid Valve Interventions and Management of Advanced Heart Failure with India Centric Focus. There is decent coverage on arrhythmia, syncope and sudden death with advances in diagnosis and management, with the chapters on leadless pacemakers and role of wearable devices encompassing digital health technology in current cardiovascular practice. With continuing medical research and education, the subspecialties in cardiology have expanded to provide detailed expert content on clinical lipidology, genetics and molecular cardiology to which the editors have given due attention.

It is a well-known fact that cardiovascular surgery has had an enormous impact on the management of patients with heart disease. However, there was an unmet need in several cardiac conditions where surgery was prohibitive due to high STS scores in elderly, frail patients, but now due to phenomenal technological advances in catheter-based interventions in those patients who otherwise had no treatment options, are now surviving with reasonably good quality of life, with coronary and structural heart interventions. Hence, in this update book, editors have covered these interventions in greater detail to emphasize this.

In preparing the preface of this Update Book, the editors thought that it is appropriate to reflect the prescient guiding principle of the use of technology like artificial intelligence being incorporated into machines used for cardiac evaluations which at times used to be difficult to evaluate by physicians despite having insight into expertise. Taking into consideration the serious global menace of increasing BMI and CVD risk, editors have dedicated the chapter on the science of healthy diet and physical exercise to depict how lifestyle change can reverse the global trend of increasing BMI and CVD risk, highlighting the power of lifestyle change which is indicating importance of motivating global community population to understand the value of healthy diet and regular physical exercise.

The editors have placed significant emphasis on conveying succinctly how this knowledge informs both the prevention and treatment of cardiovascular diseases. There are 11 sections covering 140 chapters written by around 250 renowned authors, including 1,000 figures and 400 tables and all the content has been colourfully and digitally enhanced with particular attention to the importance of using appropriate guidelines in the diagnosis and management of cardiovascular diseases. A topic on the latest practice impacting trials has also been incorporated in a dedicated chapter on landmark trials. The editors would like to highlight several exciting changes with a new addition of knowledge on genetics and a section on cardiac oncology.

The editors have made sure that all the manuscripts have gone through peer-review, plagiarism testing, proofreading and editing in minute details with emphasis on the latest research, education and learning. We are sure that readers will find this update book educative and helpful in day-to-day practice.

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Vijay Bang

CONTENTS

VOLUME 1

SECTION 1: BEDSIDE CARDIOLOGY

1. Jugular Venous Pulse, Arterial Pulse, and Blood Pressure Recording in Children and Adults **3**

Kamal Sharma

Jugular venous pulse 3
Evaluation of arterial pulse 5
Pulsus bisferiens 6
Blood pressure 6

2. ECG and X-ray in Congenital Heart Disease **9**

Parag Bhalgat, Pooja Bhalgat

ECG in congenital heart diseases 9
X-ray in congenital heart disease 18

3. Approach to Echocardiography in Cyanotic Congenital Heart Disease **30**

Nitin Rao, Suman Vyas, Rajesh Gudipati

Segmental approach 30
Specific conditions 31

4. Approach to Cyanosis from Newborn to Adult: Hemodynamics and Management Strategies **44**

Sakshi Sachdeva, Anita Saxena

Co-relation between cyanosis, PO_2, and oxygen saturation of hemoglobin 44
Cyanosis due to heart diseases 45
Cyanosis due to pulmonary diseases 45
Neurological causes of cyanosis 46
Hematologic/Metabolic causes of cyanosis 46
Approach to a patient with cyanosis 46
Hyperoxia test 46
Approach to a patient with cyanotic congenital heart disease 46
Examination of a patient with suspected cyanotic congenital heart disease 47
Management 51

5. Relevance of Stethoscope in Contemporary Cardiology **54**
Satyavan Sharma, Vishal Patil
Discovery of the stethoscope 54
Advances in stethoscope technology 55
Rise and decline of auscultation 56
Auscultation or echocardiography? 56
Stethoscope in coronavirus disease 2019 era 56
Future of the stethoscope 57

6. Approach to Chest Pain: The New Perspective **58**
Vijay Bang, Mustafa Taskeen
Causes of acute chest pain 58
Diagnostic considerations 59
The clinical decision pathway for acute chest pain 60
The clinical decision pathway for stable chest pain 60

7. Heart Sounds and Murmurs **64**
Mohsin Raj Mantoo, Sivasubramanian Ramakrishnan
Heart sounds 64
Murmurs 69

8. Artificial Intelligence in General Cardiology **76**
Saurabh Deshpande, Deepak Padmanabhan
History of artificial intelligence 76
General principles of artificial intelligence for the clinicians 77
Applications of artificial intelligence (success stories) in cardiology 77
Current state of artificial intelligence in India 81
Challenges of artificial intelligence 81
Future of artificial intelligence 81

9. Clinical and Noninvasive Assessment of Aortic Stenosis **85**
Shraddha Ranjan, Ravi R Kasliwal, Manish Bansal
Hemodynamic classification of aortic stenosis 85
Assessment of aortic stenosis 86

10. Clinical Approach to Mitral Regurgitation **98**
MS Ravi, J Cecily Mary Majella
Etiology and pathophysiology 98
Etiology 99
Epidemiology 100
Clinical manifestations 100
Auscultation 101
Diagnosis and evaluation 102
Percutaneous treatment of mitral regurgitation 106

11. Interpretation of Cardiac Symptoms **109**

Chandan Kumar Das

History taking 110
Angina 110
Acute coronary syndrome 111
Dyspnea (breathlessness) 113
Dyspnea in a child 115
Fatigue 115
Syncope 115
Palpitation 116
Pedal edema 116
Cough and hemoptysis 117
Other uncommon but significant cardiac symptoms 117

SECTION 2: GENERAL CARDIOLOGY

12. Clinical Approach to Resistant Hypertension **121**

PS Banerjee, Tanmay Mukhopadhyay, Gourav Bhattacharya

Definition 121
Why is there a need for definition of resistant hypertension? 122
Epidemiology of resistant hypertension 122
Prognosis of resistant hypertension 122
Who is at risk? 122
Evaluation of resistant hypertension 124
Management of resistant hypertension 126
Device-based treatment of resistant hypertension 129

13. Recent Landmark Trials in Cardiology **132**

Vineet Bhatia, VK Bahl

Trials in heart failure with preserved ejection fraction 132
Hemodynamic-guided management of heart failure (guide-HF): A randomized controlled trial 133
Exploring the role of ARNI in acute MI setting: Expanding indications 133
Influenza vaccination after myocardial infarction: IAMI trial 133
Comparing effectiveness of CT and invasive coronary imaging in the management of CAD to reduce the frequency of major adverse coronary events 133
Master DAPT trial comparing abbreviated versus standard antiplatelet therapy among patients undergoing percutaneous intervention with a biodegradable polymer sirolimus-eluting stent 134
Flower MI trial: Flow evaluation to guide revascularization in multivessel ST-elevation myocardial infarction trial 134
Unguided de-escalation from ticagrelor to clopidogrel in stabilized patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI): An investigator-initiated, open-label, multicenter, noninferiority, randomized trial 134

14. Rheumatic Fever and Rheumatic Heart Disease: Recent Trends in India **136**
IB Vijayalakshmi
Background 136
Epidemiology 136
Methods of detection 136
Juvenile rheumatic heart disease 139
Pregnancy and rheumatic heart disease 139
Manifestations of heart failure in rheumatic heart disease 141
Surgery in rheumatic heart disease 142
Future 143

15. Stuck Prosthetic Valves: Diagnosis and Management Challenges **146**
Latchumanadhas Kalidoss
Background 146
Mechanisms of mechanical valve dysfunction 147
Clinical presentation 147
Diagnosis of mechanical valve dysfunction 148
Management of prosthetic valve thrombosis 151
Prevention of prosthetic valve thrombosis 154

16. Atypical Infective Endocarditis: Challenges of Appropriate Antibiotic Strategies **157**
Vasant Nagvekar, Shalmali Inamdar
Overview 157
Rare or atypical organisms causing infective endocarditis 158
Culture negative endocarditis 160
Marantic endocarditis 161

17. Clinical Assessment of the Severity of Valvular Heart Disease and Pitfalls **165**
Mandava Satya Sahitya, Rajesh Vijayvergiya
Aortic valve disease 165
Mitral valve disease 167
Mitral regurgitation 167
Tricuspid valve 168
Pulmonary valve 168

18. Sleep Apnea and Heart Disease: Management Strategies **170**
Amal Kumar Khan, Amartya Khan, Indrani Mandal
Risk factors 170
Signs and symptoms of obstructive sleep apnea 171
Cardiovascular complication of obstructive sleep apnea 171
Management strategies 173
Treatment 173

19. Left Ventricular Noncompaction **175**
Satyavir Yadav, Rakesh Yadav
Embryology 175
Epidemiology 175
Genetics 176
Classification 176
Diagnostic modalities 177
Clinical presentation 177
Role of genetic testing 177
Differential diagnosis 177
Treatment 178
Prognosis 178

20. Diagnosis and Management of Mid-cavitary Hypertrophic Obstructive Cardiomyopathy **181**
Vaibhav Bandil, Suman Bhandari
Definitions 181
Clinical course 181
Diagnosis 182
Treatment 183

21. Environment and Cardiovascular Health **185**
Vivek Gupta, Chinmay Gupta, Chaitanya Gupta
Epidemiology of pollution-induced cardiovascular disease mortality 186
Discussion 188

22. Proteomics and Metabolomics **192**
Gopala Krishna Koduru, Venkata RS Subrahmanya Sarma Palaparthi
Mass spectrometry-based metabolomics 193
Stable isotope applications to metabolomics 193
Statistical approaches and data reduction for "omics" approaches 194
Applications of metabolomics in cardiovascular disease 194

23. Epidemiology of Aortic Valve Disease in India **197**
Manik Chopra, Vyom Mori, Maqbool Sohil, Sumit Dheer
Trends of valvular heart disease in India 197

24. Dual Pathway Inhibition to Prevent Atherothrombotic Vascular Events: Current Status **199**
Vibhav Sharma, Nitish Naik
Pathophysiology of atherothrombosis and the rationale behind the use of anticoagulation 200
Review of available direct oral anticoagulants: Pharmacokinetics and pharmacodynamics 200
Stable coronary artery disease 200
Acute coronary syndrome 201

25. Renal Denervation Therapy, Is it the Way Forward? 205
Sameer Gupta, Purshotam Lal, Prashant T Upasani
Role of sympathetic nervous system in hypertension 205
Anatomy and physiology of the renal sympathetic nervous system 207
Clinical results of renal denervation in humans 208
Experience from the first-generation radiofrequency ablation system 208
Second-generation ablation systems 210
Other renal denervation ablation systems 211
Reinnervation after renal denervation 213
Benefits beyond blood pressure control 213
What does all this mean? 214

26. Diagnosis and Management of Acute Pulmonary Embolism 218
Prashant T Upasani, Sameer Gupta, Purshotam Lal
Risk factors for pulmonary embolism 218
Classification of pulmonary embolism 219
Diagnosis 220
Assessment of clinical (pretest) probability 220
D-dimer testing 221
Computed tomography pulmonary angiography 221
Lung scintigraphy 222
Pulmonary angiography 222
Magnetic resonance angiography 222
Echocardiography 222
Compression ultrasonography 223
Markers of myocardial injury 223
Markers of right ventricular dysfunction 223
Integration of aggravating conditions and comorbidity into risk assessment of acute pulmonary embolism 223
Treatment in the acute phase 223
Initial anticoagulation 225
Reperfusion treatment 226
Integrated risk-adapted diagnosis and management 228
Treatment strategies 228

27. Management of Primary Pulmonary Hypertension 233
Dipankar Mukherjee, Subir Sen, Saikat Prasad Dutta
Definition of pulmonary hypertension 233
The difficult issue of defining exercise pulmonary hypertension 234
Diagnostic strategies in pulmonary hypertension 234
Management of primary pulmonary hypertension 235

28. Anticoagulation, Dual Antiplatelet Therapy, and Perioperative Management **252**

Rathindra Nath Karmakar, Auriom Kar, Gaurav Agarwal, Sunandan Sikdar

Managing anticoagulants 252
Managing antiplatelets 255
Deciding perioperative strategy 255
Device implantation 258
Emergency procedures 258

29. Emerging Role of Impedance Cardiography: A New Tool **260**

Bhabani Prasad Chattopadhyay, Sudipta Ghosh, Nasim Mandal, Kalyan Saha

Basic principle of impedance cardiography 260
Few research works on ICG done in the laboratories of medical college, Kolkata and IIT Kharagpur 262

30. Women and Valvular Heart Disease **263**

Sujatha Vipperla

Epidemiology 263
Mitral stenosis 263
Mitral regurgitation 263
Aortic stenosis 264
Aortic regurgitation 265
Tricuspid regurgitation 265
Valvular heart disease in pregnancy 265
Mitral stenosis 266
Aortic stenosis 266
Mitral and aortic regurgitation 266
Prosthetic valves 266

31. Women and Cardiomyopathy **269**

Meenakshi Subbiah

Gender-specific differences in heart failure 269
Cardiac amyloidosis 273
Cardiac sarcoidosis 274

32. Meditation and Cardiac Health **277**

Ramajayram Govindaraj, Mohit D Gupta, Girish MP

Understanding meditation 277
Mechanism of heart diseases and rationale for meditation use 278
Role of meditation in different disorders including risk factors 279
Meditation and plausible molecular mechanisms for cardiac health 282

33. Post-coronavirus Disease 2019 Long-term Cardiovascular Manifestations **291**
SN Routray, Shishu Shankar Mishra, Dipak Ranjan Das
Long-COVID or post-COVID 292
Post-COVID-19 long-term cardiovascular clinical manifestations 292
Mechanism 293
Biomarkers 293
Treatment 294

34. Approach to Angiography in Cyanotic Congenital Heart Disease **295**
Jayranganath Mahimarangaiah, Varun Marimuthu
Classification of cyanotic congenital heart diseases 295
Cardiac catheterization and angiography: Advantages 296
Preprocedural planning 296
Cardiac catheterization: Basic principles 296
Angiography in cyanotic congenital heart diseases 299
Angiography in postoperative cyanotic congenital heart diseases 308

35. Antiplatelets in High Bleeding Risk Patients **315**
Dharmendra Jain, Umesh Kumar Pandey, Suyash Tripathi, Bhupendra Verma, Soumik Ghosh, Rajpal Prajapati, Abhijeet
Antiplatelet agents 315
Assessing high bleeding risk 315
Discussion 321

SECTION 3: PREVENTIVE CARDIOLOGY

36. Revisiting Secondary Prevention in Coronary Artery Disease **325**
Prem Ratan Degawat, Sumit Kumar, Rajeev Gupta
Status of secondary prevention in India 325
Secondary prevention interventions 326
Pharmacotherapy 328
Adherence to secondary prevention 331

37. Genetic Risk Scores for Premature Coronary Artery Disease in India **335**
Rajeev Gupta
Clinical risk stratification 337
Imaging-based risk stratification 338
Genetic risk factors and risk stratification 338
Monogenic risk factors 339
Lipid genes and hypercholesterolemia 340
Polygenic risk scores 341
Indian data 344
Implications 344

38. Exercise and Cardiovascular Health **349**
Chetan P Shah, Charan Reddy KV
Effect of various types of exercise on cardiovascular system 349
Physiological effects of exercise on blood pressure 350
Physiological effects of exercise on lipids and atherogenesis 351
Physiological effects of exercise on insulin signaling 351
Various cardiovascular and peripheral adaptation to physical exercise 351
Sudden cardiac death in sport 351
Can exercise damage a previously normal heart? 352

39. Lipid Profile: Clinical Interpretation and Management Strategies **355**
SS Iyengar, Saikat Kanjilal
Atherosclerotic process 355
Lipid profile 355
Indian data 356
Atherosclerotic cardiovascular disease risk assessment 357
Lipid targets 357
Treatment of hypertriglyceridemia 359

40. Lipoprotein(a): Atherogenic Risk and Management Challenges **361**
JPS Sawhney, Kushal Madan, Ashwani Mehta
What is lipoprotein(a)? 362
Pathogenicity of lipoprotein(a) 362
Ethnic gender and age considerations of lipoprotein(a) 362
Issues in the measurement of lipoprotein(a) 362
Lipoprotein(a) and primary prevention 362
Lipoprotein(a) and secondary prevention 363
Lipoprotein(a) and risk stratification 363
Lipoprotein(a) mediates calcific aortic valvular stenosis 363
Lipoprotein(a) and guideline recommendation 363
Elevated lipoprotein(a) in Indians 364
Treatment in elevated lipoprotein(a) 364

41. Prevention of Atherosclerosis in Childhood and Adolescents **368**
Sunil Modi, Ranjan Modi, Shaan Khetrapal
High blood pressure 368
Smoking 369
Obesity 369
Physical inactivity 369
Dyslipidemia in childhood and adolescence 370

42. Management of Dyslipidemia in Statin Intolerance **374**
Manu Gupta, Rajeev Gupta, Nitesh Arora, Anuj Gupta
Definitions and diagnostic criteria for intolerance to statin therapy 374
Prevalence of the problem 374
Management of dyslipidemias in statin intolerance 375

43. Coronary Artery Calcification in Risk Stratification of Coronary Artery Disease 380
Kajal Ganguly, Mainak Mukhopadhyay, Subhasis Roy Chowdhury, Arijit Ghosh
Pathophysiology of coronary calcification 380
Epidemiology of coronary artery calcification 381
Types of coronary artery calcification 382
Modalities to detect coronary artery calcification 382
Clinical significance of coronary calcification 382
Grading and risk stratification 383
Real-world evidence and medical therapy 384
Coronary intervention in the light of calcified plaque and calcium nodule 385
Future newer insights 386

44. Atherogenic Risk of Low Density Lipoprotein and Management Strategies 389
Kannan Kumaresan, Prabhakar Dorairaj
Atherogenic risk of low-density lipoprotein cholesterol 389
Cumulative loading of low-density lipoprotein cholesterol 390
Interpretation of low-density lipoprotein cholesterol 390
Management of dyslipidemia 391
Alternatives to statin therapy 391
Newer drugs in the pipeline 392

45. Primary Prevention of Cardiovascular Disease: The Current Approach 394
G Rajendiran, Puneeth Kumar
Guidelines 396
Approach to individual traditional risk factors 398
Risk-enhancing factors 400
Physical activity 400
Nutrition 400
Special populations 401
Indian scenario 401
Need of the hour 401

46. Use of Biomarkers: Troponin and B-type Natriuretic Peptide—in Cardiovascular Risk Stratification and Disease Prevention 405
Mini G Varughese, Vijay Nambi
Evolution of the use of cardiac troponin in cardiovascular diseases 406
Evolution of natriuretic peptide system 407
Detection and significance of troponin in asymptomatic general population 407
Significance of measuring BNP and NT-proBNP in the general population 409

47. Reducing Cardiometabolic Risk Through Diet and Exercise: The Power of Lifestyle Change 413
Roshani Sanghani
Dietary changes to reduce cardiac risk 414
Label reading 416

Exercise 419
From literature to life 420
Hope for the future 420

SECTION 4: STABLE CORONARY ARTERY DISEASE

48. Only Ischemia-guided Percutaneous Coronary Intervention is Appropriate in Stable Coronary Artery Disease, Myth or Truth? 425
Ashwin B Mehta, Rahul Chhabria
Pitfalls of coronary angiography 426
Controversial outcomes with revascularization 426
Evaluating coronary physiology 427
Anatomy versus physiology 427
Guidelines recommendations 429

49. Current Status of Exercise Stress Testing vis-à-vis Noninvasive Imaging in Stable Coronary Artery Disease 431
Suraj Kumar, Gurpreet S Wander
Other noninvasive tests for coronary artery disease 431
Exercise electrocardiogram testing components 433
Exercise electrocardiogram in special situations 434
Patient-centered approach 435

50. FFR–MLA Symbiosis: Is it the Way Forward for Intermediate Lesions? 437
Darshan Jhala, Malav Jhala
Invasive hemodynamic indices 438
Invasive hyperemic indices (pressure based) 438
Invasive nonhyperemic indices 441
Flow-based invasive hyperemic indices 443
Coronary microvascular disease and ischemia in nonobstructive coronaries 443
Coronary flow reserve and index of microvascular resistance 445

51. Cardiometabolic Syndrome: Approach in the Current Era 449
PC Manoria

52. Approach to Microvascular Dysfunction Syndromes 452
KU Natarajan, Nischal N Hegde
Extent of the problem 452
Functional anatomy of coronary arterial system 453
Pathogenesis 454
Type-specific clinical implications 454
Diagnosis 456
Type-specific management 459

53. Aspirin-free Antiplatelet Therapy: Is it the Future? 461
Ashish Kumar Jain, RR Mantri
Evidence supporting shortened duration of dual antiplatelet therapy 461
Meta-analysis supporting short-term dual antiplatelet therapy 463
Trial on chronic maintenance therapy with P2Y12 inhibitor 463

54. Approach to Antiplatelet Resistance 466
PK Asokan, Anjana AJ
Definition of antiplatelet resistance 466
Aspirin resistance 467
Clopidogrel resistance 467
High on-treatment platelet reactivity 468
Low on-treatment platelet reactivity 468
Therapeutic window strategy 469
Studies investigating de-escalation of antiplatelet treatment 469
Current place of platelet function testing in everyday clinical practice 469
Prediction rule for nonresponse to clopidogrel: Age, body mass index, chronic kidney disease, diabetes, and genotyping score 469

55. Coronary Atherosclerosis and Endothelial Dysfunction 472
Anindya Mukherjee, Manoranjan Mandal, Ranjan Kumar Sharma
Timeline 472
Pathophysiology 473
Clinical implications of endothelial dysfunction 474
Recent advances 476
Future directions 476

56. Myocardial Bridge 480
Shibba Takkar Chhabra, Sushil Kumar, Riya Aggarwal
Pathophysiology 480
Histology 481
Clinical presentation 481
Diagnosis 481
Investigations for myocardial bridging 483
Treatment 483

SECTION 5: ACUTE CORONARY SYNDROME

57. Approach to Large Thrombus Burden in ST-elevation Myocardial Infarction 489
Vijay Bang, Ashish Deshpande, Rajkumar Ghumare
Pathophysiology of intracoronary thrombus 489
Grading of thrombus burden 490
Prognostic importance of intracoronary thrombus 490
Management 491
Pharmacological interventions 491

58. High-dose Statin in Acute Coronary Syndrome Percutaneous Coronary Intervention **498**

Subhasish Dey, Debabrata Roy

How early should we start statin? 498
Loading dose: Yes or no? 499
How long to continue high-dose statin? 500
Adverse effects 500

59. Myocardial Reperfusion Injury after Acute Myocardial Infarction Interventions: Bedside Evaluation **502**

Jagdish C Mohan, Madhu Shukla

Pathogenesis of myocardial edema 504
Detection of myocardial edema 505
Consequences of abnormal myocardial thickening and myocardial edema 506
Natural history of myocardial edema 511
Prevention and management 514

60. Women and Spontaneous Coronary Artery Dissection: Is it Different? **516**

Lekha Adik Pathak, Ronak V Ruparelia

Demographics and prevalence 516
Natural history 516
Presentation and diagnosis 517
Associated conditions 517
Short-term management 518
Long-term management 518

61. STEMI in Women: Is it Different? **520**

Jyotsna Maddury

STEMI: Global scenario 520
STEMI: Indian scenario 520
Pattern of presentation 520
Probable causes for gender difference 521
Fallacies and controversies about STEMI in women 522
Treatment of acute myocardial infarction in women 522
Treatment of acute myocardial infarction in women: Outcomes and guideline-based recommendations 522
Postmyocardial infarction complications 523
Studies 524
GAPS in knowledge and required fields of research in women with STEMI 524
Measures to improve the disparity 525

62. An Approach to STEMI: Late Presenters **529**

Lijo Varghese, Balakumaran Jeyakumaran, Thomas Alexander

Current guidelines 529
Management algorithm in late presenters 532
Complications in late presenters 533

63. Culprit Vessel or Multivessel PCI during PAMI: Which One to Adopt? 535
Dev B Pahlajani
Patients without cardiogenic shock 536
STEMI with compromised hemodynamics and cardiogenic shock 537

64. Plaque Rupture versus Erosion: Common Consensus in ST-elevation Myocardial Infarction 540
Dhiman Kahali, Ritwik Ghosal, Asit Das
Causes 540
Mechanism of formation of plaque 540
Clinical strategies and outcomes in patients with plaque erosion 541

65. Colchicine and Cardiology: What is New? 547
Sudhir Chandra Sinha, T Suresh Babu, Siva Kumar Damireddy, G Venkateshwar Reddy
Evidence that inflammation triggers acute cardiovascular events 547
Colchicine as an anti-inflammatory agent 548
Clinical trial evidence of colchicine in cardiology 548

66. Mechanical Complications of Acute Myocardial Infarction: Diagnosis and Management 553
P Rajendra Kumar Jain, Mohammed Sadiq Azam
Incidence 553
Clinical presentation 553
Prognosis 557
Differential diagnosis of mechanical complications of acute myocardial infarction 558

67. Free Wall Rupture, Can We Mend the Broken Heart? 560
Ashesh Halder, DP Sinha
Causes of cardiac rupture 560
Clinical presentation 561
Diagnosis of free wall rupture 561
Management 561
Prognosis 564

68. ECG Localization of Culprit Artery in Acute Myocardial Infarction 568
Dipak Sarma, MS Chaliha, Shekharjyoti Gogoi
Anatomy of coronary artery 568
Left anterior descending artery occlusion 570
Inferior wall myocardial infarction 572
Posterior wall infarction 573
Culprit artery localization in acute non-ST-elevation myocardial infarction 574
Limitations of ECG 574

69. Management of Atrial Fibrillation after Acute Coronary Syndrome Intervention **576**

Asok Kumar Kar, Ayan Kar

Background 576
Dual antithrombotic versus triple therapy 577
Role of aspirin and the risk of stent thrombosis 580
Duration of therapy 580
Choice of concomitant P2Y12 inhibitor 580
When to start dual antithrombotic therapy 580
Definition of bleeding and thrombotic risk 580

70. Coronary Ectasia and Aneurysm, Diagnosis and Management **583**

Dharmesh Solanki, Jaydeep Desai, Dharmil Patel, Jay Vithlani

Clinical presentation 583
Diagnosis 583
Management of coronary artery aneurysm and coronary artery ectasia 584
Asymptomatic patients 584
Symptomatic patients 584
Percutaneous coronary intervention 584
Surgical management 586
A suggested algorithm for management of patients with coronary artery aneurysm 586
Conclusion and future perspectives 586

71. Approach to Non-ST-elevation Myocardial Infarction **588**

Satish M Roplekar, Kedar S Roplekar, Kanchan S Roplekar

Clinical assessment 588
Risk assessment 591
Management 591
Selection and duration of dual antiplatelet therapy in NSTE-ACS 595
Conditions requiring both oral anticoagulant and antiplatelet therapy 598
Invasive versus conservative management 599
Lipid-lowering therapy 600
Special groups and subsets 601

72. Acute Myocardial Infarction: Primary Angioplasty in Myocardial Infarction versus Lytics **605**

Y Vijayachandra Reddy, Antony Wilson, Shalini M

Reperfusion strategies: More different than similar 605
Practical considerations of reperfusion strategies 606
A detailed discussion of the two strategies 607
Pharmacoinvasive percutaneous coronary intervention 607
Fibrinolysis versus primary percutaneous coronary intervention in STEMI cardiogenic shock 609
The Indian scenario 609

73. Left Ventricular Thrombus Following Acute Myocardial Infarction **612**
Saumitra Ray, Supratip Kundu
Epidemiology 612
Pathophysiology 613
Diagnosis 613
Prophylaxis 613
Treatment 614
Algorithmic approach 614

74. Postmyocardial Infarction Ventricular Septal Rupture: Challenges in Diagnosis and Management **616**
Smit Shrivastava
History 616
Pathophysiology 616
Clinical presentation 617
Diagnosis 617
Differential diagnosis 619
Treatment 619
Timing of the closure 619
Factors influencing outcomes 620
Stabilization before procedure 620
Mechanical support devices 620
Future direction for research and treatment 621
Author's experience 621

75. Left Ventricular Remodeling after Myocardial Infarction: The Current Approach and Novel Interventions **622**
Sandeep Bansal, Aseem Basha M
Epidemiology 622
Pathophysiology of left ventricular remodeling post myocardial infarction 623
(MAL)adaptations consequent to alterations in left ventricular geometry 624
(UN)natural course of left ventricular remodeling post myocardial infarction 624
Imaging modalities for left ventricular remodeling 625
Management 626

Index ***i1–i34***

VOLUME 2

SECTION 6: CORONARY INTERVENTIONS

76. Percutaneous Recanalization of Chronic Total Occlusions: From Start to Finish **633**
Daniel Jeffery, Tharindra Dissanayake, Majd Protty, Ahmed Hailan, Anirban Choudhury
Epidemiology 633
Collateral physiology in CTO vessels 633
Rationale for CTO renalization 634
Current evidence base for CTO recanalization 634
Technical approaches for CTO recanalization 636
Institutional components of a CTO program 644

77. Appropriate Tools in Calcified Lesion Complex Percutaneous Coronary Intervention with Tips and Tricks **652**
Mathew Samuel Kalarickal, Karthikeyan Balakrishnan, Vijayakumar Subban
Procedure planning 652
Risk assessment 653
Treatment of calcified lesions 653

78. Chronic Total Occlusions Toolkit **663**
Pravin K Goel, Ankit Kumar Sahu, Gautam Das
Chronic total occlusion histopathology and its applied anatomy 663
Essential chronic total occlusion-percutaneous coronary intervention toolbox 664
Peripheral vascular sheath 664
Guiding catheter 664
Guide catheter extension 665
Coronary guidewires for chronic total occlusion-percutaneous coronary intervention 665
Microcatheters 669
Antegrade dissection reentry system 671
Low-profile dedicated chronic total occlusion balloons 671
Excimer laser 672
Atherectomy (rotational or orbital) 672
High-pressure noncompliant balloon 672
Intravascular imaging 672
Equipment specific for retrograde CTO-PCI approach 672
Equipment for managing complications 672

79. Intravascular Ultrasound: Basics and Beyond **674**
Karthikeyan Balakrishnan, Vijayakumar Subban
Principles and imaging systems 674
Image interpretation 675
Clinical applications of intravascular ultrasound 675
Clinical evidence for intravascular ultrasound-guided coronary intervention 680

Intravascular ultrasound in specific lesion subsets 680
Future perspectives 683

80. Optical Coherence Tomography: Basics and Beyond 688

Rony Mathew, Jabir A

Optical coherence tomography basics 688
Clinical evidence for optical coherence tomography and intravascular imaging 689
Image acquisition and display 689
Plaque assessment 690
Optical coherence tomography plaque morphology 692
Optical coherence tomography for percutaneous coronary intervention planning 694
Optical coherence tomography for post-percutaneous coronary intervention optimization 696
Artifacts in optical coherence tomography 697
Optical coherence tomography in lesion subsets 699
Future directions 702

81. Intracoronary Stent Restenosis: Diagnosis and Management Strategies 706

Majd Protty, Tharindra Dissanayake, Daniel Jeffery, Anirban Choudhury

Definition of ISR 706
Incidence of ISR 706
Factors influencing development of ISR 707
Pathophysiology of ISR 707
Diagnosis and assessment of ISR 708
Management of ISR 708
Clinical cases of ISR focusing on diagnosis and management 709

82. Anomalous Coronaries: Diagnostic and Percutaneous Coronary Intervention Technical Challenges and Strategies 720

Ajit Desai, Nikesh Jain

Percutaneous evaluation of coronary artery anomaly 720
Left anterior descending anomalies 725
Left main coronary artery anomalies 725
Septal pathway 725
Anterior free wall course 725
Retroaortic course 725
Interarterial course 727
Single coronary artery 727
Dextrocardia 727
Intervention for anomalous coronary arteries 727

83. Utility and Progress of Robotic Percutaneous Coronary Intervention in Current Practice: A Case-based Discussion 730

Tejas M Patel, Sanjay C Shah, Samir B Pancholy

About Corindus CorPath® GRX robotic system 730
About TechnIQ smart procedural automation 731

What is the evidence base? 734
What is the future? 736

84. Approach to Catheter-induced Left Main Coronary Artery and Right Coronary Artery Ostial Dissection with Retrograde Aortic Extension 738
Pratap Kumar N, Manu R, Praveen

Incidence 738
Causes of iatrogenic aortocoronary dissection 738
Vascular factors 739
How to identify and diagnose iatrogenic aortocoronary dissection? 739
Classifications 739
How to manage iatrogenic aortocoronary dissection? 741
Points to remember during bailout stenting in iatrogenic aortocoronary dissection 742

85. Appropriateness of CTO PCI in Stable CAD: The Current Approach 745
Anil Dhall, Puneet Gupta

Clinical benefit of chronic total occlusion revascularization 746
Decision-chronic total occlusion 746
Euro-chronic total occlusion 747
Ischemia-chronic total occlusion trial 747
Chronic total occlusion academic research consortium 748
Complexity scores 748
Crossing algorithms 748
Global chronic total occlusion algorithm 748
Future strategies 754

86. Provisional versus Elective Double Stenting in Bifurcation: Evidence-based Approach 758
DS Gambhir

Stenting for bifurcation lesions 758
Provisional versus elective two-stent strategy 758
Randomized studies 759
Approach to left main bifurcation stenting 760

87. Bifurcation Stenting Techniques: Update 762
Mahesh K Shah

Anatomic considerations 762
Special technical considerations in bifurcation stenting: Tips and tricks 763
Approaches to bifurcation stenting 765
Two-stent techniques 766

88. Coronary Bioresorbable Scaffolds: Current Evidence 770
Balbir Singh

The necessity for invention 770
The story so far 771

Experience with other bioresorbable scaffolds 773
Bioabsorbable metal scaffolds 775

89. Radial versus Distal Radial Access: Current Evidence 778
Yashasvi Chugh, Sunita Chugh, Sanjay Kumar Chugh
What's the evidences data? 778
Discussion 779

90. Radial versus Femoral Access in STEMI: Is there still a Debate? 782
Harikrishnan Parthasarthy
Major trials comparing transradial approach versus transfemoral approach in STEMI 783
Summary of interpretation of the available evidence 784
Transradial approach in acute coronary syndrome: What are the potential issues? 785
How to further improve outcomes with transradial approach in ST-elevation myocardial infarction/acute coronary syndrome and summary 786

91. Challenges in Management of Groin Complications (Routine and Wide Bore Access) 788
Vijay Kumar Sinha, Vishal Rastogi, Vivudh Pratap Singh, Dhananjay Kumar, Avinash Mani, Ashok Seth
"Complication prone" vascular anatomy of the groin 788
Challenges in the management of groin complications 790
Best practices and challenges in managing different complications 794

92. CrossBoss® and Stingray®: Step-by-step 797
Sharath Reddy, Himanshu Gupta, Sridhar P
Before Switching to antegrade dissection re-entry 797
CrossBoss® and Stingray® system 798
CrossBoss® not advancing 801
Stingray® system 802
Managing subintimal hematoma 805
Failed re-entry 805

93. Trifurcation and Quadrifurcation Left Main Coronary Artery Percutaneous Coronary Interventions: Challenges and Strategies with Tips and Tricks 809
Shirish MS Hiremath, Satishkumar S Kolekar
Comparison of percutaneous coronary intervention and coronary artery bypass grafting for distal left main coronary artery stenosis 809

94. Stent Failure: Mechanism and Management Strategies 817
Kamal K Sethi, Kabir Sethi
Etiopathogenesis of stent failure 817
Role of intracoronary imaging in in-stent restenosis 818
Stent thrombosis 818
Management of stent failure 819

95. Metallic Stents: Past, Present, and Future **822**
Nishith Chandra
Background 822
How are stents made? 822
Classification and nomenclature 823
Overview of stent design 825

96. Bench Testing to Practice in Cath Lab: Percutaneous Coronary Intervention Tips and Tricks **829**
Vijay Bang, Vladimír Džavík, Sachin Narendra Patil, Ashish Deshpande, Swaroop G Bharadi, Y Suresh, Pragathi
Scaling laws of flow 829
Models and model construction materials 830
Imaging of stents or scaffolds in coronary bifurcation models 831
Proximal optimization technique: Insights from bench testing 832
Proximal versus distal crossing in bench testing 833
Difficulty of balloon passage in the side branch 834
Dilation through the side of a stent and distortion correction strategies 834
T-stenting and tap 834
Bench testing in culotte technique 834
Simultaneous kissing stents technique 835
Crush technique 835
Polymer damage and implications 837
Role of 3D printing in bench testing 838

97. Slow Flow, No Flow Phenomenon: What is New? **842**
Harnish Singh Bhatia, Subhash Chandra
Definition 842
Clinical presentation 842
Pathophysiologic mechanisms 842
Management 844
Other interventions 846

98. Artificial Intelligence in the Diagnosis and Invasive Management of Coronary Artery Disease **850**
Vijay Bang, Ashish Deshpande
What is artificial intelligence? 851
Electrocardiogram and artificial intelligence for the detection of cad and prediction of the obstructed coronary artery 851
Artificial intelligence: Cardiology imaging applications for the diagnosis of CAD 852
Artificial intelligence to predict functional significance of obstructive and lesion-specific ischemia 853
Artificial intelligence in the optimization of peri-intervention workflow 856
Artificial intelligence-based postprocedure risk prediction models 856

Artificial intelligence-based major adverse cardiovascular event and long-term mortality prediction 857
Software programs in clinical practice that incorporate artificial intelligence 857
Advantages and challenges of artificial intelligence in interventional cardiology 859
Future applications of artificial intelligence 860

99. Complex High-risk Patient Subsets: Nitty Gritty and Management Challenges **863**
Rohit Mody, Debabrata Dash, Inderjeet Singh Monga
Scoring system 864
Complex high-risk patient subsets 865
Discussion 904

100. Dual Antiplatelet Therapy after PCI: Current Status **913**
Vijay Bang, Pankaj Harkut, Khushal Sharnagat
Why there is a need to redefine the duration of DAPT? 913
Duration of dual antiplatelet therapy 915
Recent guidelines on dual antiplatelet therapy 916

SECTION 7: HEART FAILURE

101. Heart Failure: From Device Intervention to Transplant **921**
KR Balakrishnan, R Ravikumar, KG Suresh Rao
Grades of heart failure with mortality 921
Device interventions for heart failure 921
Types of mechanical circulatory support devices 921
Heart transplantation 922
International data/guidelines on the subject 923
High-risk factors after heart transplant 924
Classical indications of heart transplant 924
Absolute contraindications 924
High-risk criteria for donors 924
Matching of donors versus recipients 925
Published Indian data 925
Critical discussion on application of international guidelines to Indian patients 925
Future directions 927

102. Role of Echocardiography in Heart Failure **930**
CK Ponde, Akshay Pawar, Mufaddal Lunawadawala
Spectrum of heart failure and role of echocardiography 930
Novel echocardiographic parameters in heart failure with preserved ejection fraction 935

103. Digital Technology in the Management of Heart Failure **938**
Mrinal Kanti Das, Shishu Shankar Mishra
Digital Twin 938
Telemedicine and telerehabiltation 940
Digital technology leading to precision medicine 940
Artificial intelligence-based therapeutics for heart failure 942

104. Advances in Medical Management of Heart Failure **944**
Rajeev Krishna Choudhary, Gaurav Chaudhary, Sharad Chandra
Angiotensin–neprilysin inhibition 945
Sodium-glucose cotransporter-2 inhibitors 947
Soluble guanylate cyclase stimulator 951
Cardiac myosin activator 952
Heart failure with preserved ejection fraction 955
Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers 955
Mineralocorticoid receptor antagonist 956
Angiotensin receptor and neprilysin inhibitor 958
Soluble guanylate cyclase stimulators 958
Sodium-glucose cotransporter-2 inhibitors 958

105. Approach to Mechanical Circulatory Support in Cardiogenic Shock **965**
M Subroto, S Adhikari, R Gupta, D Jain, S Garde
Left ventricular failure 965
Short-term devices 966
Right ventricular failure 968
Total artificial heart 968
Extracorporeal membranous oxygenation 968
Mechanical circulatory support for pulmonary failure 969
Intra-aortic balloon pump and kidney injury 969
Left ventricular assist device and kidney injury 969
Extracorporeal membrane oxygenation and kidney injury 970

106. Right Ventricle Function Evaluation and Management of Right Ventricler Failure **972**
PC Mondal
Embryologic and anatomical peculiarities of right ventricle 972
Functional analysis of right ventricle 973
Etiopathology of right ventricular failure 973
Hemodynamic indices to define right ventricular failure 973
Diagnosis of right ventricular failure 973
Medical therapy of acute right ventricular failure 974
Other medical therapies 974
Cardiac arrhythmias and right ventricular dysfunction 974
Mechanical circulatory supports for refractory right ventricular failure 975

107. Hemodynamics of Heart Failure and Appropriate Mechanical Circulatory Support Considerations **976**

Deepanjan Bhattacharya, Harikrishnan S

Determinants of cardiac output 976
Heart failure 978
Response to exercise 979
Measurements of mechanical efficiency 979
Hemodynamics in mechanical circulatory support 980

108. Renal Compression in Heart Failure: The Renal Tamponade Hypothesis **982**

Satyavir Yadav, Ambuj Roy

Background 982
Anatomy 983
Pathophysiology 984

SECTION 8: STRUCTURAL HEART DISEASE

109. MitraClip in Secondary Mitral Regurgitation **991**

Tikal Kansara, Toshiaki Isogai, Serge Harb, Samir Kapadia

Classification of mitral regurgitation 991
Indications 992
Step-by-step MitraClip procedure 993
Complications of MitraClip procedure 999
Postprocedure follow-up 999
COAPT trial 1000
MITRA-FR trial 1002
Discrepancies between COAPT and MITRA-FR trail 1002
Other studies 1003

110. Cardiovascular Magnetic Resonance in Structural Heart Disease **1007**

Priya Chudgar, Nitin Burkule

Imaging 1007
Case examples 1007

111. Closure of Patent Foramen Ovale: When and Why **1014**

Vigyan Vijay Bang

Embryology 1014
Patent foramen ovale anatomy 1014
Evolution of evidence on patent foramen ovale closure 1015
Other clinical scenarios 1015
Assessment of a patient for patent foramen ovale closure 1018
Patent foramen ovale closure procedure 1018
Future direction 1020

112. Septal Ablation: Current Status **1021**
Ajay J Swamy, Navjyot Kaur, Rajeev Chauhan
Management of left ventricular outflow tract obstruction 1021
Percutaneous alcohol septal ablation 1022
Limitations 1023
Comparison of alcohol septal ablation with surgical myomectomy 1023
Future 1024

113. Percutaneous Tricuspid Valve Interventions: Current Status **1026**
Sridhar Kasturi
Etiology of tricuspid regurgitation 1027
Diagnosis of tricuspid regurgitation 1027
Surgical management 1029
Current status of transcatheter device therapy for tricuspid regurgitation 1030
Transcatheter valve replacement of tricuspid valve 1032
Strategic approach to device therapy of tricuspid regurgitation 1033

114. Left Atrial Appendage Closure: Indications and Technique **1035**
Ranjan Shetty, Soorampally Vijay
Rationale 1035
Evidence 1035
Indications 1036
Technique 1037
Postprocedure treatment and follow-up 1039
Possible complications 1039

115. Transseptal Puncture: Procedural Challenges and Complications **1040**
Milan C Chag, Anuj A Thakre, Aenasha Chag
Indications 1040
Standard step-by-step transseptal puncture: Tips for the fluoroscopic guidance 1040
Contraindications and challenges for transseptal puncture 1043
Complications 1051

116. Alternative Access in Transcatheter Aortic Valve Implantation **1054**
Maulik Parekh
Access sites for transcatheter aortic valve replacement 1054
Alternative access options for transcatheter aortic valve replacement 1055
Extrathoracic access sites 1056
The contemporary approach 1058

117. Management of Paravalvular and Central Leak in Transcatheter Aortic Valve Implantation **1059**
Nagendra Chouhan, Praveen Chandra
Incidence 1059
Risk factors 1059

Mechanism of paravalvular leak 1060
Diagnosis and quantification of paravalvular leak 1060
Prevention and management 1060
Prevention 1060

118. Transcatheter Mitral Valve Replacement Indications and Technical Tips and Tricks **1064**
Sanjay Mehrotra
Transcatheter mitral valve replacement 1065
Case description to explain the workup and the procedure 1065

119. Approach to Valve-in-valve by Percutaneous Intervention **1071**
G Sengottuvelu, Senthilraj Thangasami
Transcatheter aortic valve in valve implantation 1071
Transcatheter mitral valve in valve implantation 1081

120. Appropriateness of TAVR and Current TAVR Scenario in India **1088**
Vivudh Pratap Singh, Ashok Seth
Current TAVR scenario in India 1089
Status of TAVR in India 1091
TAVR valves 1091

121. Annular Rupture: A Feared Complication of Transcatheter Aortic Valve Replacement **1094**
Vigyan Vijay Bang
Pathoanatomy 1094
Classification 1094
Presentation 1095
Diagnosis 1095
Management 1095
Outcome 1096
Prevention 1096

122. Transesophageal Echocardiography and Adult Percutaneous Interventions: Tips and Tricks **1097**
Sameer Shrivastava, Arif Mustaqueem, Vinay Sharma
Comprehensive transesophageal echocardiography examination two-dimensional echocardiographic acquisition 1098
Transesophageal echocardiography probe positions 1099
Transeptal puncture 1099
Cardiac perforation and tamponade 1099
Thromboembolism 1099
Air embolism 1099
Left atrial appendage 1101

Transcatheter mitral valve intervention 1101
Imaging intraprocedural transesophageal echocardiography 1107
Percutaneous device closure of paravalvular leak 1109
Transesophageal echocardiography measurement of coronary ostial height 1111
Transcatheter aortic valve replacement stent expansion 1114

123. Pre-TAVR/TMVR: Computed Tomography Evaluation and Challenges 1118

Mona Bhatia, Parveen Kumar, Prasit Maity, Natisha Arora

Introduction and procedural overview of transcatheter aortic valve replacement 1118
Computed tomography acquisition protocols for pre-transcatheter aortic valve replacement imaging 1118
Pre-transcatheter aortic valve replacement-computed tomography assessment 1119
Transcatheter aortic valve replacement in bicuspid aortic valve disease 1122
Introduction and procedural overview of transcatheter mitral valve replacement 1122
Computed tomography acquisition protocols for pre-transcatheter mitral valve replacement imaging 1122
Pre-transcatheter mitral valve replacement-computed tomography assessment 1123
Special considerations 1124

124. Balloon Mitral Valvuloplasty: Tips and Tricks 1127

Justin Paul, J Cecily Mary Majella, Anne Princy

Choosing the patient 1127
Echocardiographic evaluation 1127
Understanding the hardware 1128
Preparing the hardware 1129
PTMC procedure: Step by step 1129
Situations requiring modifications from usual technique 1136
Complications and surgical intervention 1137

125. Mavacamten in Hypertrophic Obstructive Cardiomyopathy 1139

Asha Moorthy, Jain T Kallarakkal, G Manohar

Mavacamten 1139

SECTION 9: ELECTROPHYSIOLOGY

126. Physiological Pacing: An Overview 1143

Dilip Kumar, Saurav Das, Debapriyo Mandal, Rabindra Nath Chakraborty, Abhishek Roy

Conduction system pacing 1143
His-bundle pacing 1144
Left bundle branch pacing 1144
Causes of procedure failure 1145
Complications of left bundle branch pacing 1146
Study of outcomes 1146

127. Prevention of Atrial Fibrillation **1149**
Vijay Surampalli, Yash Lokhandwala
Prevention of atrial fibrillation 1149
Upstream therapy of atrial fibrillation 1152

128. Localization and Management of Broad QRS Tachycardia **1154**
Rabindra Nath Chakraborty, Sanjeev S Mukherjee, Ashesh Halder
Look for structural heart disease 1154
Epicardial origin 1159
Management of wide QRS tachycardia 1161

129. Leadless Cardiac Pacemaker **1164**
PK Hazra, Supratip Kundu
Pacemaker history 1165
Complications associated with conventional pacemaker 1165
Leadless pacing system 1166
Leadless system for right ventricular pacemaker 1167
Leadless system for left ventricular pacemaker 1168

130. Wearable Devices in Cardiovascular Practice **1171**
Ashutosh Arora, Pawan Suri, Vivek Kumar, Vanita Arora
What are "wearable devices"? 1171
Types of wearable devices 1172

131. Sudden Cardiac Death: Mechanism, Prevention, and Management Strategies **1176**
Ashish Nabar
Malady of sudden cardiac death 1176
Understanding the SCD conundrum 1176
Noninvasive risk stratification 1183
Therapeutics 1185

132. Newer Antiarrhythmics in Atrial Fibrillation **1188**
Dipankar Ghosh Dastidar, Nandita Ghosh Dastidar
Established antiarrhythmic drugs for rhythm control 1188
Non-pharmacological interventions in AF 1192
Anticoagulation strategies 1192
Changing therapeutic paradigm 1192
New antiarrhythmic drugs for rhythm control 1193
Targeting pathophysiological mechanisms 1196
Targeting progressive "atriomyopathy" 1197

133. Update on Out-of-Hospital Cardiac Arrest **1201**
Srinivas Ramaka, Vemuri S Murthy, Vasudeva Murthy Sindgi
Global data on OHCA 1201
Measures for quality of resuscitation care 1202

The national academy of medicine's report on strategies to improve cardiac arrest survival: A time to act 1203
Barriers to layperson response 1203
Bystander effect 1203
Impact of dispatcher-assisted CPR instruction 1204
Telecommunicator CPR 1204
Barriers to completing CPR instructions 1205
Manual versus mechanical CPR 1205
High-quality CPR: Improving cardiac resuscitation outcomes both inside and outside the hospital 1205
Community-focused initiatives 1205
Willingness to perform bystander CPR: A scoping review 1205
Automated external defibrillator 1206
Public-access defibrillation 1206
Utstein formula to improve survival 1206
Predictors of survival after OHCA 1206
Factors impacting the survival of OHCA subjects 1207
Referral and receiving facilities 1207
Evidence-based management of OHCA subjects 1207
Prognostication after OHCA 1207
Assessment and risk stratification 1208
Factors associated with poor outcomes of OHCA patients 1208
Risk scores in OHCA 1208
Neuroprognostication 1208
Targeted temperature management in OHCA 1208
Postcardiac arrest syndrome 1209
Risk stratification 1209
Role of cardiac catheterization lab in the management of OHCA 1209
Presence of coronary artery disease in patients with OHCA 1210
Randomized controlled trials in OHCA 1211
Refractory OHCA and the role of the cardiac catheterization laboratory 1212
Mechanical circulatory support (IABP, impella, and ECMO for cardiogenic support) 1212
Strategies to improve survival from OHCA 1212
OHCA in low-resource settings 1212
COVID-19 and OHCA 1212
Improving survival from OHCA 1214

SECTION 10: CARDIO ONCOLOGY

134. Cardio-oncology: Approach to the Patient **1219**
Biswajit Majumder, Shibsankar Sarkar, Pallab Biswas
Shared pathophysiology of cardiovascular diseases and cancer 1219
Reverse cardio-oncology 1220
Cardio-oncology syndromes 1220
Chemotherapy-associated cardiotoxicity 1220
Management of chemotherapy-induced cardiotoxicity 1222

Screening before anticancer therapy 1222
Cardiovascular monitoring during cancer treatment 1222
Principles of treatment of chemotherapy-induced cardiotoxicity 1224
Management of cardiotoxicity occurring during the cancer treatments 1224
Cardiac arrhythmias related to cytotoxic chemotherapy agents 1225
Areas of implementation and future perspectives 1225

135. Percutaneous Coronary Intervention in Patients with Cancer: Clinical Challenges and Management Strategies 1228

Gemina Doolub, Mamas A Mamas

Shared modifiable risk factors 1228
Inflammation 1229
Cardiotoxic cancer therapies 1229
Percutaneous coronary intervention in cancer: Challenges 1229
Percutaneous coronary intervention outcomes in cancer 1229
Multidisciplinary approach 1231
Vascular access 1231
Pharmacology 1231
Thrombocytopenia 1232
Stent choice 1232
Intravascular imaging 1232
Other considerations 1232

136. Cardiac Toxicity of Oncology Drugs: Challenges in Diagnosis and Management 1235

K Venugopal

Types of cardiac toxicity 1235
Specific cardiovascular problems 1236
Early diagnosis of cardiotoxicity 1237
Definition of cardiotoxicity 1238
Imaging in assessment of cardiac toxicity 1238
Role of biomarkers in assessing cardiotoxicity 1239
Treatment of cardiotoxicity-pharmacologic approaches 1239
Establishing a cardio-oncology unit 1239
Challenges in India 1239

SECTION 11: ENDOVASCULAR PERIPHERAL

137. Renal Artery Stenosis: Our Experience 1243

Vijay Bang, Pankaj Harkut

Presentation 1243
Diagnosis 1244
Study findings at our center 1244
Our study conclusion 1245
Management 1245

138. Aortic Dissection: Diagnosis and Management Challenges **1247**
Mahpaekar Mashhadi, Dhanya Nair, Sameer Dani
Normal and aging aorta 1247
Classification 1248
Clinical manifestations 1249
Diagnosis 1249
Evaluation and management 1251
Treatment of type B aortic dissection 1255

139. Diagnosis and Management of Thoracic and Abdominal Aortic Aneurysms **1259**
Suparna Rao, NN Khanna
Classification 1259
Aortic aneurysms 1259
Thoracic aortic aneurysms 1261
Abdominal aortic aneurysms 1263
Role of intravascular ultrasound 1265
Endograft surveillance 1266
Endoleak 1266
Recent advances in endovascular aortic aneurysm repair 1266
Future directions: Epigenetics 1267

140. Aortic Dissection: Surgical Challenges and Management Strategies **1272**
Bashi Velayudhan, Mohammed Idhrees, Mohammed Ibrahim
History 1272
What is aortic dissection? 1272
Pathophysiology 1273
Epidemiology 1273
Risk factors 1273
Classification 1274
Signs and symptoms 1275
Why is aortic dissection missed? 1275
Cardiovascular imaging 1275
Management 1277
Malperfusion syndrome 1278

Index ***i1–i26***

SECTION 1

BEDSIDE CARDIOLOGY

CHAPTER 1: **Jugular Venous Pulse, Arterial Pulse, and Blood Pressure Recording in Children and Adults**
Kamal Sharma

CHAPTER 2: **ECG and X-ray in Congenital Heart Disease**
Parag Bhalgat, Pooja Bhalgat

CHAPTER 3: **Approach to Echocardiography in Cyanotic Congenital Heart Disease**
Nitin Rao, Suman Vyas, Rajesh Gudipati

CHAPTER 4: **Approach to Cyanosis from Newborn to Adult: Hemodynamics and Management Strategies**
Sakshi Sachdeva, Anita Saxena

CHAPTER 5: **Relevance of Stethoscope in Contemporary Cardiology**
Satyavan Sharma, Vishal Patil

CHAPTER 6: **Approach to Chest Pain: The New Perspective**
Vijay Bang, Mustafa Taskeen

CHAPTER 7: **Heart Sounds and Murmurs**
Mohsin Raj Mantoo, Sivasubramanian Ramakrishnan

CHAPTER 8: **Artificial Intelligence in General Cardiology**
Saurabh Deshpande, Deepak Padmanabhan

CHAPTER 9: **Clinical and Noninvasive Assessment of Aortic Stenosis**
Shraddha Ranjan, Ravi R Kasliwal, Manish Bansal

CHAPTER 10: **Clinical Approach to Mitral Regurgitation**
MS Ravi, J Cecily Mary Majella

CHAPTER 11: **Interpretation of Cardiac Symptoms**
Chandan Kumar Das

CHAPTER 1

Jugular Venous Pulse, Arterial Pulse, and Blood Pressure Recording in Children and Adults

Kamal Sharma

ABSTRACT

In the era of artificial intelligence (AI) enabled "wearables and peripherals", the time-tested "peripheral cardiovascular system (CVS)" evaluation with jugular venous pulse (JVP) reflecting right heart hemodynamics and pulse and blood pressure (BP) reflecting the left heart hemodynamics have done the job for more than a century now. JVP findings have long reflected right atrial (RA) hemodynamics in systole and both RA and right ventricle (RV) hemodynamics in diastole in health as well as diseases of not just myocardium but even those of pericardium and pulmonary vascular bed. Pulse and BP evaluation the same way reflects the left ventricle (LV). Various valvular disorders and hemodynamic states hence have not only been used to diagnose various cardiovascular (CV) disorders but also quantify the same using various signs like Hill's sign. These signs are now being quantified in newer studies for their likelihood-ratio (LR) and their sensitivity and specificity for the detection of various CV disorders. This chapter elucidates the relevance and clinical implication of JVP, pulse and BP in health, and disease both in children and adults.

INTRODUCTION

Evaluation of the "Central" cardiovascular system (CVS) can be inferred to a great extent using the "peripheral CVS" as assessed by jugular venous pulse (JVP), arterial pulse (AP) evaluation, and blood pressure (BP) assessment. The direct continuation of JVP with right atrium (RA) in systole and right ventricle (RV) in diastole reflects the hemodynamics of the right heart while the AP and BP would together reflect the status of the left ventricle (LV) and its outflow obstruction if any, along with the systemic vascular compliance/resistance with its interplay with the condition of the arterial wall.[1]

JUGULAR VENOUS PULSE

It is assessed in the right internal jugular vein (IJV) as the external jugular vein (EJV) is more prone to kinking and calcification and tends to underestimate the pressure due to the "venturi effect" as a smaller EJV joins the IJV.

Jugular venous pulse is assessed and evaluated for the following parameters:[1]

- Jugular venous *pressure*
- Waveforms: *a, x, c, x', v, y,* and *h* waves
- *Pulsatility*: Pulsatile or nonpulsatile
- Respiratory variation
- Abdominojugular reflux
- Kussmaul's sign

Pressures

Jugular venous pressure can be assessed at all inclinations and 45° is not a must though it is the most commonly used inclination. Its *normal value* is 3–4 cm of the venous column and in *recumbent position* 2 cm from the angle of Louis. The JVP is to be calculated from the center of the RA which is the "*Phlebostatic axis*" for assessing the venous pressures and is roughly arrived at by adding 5 cm to the venous column. The venous column is converted to mm Hg by dividing the value by a factor of 1.36. Now it is suggested that the distance of RA to sternal angle is:

- 5 cm in a flat horizontal position at 0°
- 8 cm when elevated 30°
- 10 cm when the upper body is elevated >45°
- This is based upon the vertical distance between the sternal angle and the level of the RA by computed tomography (CT) scan.[2,3] In patients with body mass index > 35 kg/m^2, a jugular venous column more than the clavicle is likely to indicate elevated JVP.

Estimating the right atrial pressure (RAP): The JVP can estimate RAP subject to clinical settings as published in a review of 10 studies:[4]

- Whether the JVP is interpretable or not varies on the clinical scenario and examiner's experience.
- The clinical evaluation of JVP tends to underestimate central venous pressure (CVP) due to the underestimation of the distance between the sternal angle and the central RA, traditionally counted as 5 cm. However, some imaging studies have shown that the actual distance varies with the patient's position.[5]
- The accuracy of JVP with sensitivity for elevated CVP ranged from 14 to 86% in a review.[4]
- The *ESCAPE (Evaluation Study of Congestive heart failure and Pulmonary artery catheterization Effectiveness) trial* investigators who were skilled in the care of patients with heart failure (HF) were able to estimate whether the RAP was < 8 mm Hg (likelihood ratio = 16.6) and the area under the curve (AUC) of the survival curve for estimated RAP > 12 mm Hg was 0.74.[6] Also in this trial, the findings associated with an elevated pulmonary capillary wedge pressure (PCWP) were the presence of orthopnea or an elevated JVP.[6] In another observational study, the accuracy of the RAP was greater for staff cardiologists compared with trainees (82% vs. 67%).[7]

Diagnosing and prognosticating the HF: The elevated JVP had a diagnostic value for detection of LV systolic dysfunction [odds ratio (OR) = 15.1].[8] In patients with chronic HF with reduced ejection fraction (HFrEF), the RAP and PCWP are "concordant" in 70–75% of patients with HFrEF.[6,9] and even in HF with preserved ejection fraction (HFpEF).[10] One study suggested a similar concordance rate in patients with HFpEF.[10] In patients with discordance of the RAP and PCWP, assessment of the LV filling pressures hence estimate of the JVP will be inaccurate. Data from a post-hoc analysis of SOLVD (the Studies of Left Ventricular Dysfunction) trial, asymptomatic or mildly symptomatic LV systolic dysfunction, presence of elevated JVP, and presence of a third heart sound were independent predictors of an increased risk of progression to symptomatic HF.[11] In another subgroup analysis from the SOLVD trial, elevated JVP was associated with an increased risk of hospitalization for HF, death or hospitalization for HF, and death from pump failure.

Jugular Venous Pulse Waveforms[1]

Table 1 shows jugular venous pulse waveforms.

TABLE 1: Jugular venous pulse waveforms along with heart sound and ECG.

Wave form	Heart sound	ECG
"a"	S4	Follows "P"
"c"	S1 precedes	Follows "R"
"x"	–	
"v"	S2	
"y"	S3 follows	Precedes "T"

- *Abnormalities of "a" waves in JVP*: "a" wave coincides with atrial contraction hence, it is—
  - *Absent*: atrial fibrillation, rarely sinus tachycardia
  - *Giant "a"*: (*Causes from RV inflow to outflow*) RA myxoma, tricuspid stenosis (TS), tricuspid atresia, pulmonary hypertension, pulmonary stenosis, RV failure—pulmonary embolism, RV cardiomyopathy, right ventricular myocardial infarction (RVMI), severe AS, and hypertrophic cardiomyopathy (HCM) (Bernheim effect)
  - *Cannon "a"*
    - Regular
      - Junctional
      - Isolated atrioventricular (AV) dissociation
    - Irregular
      - Ventricular tachycardia (VT)
      - Complete heart block
      - VVI pacemaker
      - Ventricular premature contractions (VPCs)
- Prominent *"x"* descent occurs in cardiac tamponade, constrictive pericarditis and atrial septal defect (ASD).
- Prominent *"y"* descent occurs in constrictive pericarditis, RVMI, tricuspid regurgitation (TR), ASD with mitral regurgitation (MR)
- Absent "*x*" descent is caused by TR (CV fusion: S wave)
- Absent "*y*" descent is caused by TS, RA myxoma, and cardiac tamponade.
- A positive "*x*" wave (i.e., ascent rather than the descent as would occur in TR or RVMI) is described by some as an "S" wave. "S" wave with a prominent "v" wave is known as a giant "v" wave.
- *"W"-shaped complexion of JVP encountered*: In constrictive pericarditis.
- *h wave*: When the diastole is long as in slow heart rates, ascending limb of the "y" wave is often followed by a small brief positive wave known as the *h* wave, which occurs prior to the next *a* wave during the period of diastasis. It was described by Hirschfelder in 1907 (*h* from Hirschfelder).
  - *Prominent h wave*: Restrictive cardiomyopathy, constrictive pericarditis and RV infarction. "h" wave represents diastasis in the cardiac cycle.
- Normally *"a"* > *"v"* and *"x"* > *"y"*. *"x"* and *"y"* increase with inspiration and "a" decreases with expiration.
- *Rapid "y" descent*: Constrictive pericarditis, TR, and congestive cardiac failure (CCF).
- *Lancisi's sign*: Large venous wave, or giant "*v*" wave, is visible in the jugular vein in patients with TR with obliteration of "x" descent which is evident as ventricularization of JVP.
  - *The pulsatile JVP can be seen in*:[1]
    - Tricuspid stenosis and/or TR
    - Right ventricle failure
    - Hyperdynamic circulation
    - Chronic obstructive pulmonary disease (COPD)
  - *The causes of nonpulsatile raised JVP are*:
    - Superior vena cava (SVC) obstruction: Usually associated with bilateral with prominent distended veins in the upper extremities and in the upper torso.
    - Cardiac tamponade

Effect of Respiration on Jugular Venous Pulse Waveform

- Inspiration results in increased visibility of venous pulse. "a", "x", and "y" become prominent during inspiration as inspiration increases venous return to the right heart causing vigorous contraction of RA and RV. During expiration, the "v" wave may become prominent.
  - *Kussmaul's sign*: *Inspiratory* increase in the mean level of JVP (instead of the usual decrease) in patients with constrictive pericarditis, RV infarction or rarely in cardiac tamponade (effusive-constrictive) is known as Kussmaul's sign due to reduced capacity of right atria and/or ventricles to accommodate increased venous return with inspiration.
    Other causes are: RVMI, RV dysfunction, pulmonary embolism, SVC obstruction, right heart obstructive tumors, severe TR, rarely in tamponade and TS.
  - *Friedrich's sign*: The exaggerated drop in diastolic CVP seen in constrictive pericarditis (particularly with a stiff calcified pericardium) and manifested as rapid "y" decent (also "x" sometimes) in constrictive pericarditis is known as *Friedrich's sign*.

Abdominal-jugular Reflux[1]

Abdominal-jugular reflux (AJR) is said to be present if firm pressure over the abdomen (periumbilical region and not essentially right hypochondrium over *10–30 seconds*, normally JVP rises <3 cm and lasts transiently, while in LV or RV failure and/or tricuspid *regurgitation* it remains elevated for *>15 seconds*. It can be positive in RV systolic or diastolic dysfunction, tricuspid disease, constrictive pericarditis or elevated CVP. A positive AJR is associated with the PCW > 15 mm Hg in patients with dilated cardiomyopathy (DCM).[12]

- *False-positive AJR may be manifested in*:
  - Severe COPD
  - Fluid overload
  - Increased sympathetic activity due to any cause like IV catecholamine, MI, etc.

Recent Advances

Jugular venous pulse measurement has been attempted to be measured by:

- Infrared beam
- Accelerometer for detecting venous level based on flow-related acceleration
- Ultrasound beam by assessing echocardiographically inferior vena cava (IVC) diameter and respiratory collapsibility

$$\text{Caval index} = (\text{IVC exp. diameter} - \text{IVC insp. diameter})/(\text{IVC exp. diameter}) \times 100$$

- Collapse <50% suggests volume overload.
- Caval index >50% suggests fluid responsiveness.

Correlation between Right Atrial Pressure Central Venous Pressure and Inferior Vena Cava Appearance

- *Central venous pressure 0–5 cm*: Inferior vena cava totally collapses on inspiration and is <1.5 cm in diameter.
- *Central venous pressure 5–10 cm*: Inferior vena cava collapses >50% on inspiration and is 1.5–2.5 cm in diameter.
- *Central venous pressure 11–15 cm*: Inferior vena cava collapses <50% on inspiration and is 1.5–2.5 cm in diameter.
- *Central venous pressure 16–20 cm*: Inferior vena cava collapses <50% on inspiration and is >2.5 cm in diameter.
- *Central venous pressure >20 cm*: No change in IVC on inspiration and is >2.5 cm in diameter.

EVALUATION OF ARTERIAL PULSE

This method is called trisection of the pulse.[1]

- *The ring finger* prevents transmitted pulsation in the radial artery through the palmar arch.
- *The middle finger* perceives the lift imparted by the pulse and estimates the pulse volume and tension (diastolic pressure).
- *The index finger* evaluates the force required to obliterate the pulse (systolic pressure) so that it is not felt by the middle finger. It also correlates with stroke volume.

The pulse is evaluated for:

- *Rate*: Normal/tachycardia (>100 bpm)/bradycardia (<60 bpm)
- *Rhythm*: Regular/irregular (regularly or irregularly)
- Force
- Volume
- Tension
- *Condition of arterial wall*: Arteriosclerosis
- Bilateral symmetry
- *Pulse*: Apex deficit (If >10 bpm suggests—atrial fibrillation)
- Radiofemoral/Brachiofemoral delay
- Pulse character

Causes of Increased Force, Volume, and Tension

- *Hypertension*
- Causes of *high output states* cause increased force and volume but low tension. (Remembered with acronym *ABCDE*)[1]
  - *A*nemia
  - *A*V fistula—congenital or acquired as in hemodialysis patients.
  - *A*ortic regurgitation (AR)
  - *B*eriberi
  - *C*or-pulmonale
  - *C*irrhosis
  - P*D*A (*D*uctus)
  - *E*pidemic dropsy
  - Thyrotoxicosis

Causes of Decreased Force, Volume, and Tension[1]

Hypotension can be due to:

- Stenotic lesions—like mitral stenosis, aortic stenosis (AS), and other left ventricular outflow tract (LVOT) obstructions like hypertrophic obstructive cardiomyopathy (HOCM).
- Congestive cardiac failure
- Cardiomyopathies
- Cardiac tamponade

- Constrictive pericarditis
- Acute myocarditis

Various Characteristic Types of Pulse Character[1]

- *Anacrotic pulse*: Aortic stenosis
- *Bisferiens pulse*: Moderate AS with severe AR and HOCM
- *Corrigan pulse (pulsus celer and pulsus magnus—water hammer)*: Conditions of rapid distal run-off such as AR, PDA, anemia, thyrotoxicosis, etc.
- *Dicrotic pulse*: Fevers such as enteric fever, shock-like state as in CCF, and cardiac tamponade.
- *Pulsus parvus et tardus*: Severe AS
- *Pulsus alternans*: Dilated cardiomyopathy, AS with LV dysfunction, and CCF
- *Pulsus paradoxus*: Pericardial effusion and COPD (pseudoparadoxus)
- *Pulsus celer*: Aortic regurgitation
- *Pulsus tardus*: Aortic stenosis
- *Pulsus celer*: Increased rate of rise
- *Pulsus tardus*: Decreased rate of rise
- *Pulsus magnus*: Increased volume of the pulse
- *Pulsus parvus*: Decreased volume of the pulse
- *Pulsus durus*: Increased tension of pulse
- *Pulsus mollis*: Decreased tension of pulse
    - *Bilateral radial/brachial comparison* may be asymmetrical in thoracic outlet syndrome, anomalous course or embolic occlusion.
    - *Radiofemoral/brachiofemoral comparison* (brachiofemoral is preferred in adults as any delay here is better perceived than radiofemoral delay)—Coarctation of aorta.
    - *Apex and pulse rate comparison*: More than 10 bpm is suggestive of atrial fibrillation while <10 can occur with premature beats.

"Paradox" in pulsus paradoxus: It was first described by Kussmaul who reported the "paradox" of audible heart sounds with the disappearance of the pulse when the patient was breathing. It occurs due to an inspiratory increase in RV volume, which causes septal bulge to the left and hence decreased LV stroke volume and hence a fall in BP.[1] It is seen in cardiac tamponade, hypovolemic shock and COPD. Rarely, it is seen in constrictive pericarditis and restrictive cardiomyopathy. When the LV can fill through alternate means despite tamponade as in *ASD, VSD,* and *AR* (aortic dissection can cause both AR and tamponade) or raise LVEDP as in LV systolic dysfunction.

The mechanism of radiofemoral delay in coarctation of the aorta: Percussion wave in femoral arteries is the blunted and only tidal wave is palpable, which is compared to percussion wave of radial/brachial. This gives a sense of exaggerated delay. This, rather than mechanical interference in the transmission of the pulse by the coarctation segment, is responsible for the delay.

- *Pulsus alternans (mechanical alternans)* occurs with alternate beats due to changing systolic pressure is appreciated by applying light pressure on the peripheral AP and measuring the BP. On slowly lowering the cuff pressure, Korotkoff sounds are heard only during the alternate strong beats; the softer sounds of the weak beat will also appear on further lowering the pressure.
- *Causes of pulsus alternans*: The most important cause of pulsus alternans is left ventricular failure. Pulsus alternans almost exclusively occurs in HFrEF but it can occur rarely in HFpEF.
    - *Left ventricular pulsus alternans* without systemic arterial pulsus alternans has been observed in HOCM[13] which abolishes after successful myomectomy.
    - Rarely in cardiac tamponade
    - In the presence of marked tachypnea

The twice-beating pulses:

- Pulsus bisferiens
- Anacrotic pulse (both twice in systole), and
- Dicrotic pulse (Once each in systole and diastole)

PULSUS BISFERIENS

Pulsus bisferiens is characterized by two systolic peaks of the aortic pulse during left ventricular ejection separated by a mid-systolic dip.

Causes of Pulsus Bisferiens[14]

- In patients with mixed AS with AR, a bisferiens pulse occurs when AR is the predominant lesion.
- In most patients with HOCM, pulsus bisferiens is rarely palpable but often recorded. The rapid upstroke and prominent percussion wave result from rapid left ventricular ejection into the aorta during early systole. This is followed by a rapid decline as left ventricular outflow tract obstruction ensues, a result of mid-systolic obstruction and partial closure of the aortic valve. The second peak is related to the tidal wave. Sometimes, a bisferiens pulse can be brought out by the Valsalva maneuver or by inhalation of amyl nitrite.
- Pulsus bisferiens is occasionally felt in patients with a PDA or arteriovenous fistula.
- It is rarely noted in patients with significant mitral valve prolapse, and
- Very rarely in hyperdynamic circulatory state.[14]

Dicrotic pulse: Caused by the accentuated diastolic dicrotic wave in patients with decreased systemic arterial pressure and vascular resistance (e.g., fever). It can be present in patients with severe HF, hypovolemic shock, cardiac tamponade, conditions associated with a decreased stroke volume and elevated systemic vascular resistance, and during the immediate postoperative period following aortic valve replacement.[15]

BLOOD PRESSURE

The optimal length of the cuff is 35 cm for an average adult arm cuff.[16]

- The standard upper limb cuff is 5' × 10' inches, i.e., 12 cm × 24 cm size.
- The standard lower limb cuff is 18 × 36 cm in size.

The width should be 40% of arm circumference and the length should be 80% of arm circumference.

- *Correction factor = 32 – (1.05 × arm circumference).* This value is subtracted from the systolic BP in obese patients while this is added in thin patients.[17]

The auscultatory gap: The appearance of silence between Korotkoff phase 1 sound and phase 2 sound can result in an auscultatory gap. This occurs if the examiner fails to inflate the cuff above the systolic pressure determined by the palpatory method. Such an error results in falsely low systolic BP being recorded.

This can be overcome by:

- Always measuring BP by palpatory method before the auscultatory method.
- Inflating the cuff 30 mm Hg above the systolic BP measured by the palpatory method.
- Asking the patient to close and open the fist alternatively for few times and by raising the arm for a few minutes.

Other uses of the sphygmomanometer (BP instrument) apart from measuring BP are:[1]

- Augment the murmur of *aortic* regurgitation
- Demonstration of *pulsus alternans and pulsus paradoxus* (as above)
- Attain *hemostasis* (as a tourniquet) in an emergency.
- To give *IV fluids* or flush the lines (as in catheter laboratory) by wrapping the cuff around a plastic bottle.
- Demonstration of *Trousseau's sign* (carpopedal spasm)
- *Pulmonary function test*: By asking the patient to blow in the mercury column in a syringe attached to the tube and maintaining it at 40 mm Hg. (Duration >20 seconds suggests good lung function.)
- *Hess's tourniquet test (test for capillary fragility)*: Looking for petechiae after keeping the cuff inflated at 40 mm Hg.
- *Modified bleeding time*: By inflating the cuff at 40 mm Hg and noting the time taken for the bleeding to stop after a small incision is made on the forearm.
- In making the veins prominent during venesection.
- *Hill's sign* to assess the severity of AR.
- As an extension of the tourniquet principle in the management of HF/refractory angina in enhanced external counter-pulsation (EECP).
- To assess endothelial function by using ankle-brachial pressure index (ABPI) as a surrogate marker by using vascular Doppler.
- To elicit the Valsalva maneuver—the patient blows into a sphygmomanometer to raise the mercury to 40 mm Hg for 10 seconds.[18]

The various technologies being used for BP measurements are:

- Palpatory method
- Auscultatory method
- *Oscillometric method*: Newer nonmercury based instruments carry transducers that pick up the oscillations of the pulse and thus measure the pressure. They are often called noninvasive blood pressure (*NIBP*).
- *Continuous noninvasive techniques (CNAP)*: Combines the advantage of noninvasive and continuous monitoring.
- *Nonocclusive technique*: It is based on the pulse wave velocity principle which is based on the principle that the velocity of the pulse is determined by the pressure and hence just by assessing the velocity BP can be estimated without occlusive technique.

The indications for ambulatory BP monitoring (ABPM) are:

- Whitecoat hypertension
- Masked hypertension
- Drug-resistant hypertension
- Orthostatic symptoms with hypertension
- Episodic hypertension
- Autonomic imbalance (Dysautonomia)
- Chronic renal failure (CRF)
- Pregnancy
- To detect *non-dippers* (normally BP falls during night time. In patients where it does not do so, are called non-dippers. The prognosis in these patients is worse than dippers).

Pseudohypertension: Compression of the brachial artery may require a cuff pressure greater than systolic in patients with stiff vessels due to marked arterial calcification. This phenomenon, called pseudohypertension, is characterized by systolic and diastolic pressures estimated from the sphygmomanometer that are 10 mm Hg or more above the directly measured intra-arterial or oscillometric pressure.[19]

Osler's maneuver for the condition of arterial wall evaluation: It is used to identify arteriosclerosis and identify pseudohypertension. Palpability of the arterial wall despite the elevation of the mercury column above the "systolic pressure" is suggestive of calcification of the arterial wall (Monckeberg's degeneration).

Wrist blood pressure: By keeping the wrist at the level of heart, the hydrostatic pressure related higher false pressure to the lower position of the wrist relative to the heart can be nullified. Also, the wrist flexion may interfere with appropriate sensor positioning.

Automated Oscillometric Blood Pressure Measurement

- Patients do not necessarily need to rest for 5 minutes prior to having automated oscillometric blood pressure (AOBP) measured.[20] Several studies have shown that systolic pressure may be as much as 7 mm Hg lower with AOBP following an enforced rest period compared with daytime average ambulatory BP.[20,21]
- Automated oscillometric blood pressure does not need to be performed more than one time during an office visit. The fact that these devices can be programmed to automatically obtain and average three or more readings satisfy the criteria for multiple consecutive measurements.

CONCLUSION

Cardiovascular evaluation can be fairly assessed using proper assessment of JVP, pulse, and BP. The novel devices with technological evolution can lead to more precise assessment and correlation of central cardiovascular health status.

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CHAPTER 2

ECG and X-ray in Congenital Heart Disease

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ABSTRACT

Along with expert clinical examination additional tools like ECG and X-ray may be sometimes required to make a diagnosis in congenital heart disease. There may be a significant impact of availability of ECG and X-ray on examiner's diagnostic accuracy for innocent murmur, ventricular septal defect (VSD), pulmonary stenosis (PS), aortic valve disease, atrial septal defect (ASD), and patent ductus arteriosus. For example, ECG may enhance the detection of ASD and may help detect PS. X-ray enhances detection of intermediate to large VSD. X-ray and ECG are tools without demonstrable independent advantage for defect-specific diagnosis, but they help in the diagnosis and management of complications and other associated conditions as well as prognostication and also to determine the stage of the natural history of the disease. Routine use of one or both of these tests in the initial evaluation of congenital heart disease (CHD) should be individualized rather than universal.

INTRODUCTION

Congenital heart diseases (CHDs) have spectrum of clinical presentation. Along with echocardiography, X-ray chest and ECG are important investigations which help in management of congenital heart disease. Though not much of diagnostic utility, X-ray and ECG definitely help in diagnosis and management of complications as well as prognostication and stage of natural history of disease. Syndromic approach and correlation with pathophysiology, hemodynamic may help to understand various changes in X-ray and ECG.

ECG IN CONGENITAL HEART DISEASES

Improvement in diagnosis and management of CHD have brought sea of change in longevity of life. In country of size of India, we as treating physician have to take care of children as well as adults with CHD and not infrequently postcorrective or palliative surgery also. Electrocardiogram is a useful tool for diagnosis of complication and prognostication of operated as well as unoperated patients. It is an important investigation to understand the natural history of disease and formulate management plan.

This discussion tries to cover ECG changes in CHD: (1) specific to individual lesion, (2) changes in with age, (3) development of complications, (4) postintervention, and (5) pulmonary hypertension. Some CHDs are clubbed together as they can have similar findings.

P-wave Morphology, Situs, and Heterotaxy

P wave: Cardiac impulse originates in sinoatrial node and leads to atrial activation. P wave is result of atrial depolarization. Normal P wave axis is 15° and 75°. Normal P wave in lead II in pediatric population is approximately 1.5 mm and 2.5 mm for 50th and 98th percentile respectively. In situs solitus irrespective levocardia or dextrocardia, P wave is positive in I and aVL and negative in aVR because atrial depolarization originates from normally positioned right sinus node. Similarly, irrespective of cardiac axis, situs inversus will have inverted P wave in aVL and I, and positive in aVR, III and axis being 105–165° **(Fig. 1)** (with regular lead placement in situs inversus dextrocardia, frontal plane axis shows extreme right-axis deviation and left-sided chest leads have negative concordance). Left atrial ectopic rhythm produces negative P wave in lead I and V_1, and does not distinguish between situs solitus with left atrial ectopic rhythm from situs inversus. Presence of dome and dart P wave in V_1 and V_2 confirms ectopic left atrial focus irrespective of atrial situs.[1-5]

Isomerism: Right isomerism—as sinoatrial (SA) node is right-sided structure, there are two SA nodes at junction of superior vena cava (SVC) and right atrium (RA). If right one is dominant

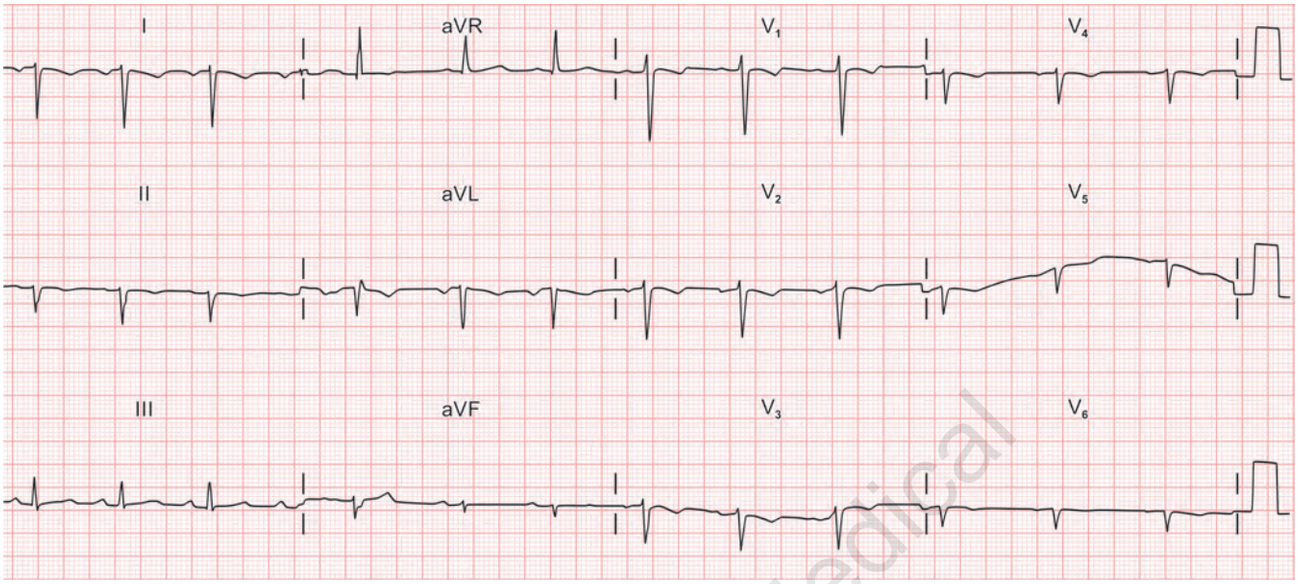

FIG. 1: ECG of situs inversus with standard lead placement. Note inverted P in I, aVL, extreme right-axis deviation.

and it produces left and downward axis of P wave. If left SA node is dominant, axis is to RT and inferior. There are two atrioventricular nodes and it can produce supraventricular tachycardia via re-entry.

Left isomerism: The SA node fails to develop normally in left isomerism, as there is venocaval connection to LA not RA. Hence, it can be absent or hypoplastic or ectopic in atrial wall or ostium of coronary sinus. It can lead to bradycardia or atrial arrhythmia like flutter or fibrillation. There are high chances of complete AV block at level of penetrating bundle producing a narrow QRS complex escape rhythm.[1-5]

ECG Changes in Individual Lesion

Atrial Septal Defect: Ostium Secundum and Sinus Venosus Type

The ECG in childhood generally has sinus rhythm and chances of atrial fibrillation and flutter generally increases with advancing age. Peaked P wave in lead II suggests right atrial enlargement **(Fig. 2)**. The PR interval prolongation is secondary to right atrial enlargement and increase in HV interval. First-degree heart block and even complete heart block are also known in a few syndromes of atrial septal defects (ASDs). With advance in age and right atrial dilatation, it leads to atrial arrhythmia like flutter or fibrillation.[1-9]

P-wave axis in sinus venosus ASD can be leftward with positive P in aVL and I and Negative P wave in II, III, and aVF. Atrial pacemaker is negative because the defect occupies site of SA node and shift of pacemaker to ectopic atrial rhythm.

When left to right shunt is significant, there is right ventricular conduction delay and right ventricular hypertrophy (RVH) [(a) rsR' in V_1, (b) RVH: qR and upright T in right precordial leads, S in V_6 > 95th percentile, abnormal R/S ratio in V_1 and V_6]. Presence of "a", "b", or both have 87% sensitivity and 96% specificity for diagnosis of ASD. Presence of crochetage pattern (notch near apex of R wave in inferior leads) has 32% sensitivity but 86% specificity. Normal ECG can be found in 18% and normal ECG and physical examination in 7%. QRS duration is at upper limit of normal and increases with age culminating into complete right bundle branch block (RBBB). Right-axis deviations with qR in V_1 are indicators of pulmonary hypertension and left-axis deviations (LADs) indicate development of left anterior hemiblock with age (for ostium secundum ASD).

ECG Changes after Closure of Atrial Septal Defect

Postdevice closure AV block is a known but rare complication. Occasionally atrial arrhythmia as flutter or fibrillation is also known in adult population. Immediately after ASD, there is decrease in heart rate and P-wave amplitude. Over intermediate and long-term follow-up of adults, there is decrease in PR interval, QRS duration, QSR-T axis, and QTc interval. Shortening of PR interval is observed immediately in children while other changes are similar to adults. Above-mentioned changes are seen following both, postsurgical and postdevice closure. On very long-term follow-up, patient undergoing surgical closure may be at higher risk of atrial arrhythmia due to scar than those opting for device closure. Risk of atrial arrhythmia in adult who undergoes surgical closure ASD after 40 years of age remains unaltered and is same as those not operated at 7 years follow-up. Similar data is not available for device closure. Those who are in atrial fibrillation before surgery, continue to remain in atrial fibrillation after ASD closure. Risk of sinus node dysfunction is high after sinus venosus ASD using older surgical technique. Possible reason includes damage to SA nodal artery and direct injury.

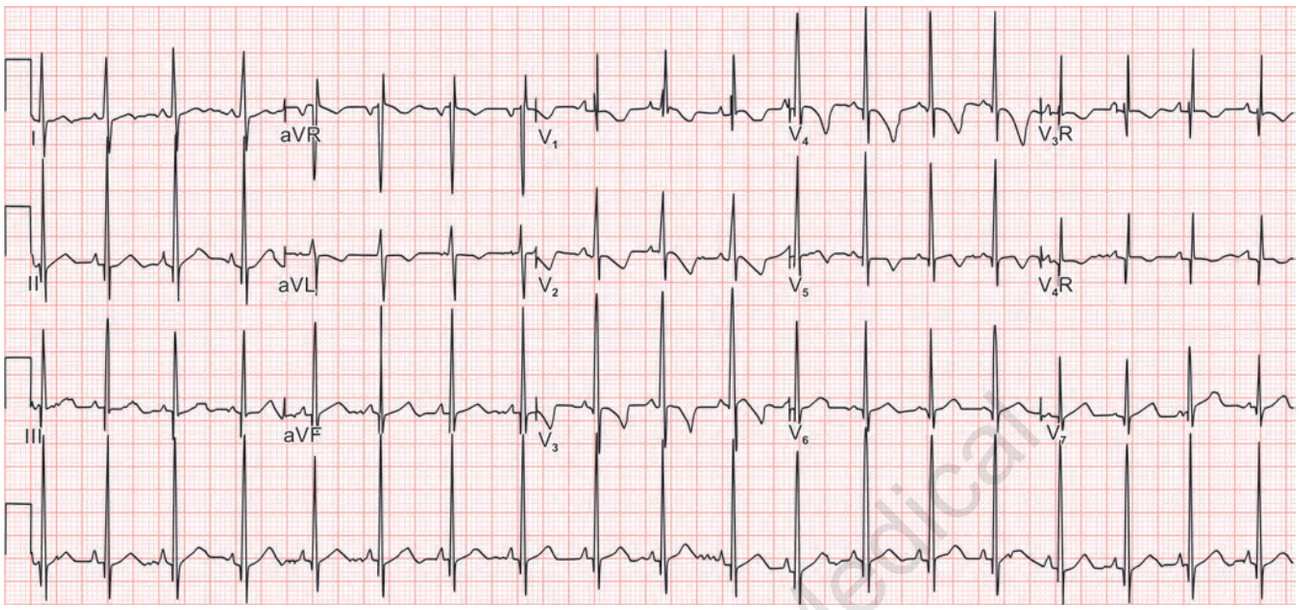

FIG. 2: ECG in ostium secundum (OS) atrial septal defect (ASD): Right-axis deviation, incomplete right bundle branch block (RBBB), notched QRS in inferior leads.

Ventricular Septal Defect

Small ventricular septal defects (VSDs) with normal pulmonary pressure generally have normal ECG for the age. Occasionally RSR' pattern can be seen in lead V_1.

Moderate-to-large VSDs are characterized by **(Fig. 3)**:

- *Left-atrial enlargement*: Broad notched P wave in I, II, aVr, and V_6. Deep broad negative P in V_1.
- There is biatrial enlargement in lead II, V_{1-2} particularly in very large VSDs.
- *Left ventricular hypertrophy and volume overload*: (a) Tall R and tall peaked T in II, III, aVF; (b) Prominent Q, tall R and T in V_{5-6}.
- *Increase in RV pressure*: rsR' in V_1 and V_4R. Increase in R' amplitude correlates with RV pressure. QRS axis may be normal unless there is RV hypertension.
- *Biventricular hypertrophy*: Equiphasic QRS complexes in mid-precordial leads (Katz–Wachtel phenomenon).[1-6]

Left-axis deviations in case of VSD generally indicate atrioventricular septal type defect or inlet position of defect. Multiple mid-muscular VSDs can occasionally have LAD but exact mechanism of same is not known.

Development of RVH with right-axis deviation in ECG indicates following:

1. Development of RV outflow obstruction/double chamber RV.
2. Severe pulmonary hypertension.

Eisenmenger syndrome ***(Fig. 4)***: P wave may be normal. Unique features of RV hypertension include: (1) Moderate right-axis deviation, (2) Prominent monophasic R in V_1 (with occasional notched upstroke) with small S, T inversion, and dominant S in left precordial leads with absence of LV forces.

Acquired RVOT obstruction: RV systolic pressure remains constant but pulmonary blood flow and LV volume decreases. Tall R in V_1 remains unchanged but QR in V_{5-6} becomes less prominent.[1-6]

Double-chambered right ventricle: RV hypertrophy is confined to RV inlet. There is normal progression of QRS in V_{1-6}. Upright T in V_3R may be only sigh of RVH.

Postsurgical Changes in ECG

There are chances of RBBB and left anterior hemiblock. Complete heart block can be seen in <1%. It is more common following perimembranous and inlet VSD closure but very rare after apical muscular or outlet VSDs. Risk of complete heart block following device closure is around 2–10%.

In adult population: Nonsustained or sustained ventricular tachycardia occurs in 5.7% of patients, particularly with higher pulmonary artery pressures. Sudden cardiac death (SCD) is uncommon but is described in patients with cardiac hypertrophy and progressive fibrosis of the conduction system. After surgical repair, late sudden death occurs in about 4% of patients. Risk factors for death include age of 5 years at time of surgery, pulmonary vascular resistance 7 Woods units, and complete heart block.

Patent Arterial Duct and Aortopulmonary Window

Small patent arterial duct/patent ductus arteriosus (PDA) without any complication may have normal ECG. Moderate-to-large PDA will have left atrial and ventricular enlargement and ECG changes are similar to those described in ECG of moderate-to-large VSD. Changes following development of Eisenmenger syndrome are also similar to VSD.

Aortopulmonary window is usually associated with large left-to-right shunt similar to large PDA and ECG may show biventricular hypertrophy. Development of irreversible

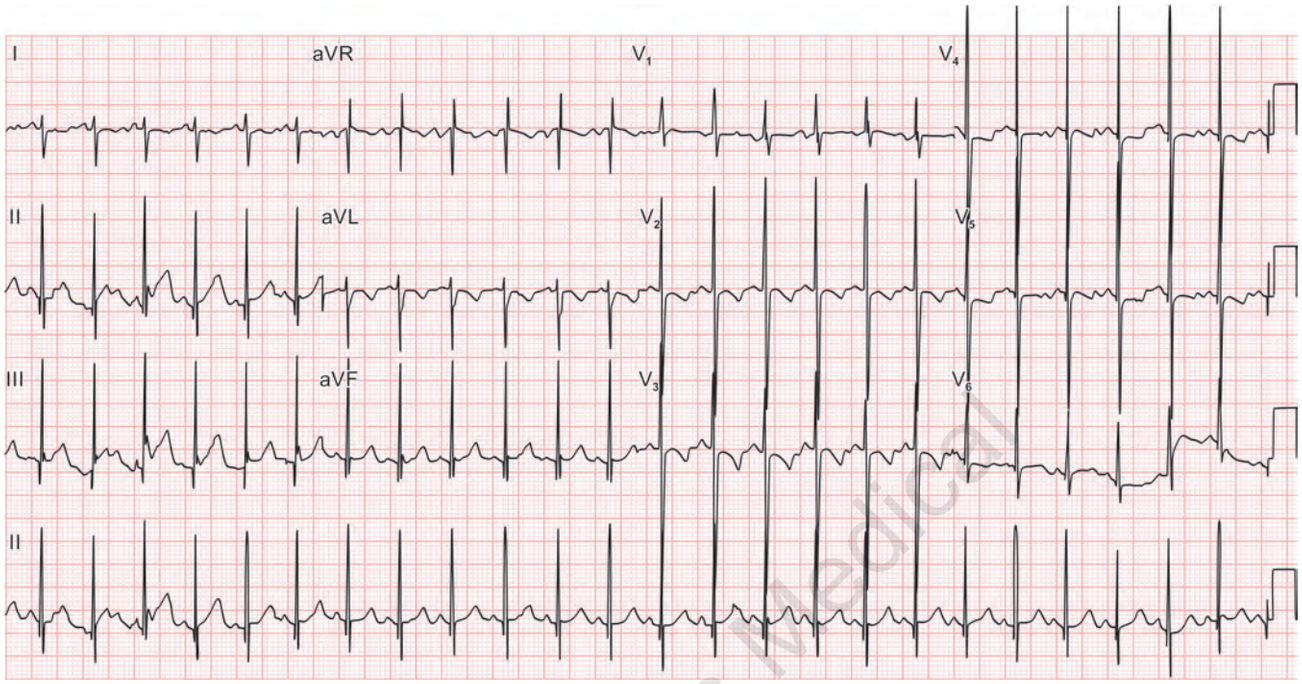

FIG. 3: Large post-tricuspid left-to-right shunt: Equiphasic QRS in mid-precordial leads. Q in $V_{5–6}$.

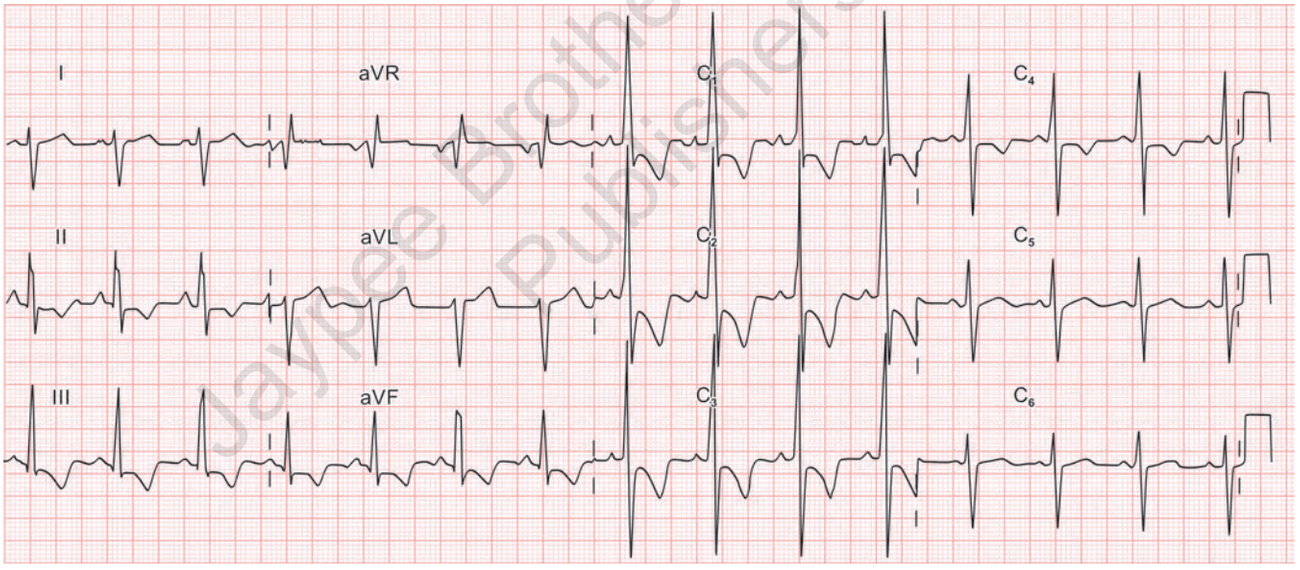

FIG. 4: Severe pulmonary hypertension in Eisenmenger complex: Right-axis deviation and dominant RV forces.

pulmonary hypertension is very fast in APW and may have RV forces as mentioned in Eisenmenger syndrome of VSD early in life.

Atrioventricular Septal Defect (Fig. 5)

P-wave axis and morphology is generally normal unless associated with visceral heterotaxia. PR interval is prolonged for the age which is due to delayed interatrial and AV nodal conduction. PR prolongation is seen in 90% cases of common AV valve orifice and 75% cases of two AV valve orifices. P wave may have right, left, or biatrial enlargement in more than half of patients.

Most distinctive feature of this anomaly is position of AV node. It is positioned inferior and posterior to coronary sinus opening. AV conduction axis penetrates only at crux and penetrating bundle is displaced posteriorly and lying along posteroinferior margin of ventricular component of defect. This leads to counterclockwise loop (Q in 1/aVL) along with extreme LAD of QRS axis (–30° to –120°). Isolated primum atrial septal defect (ASD) can have rsR' pattern in V_1 **(Fig. 5)**. Severe mitral regurgitation (MR) from cleft mitral valve may lead to dominant

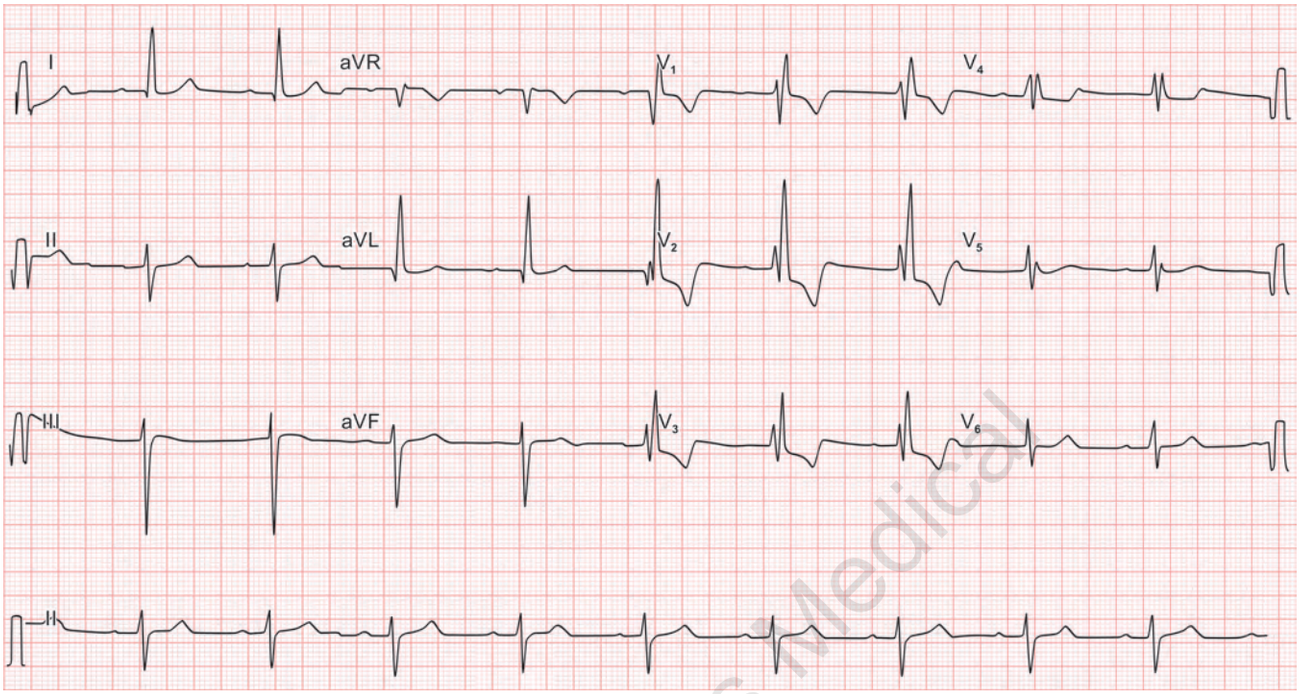

FIG. 5: Counterclockwise loop with Q in 1, aVL, incomplete right bundle branch block (RBBB), left-axis deviation.

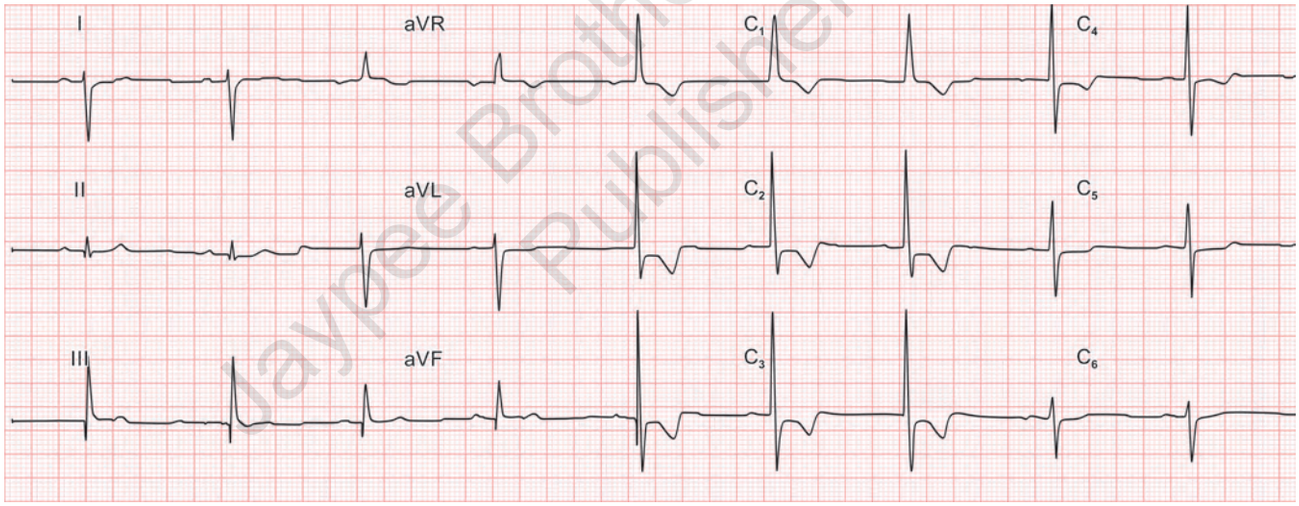

FIG. 6: Dominant right ventricular (RV) forces (R in V_1 with strain), right-axis deviation.

left ventricular forces (Q in left precordial leads and dominant R in V_{5-6}). Postoperative risk of complete AV block is 1–7%. Risk of atrial arrhythmia is also high.[1-6]

Pulmonary Stenosis (Fig. 6)

Mild pulmonary stenosis (PS) may have a normal ECG or mild right-axis deviation. In moderate stenosis, height of R in V_1 is greater than normal. RSR' pattern can also be seen occasionally. Severe PS has following findings: (1) monophasic R in V_1, which can be >20 mm (RV hypertrophy), (2) *RA enlargement*: Peak, tall P wave in II, V_1, and (3) QR in V_1 can be seen in a few cases. In pediatric age group, there is good correlation between height of R in V_1 and RV systolic pressure. (R in V_1 * 5 = RV systolic pressure). Presence of LV in setting of severe PS suggests Noonan syndrome and LVH is secondary to hypertrophic cardiomyopathy.[1-6]

Aortic Stenosis (Fig. 7)

There is poor correlation between severity of aortic stenosis and ECG changes. Except for pediatric population, a severe aortic stenosis can have a normal ECG. Anomalies in ECG may include: (1) Tall R in V_5, deep S1 in V_1, (2) ST-segment depression and T-inversion in lateral precordial leads. P-wave dispersion is high suggesting high risk of atrial fibrillation. High

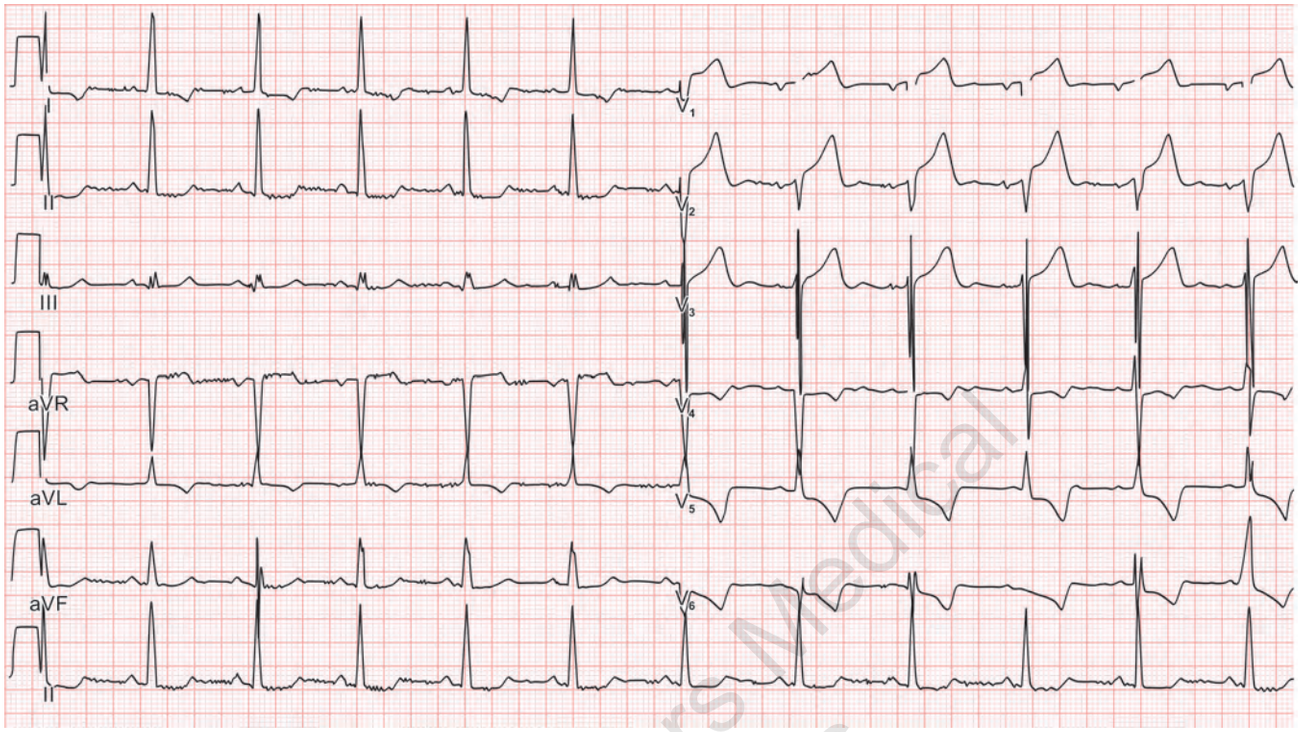

FIG. 7: Severe AS—left ventricular hypertrophy (S in V_1 + R in $V_{5/6}$) with strain (T-inversion in $V_{5–6}$).

QT-dispersion is a predictor of SCD. Following relief of aortic stenosis by balloon dilatation of valve replacement, there is decrease in QT dispersion.[1-6]

Coarctation of aorta: There are two ways of presentation.

1. *Infantile*: RVH with right-axis deviation secondary to pulmonary hypertension and RV volume overload (PFO with left-to-right shunt). RVH does not persist beyond infancy.
2. *Adult*: LVH is characterized by tall R, inverted T in $V_{5–6}$. Significant ST-segment depression in lateral leads suggests accompanying severe aortic stenosis in bicuspid aortic valve, while Q in suggests aortic regurgitation and LV volume overload.[1-6]

Coronary Anomalies

- Anomalous origin of left coronary artery from pulmonary artery (ALCAPA) **(Fig. 8)** results into ischemia and infarction of anterolateral LV wall. It manifests as deep Q in I, aVL, and lateral precordial leads ($V_{4–6}$) along with abnormal R wave progression in $V_{4–6}$. Distinguishing features from cardiomyopathy are: (1) Q > 30 ms in I, (2) Q > 3 mm in aVL, and (3) QR pattern in aVL.
- Anomalous origin of left main coronary artery (LMCA) right sinus of Valsalva or RCA from left sinus of Valsalva: These anomalies are associated with SCD on physical exertion but resting ECG is normal.[1-6]

Left transposition of great vessel (Congenitally corrected transposition of great arteries) (AV discordance or ventricular inversion).

In situs solitus, P wave axis normal. Normal (left to right) septal activation is reversed and it is activated from right to left, there is inversion of bundle branches and lie of septum is more vertical. This manifests as Q wave in right precordial leads. In presence of dextrocardia, Q wave in right precordium may not be appreciated. Septum is activated in superior direction, which manifests as Q in III, aVF, and LAD. Positive T waves in all precordial leads are seen in 80% patients and it is due to side by side nature of inverted ventricles **(Fig. 9)**.[1-6]

There are high chances of complete AV block (10–25% at initial presentation) as well as similar incidence of first and second degree AV block. Incidences of new AV block are 2% per year. Chances of AV block are directly proportional to size of pulmonary valve annulus and they are maximum with nonobstructive pulmonary blood flow and least with critical PS or atresia.

Accessory AV pathway may be present and may have pre-excitation or concealed conduction.

D Transposition of Great Arteries (Fig. 10)

ECG of newborn is generally normal for age. At end of first week, unoperated patients show absence of expected RV regression **(Fig. 10)**. Biventricular hypertrophy indicates presence of additional with large VSD. LAD is rare with transposition of great arteries (TGA) intact interventricular septum (IVS) but seen in presence of atrioventricular septal defect (AVSD) or right ventricular hypoplasia.[1-6]

After atrial switch: Following changes are observed on long-term follow-up.

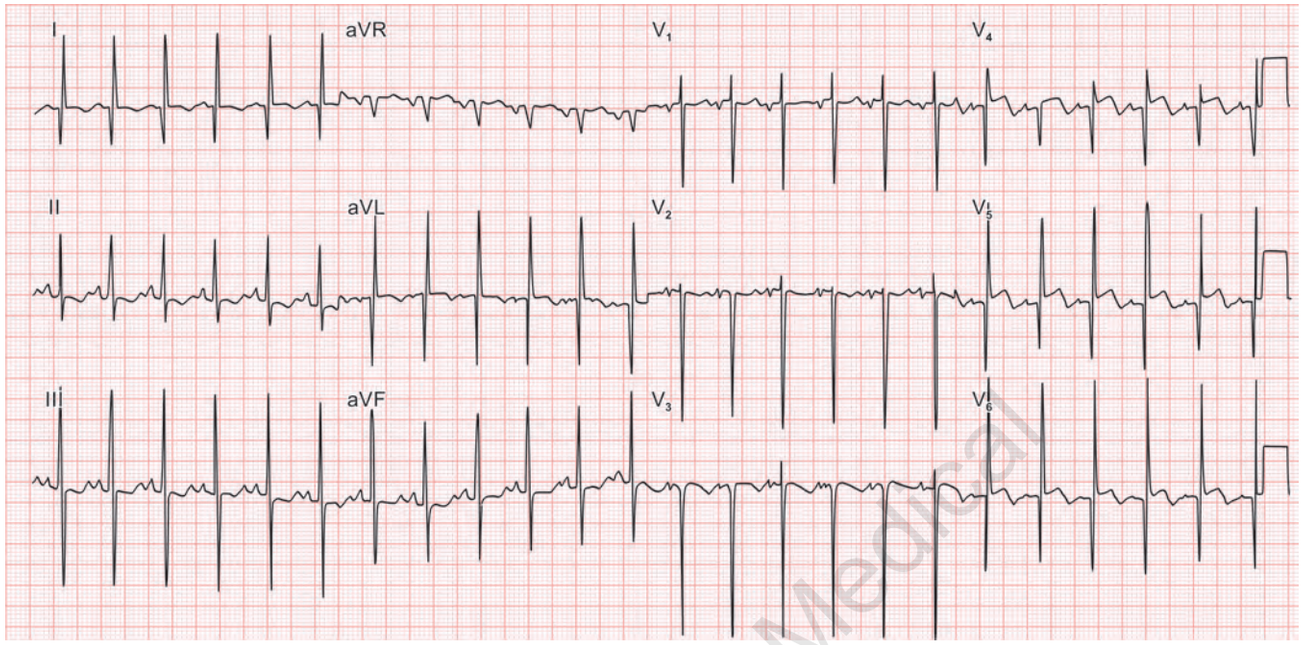

FIG. 8: Anomalous origin of left coronary artery from pulmonary artery (ALCAPA): Deep Q in I, L, $V_{4–6}$, poor R wave progression, ST elevation in $V_{4–6}$.

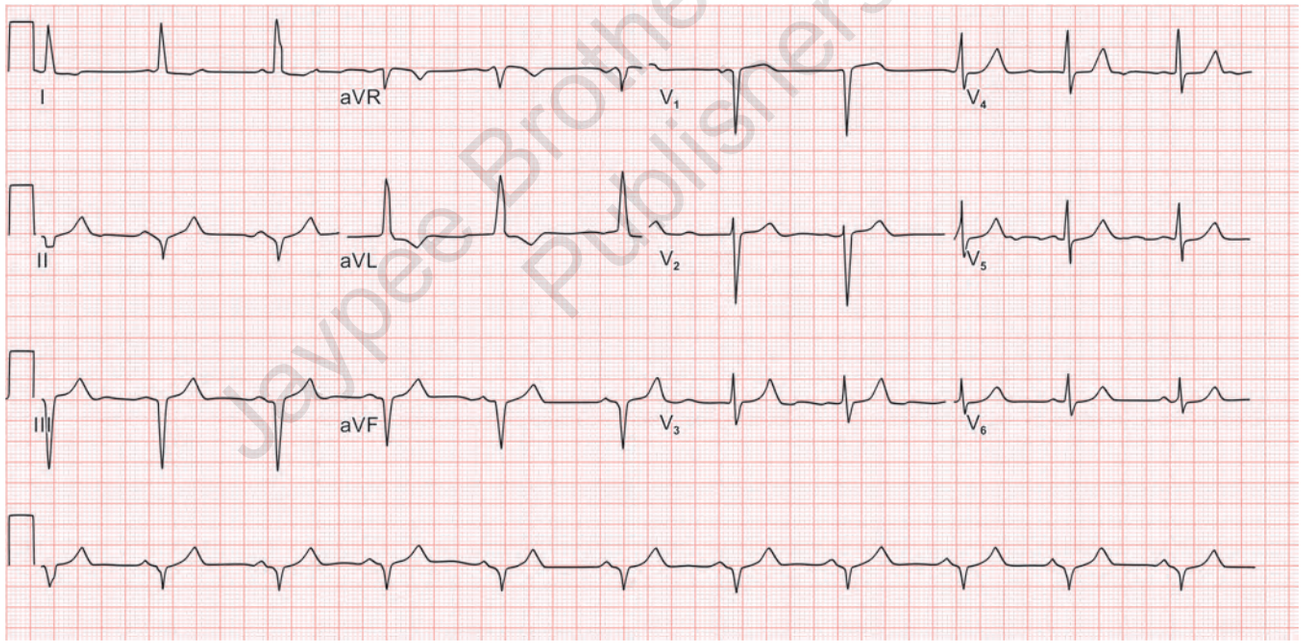

FIG. 9: Note absence of Q in lateral chest leads and extreme left-axis deviation.

- Sinoatrial node dysfunction 60% and atrial arrhythmia 24% at 20 years follow-up.
- Atrial arrhythmia (flutter/fibrillation) and ventricular dysfunction is associated with risk of SCD.

As RV is systemic ventricular, criteria for RV hypertrophy may be present along with diminutive LV forces (Absence of q, small R, and deep S in left precordial leads). AV block is more common following VSD closure and TV repair.[1-6]

Changes following arterial switch: Following coronary reimplantation, there is risk of ventricular ischemia and SCD. Immediate intraoperative ischemia may present as (1) failure to wean from bypass and (2) ventricular arrhythmia. Subacute ischemia may result into low output state after surgery. Late postoperative myocardial infarction and death have been reported in 1–2% of hospital survivor. Atrial arrhythmias are strikingly uncommon following arterial switch. Supravalvar

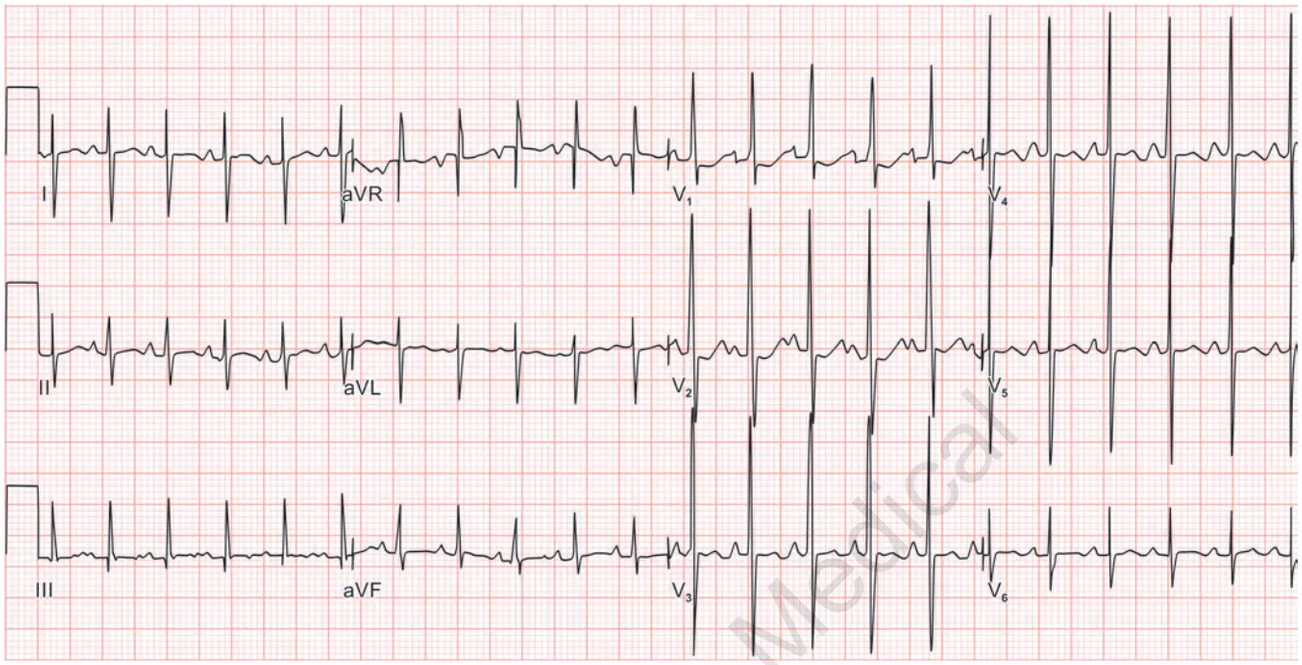

FIG. 10: Transposition of great arteries (TGA): Dominant right ventricular (RV) forces and right-axis deviation.

pulmonary or aortic stenosis may present as ventricular hypertrophy.[1-6]

Tetralogy of Fallot

At birth, ECG may be normal but there is absence of RV regression with age. Changes consistent with tetralogy of Fallot (TOF) are generally seen by the age of 3 months. P wave may be peaked but amplitude is not increased. P duration is short as LA is underfilled and small.

QRS duration and pattern of septal depolarization are normal. Right-axis deviation is rule except for presence of complete AV canal defect in Down's syndrome. RVH is characterized by tall R in V_1 and abrupt transition to rS in V_2. Q in V_{5-6} is an indicator of pulmonary blood flow. Balanced shunt may have small Q and well-developed R in V_{5-6}. Significantly reduced pulmonary blood flow may be associated with rS pattern in V_{2-6} **(Fig. 11)**.

With pulmonary atresia and significant collaterals, left side is well developed and it manifest as (1) bifid and broad P and (2) Q will be well-developed R in V_{5-6}.[1-6]

Postsurgical Changes (Fig. 12)

BT shunt: As there is increase in pulmonary blood flow, Q may appear V_{5-6} with developed R wave. However, ECG may not show any changes after shunt in most of cases.

Postcorrective surgery: Transannular patch/RVOT resection with valve preservation:—RBBB is common and it is due to delayed activation of RV outflow caused by disruption of RV conduction system during infundibular resection. QRS duration > 150 ms in pediatric age indicates: (1) large RV volume, and (2) significant pulmonary regurgitation. QRS duration directly correlates with RV volume and mass. Severe pulmonary regurgitation leads to RV dilatation and QRS widening. Pulmonary valve implantation in operated cases of TOF with transannular patch and severe PR are known to slow progression of QRS widening. QRS duration >180 ms is consistently associated with increased risk of ventricular tachycardia and SCD.

Common arterial trunk: Truncus arteriosus—ECG is greatly determined by pulmonary blood flow. If there is increase in pulmonary blood flow, LV forces are prominent. In case of decrease flow, RV forces dominates. P wave morphology and PR interval are normal.[1-6]

Pulmonary atresia intact IVS: P wave may be tall and peaked in II. QRS axis is leftward and inferior if RV is small and rightward if RV is dilated in rare cases.

Ebstein's Anomaly of Tricuspid Valve (Fig. 13)

Right atrium is dilated and it is characterized by tall peaked P wave **(Fig. 13)**. Occasional cases of atrial standstill are also known where there atrial myocardium is nonresponsive to electrical or mechanical stimulation. PR interval is prolonged which correlates with dilated, large RA. HV interval may be prolonged due to atrialized RV and lengthened conduction system.[1-6]

There is right-sided accessory pathway in 20% of patients and PR interval may be short (delta wave-Wolf Parkinson White syndrome). In those without ventricular pre-excitation, there is usually right ventricular conduction delay with a low amplitude R' wave. QRS prolongation is largely due to prolong activation of atrialized RV. Conduction disturbance is distal to right bundle and may be present despite right-sided accessory pathway.

Tachycardia in Ebstein's anomaly: Atrial arrhythmia (flutter, fibrillation, and atrial re-entrant), AV re-entrant tachycardia

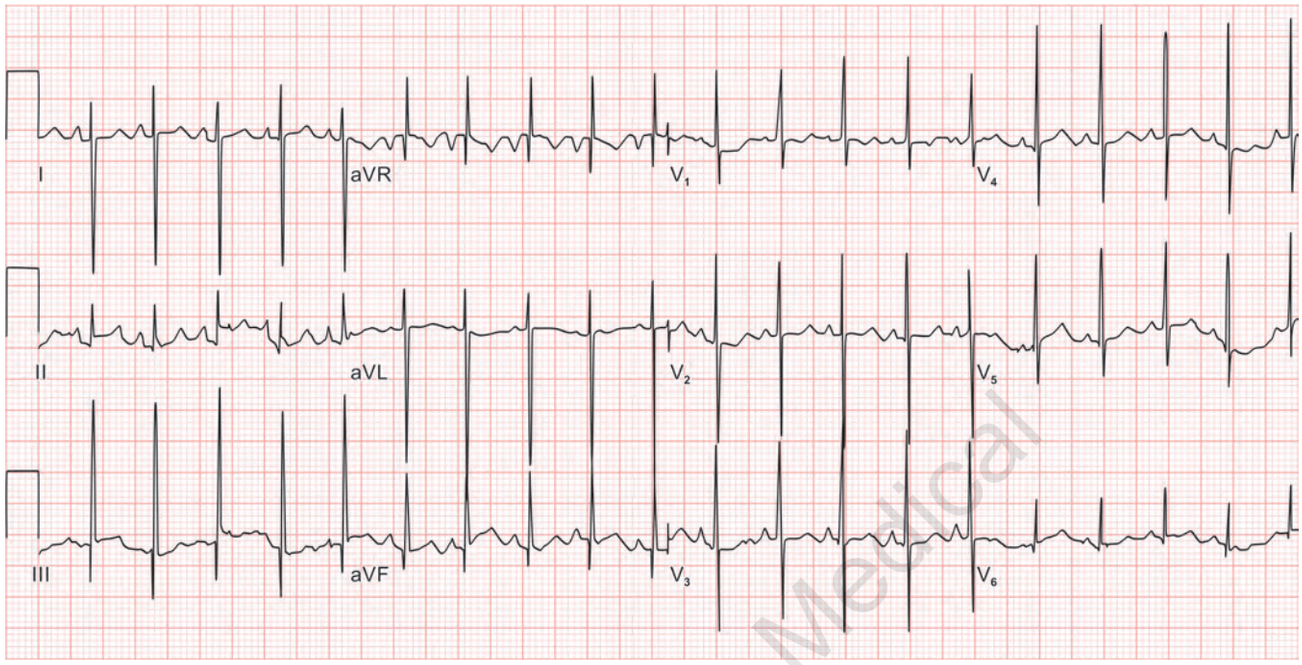

FIG. 11: Right-axis deviation and sudden transition of QRS between V_1 and V_2.

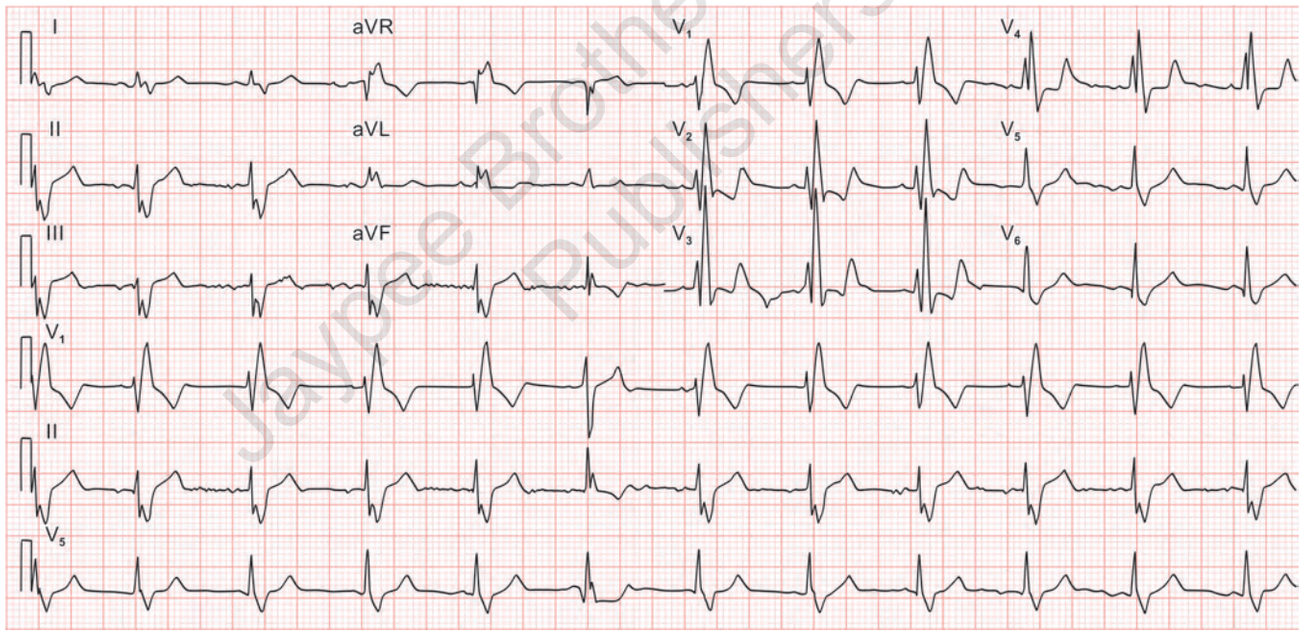

FIG. 12: Postsurgical tetralogy of Fallot (TOF): Complete right bundle branch block (RBBB), fragmented QRS.

(orthodromic, antidromic, and two pathways), and ventricular tachycardia are frequently seen. Mahaim type accessory pathways are also known.

Tricuspid Atresia (Fig. 14)

Tall peaked right atrial P wave are typical. AV conduction is normal; however, short PR and long PR have been described. Preexcitation is very uncommon. There is counterclockwise loop (Q in I, aVL). LADs, adult progression of precordial leads (S in V_1 and R in $V_{5–6}$), along with LV hypertrophy in a cyanotic child suggest TA with small restrictive VSD, small RV, and normally related great arteries. Inferior frontal plane axis is found in nearly half cases of TA and TGA. Rightward axis is rare and associated with L transposition. Patients with increased pulmonary blood flow demonstrate tall R and deep Q in V_6. Q and R in V_6 are diminutive if there is decreased pulmonary blood flow.[1-6]

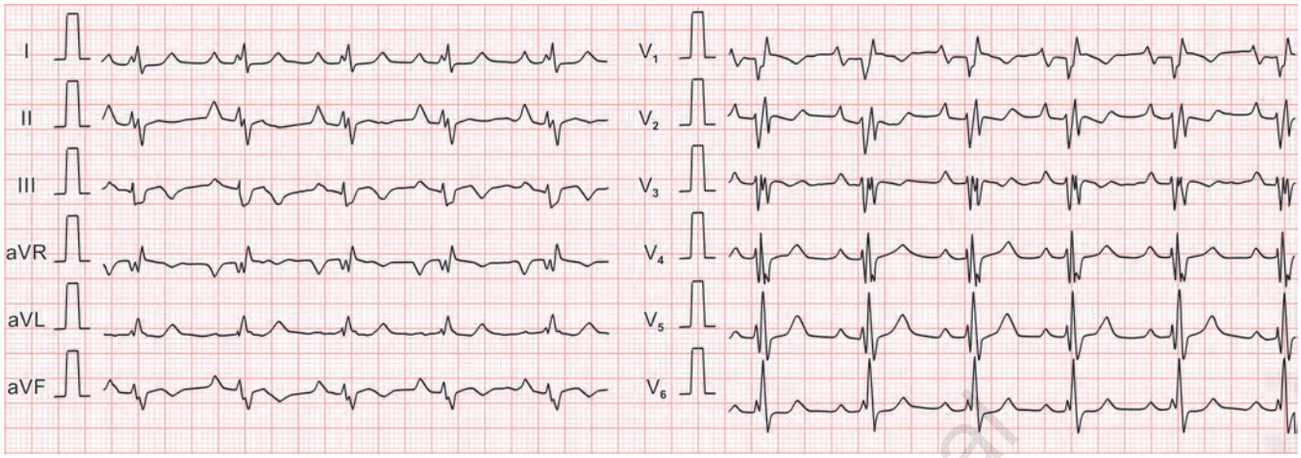

FIG. 13: Prolong PR, right atrial enlargement, fragmented QRS, right bundle branch block (RBBB).

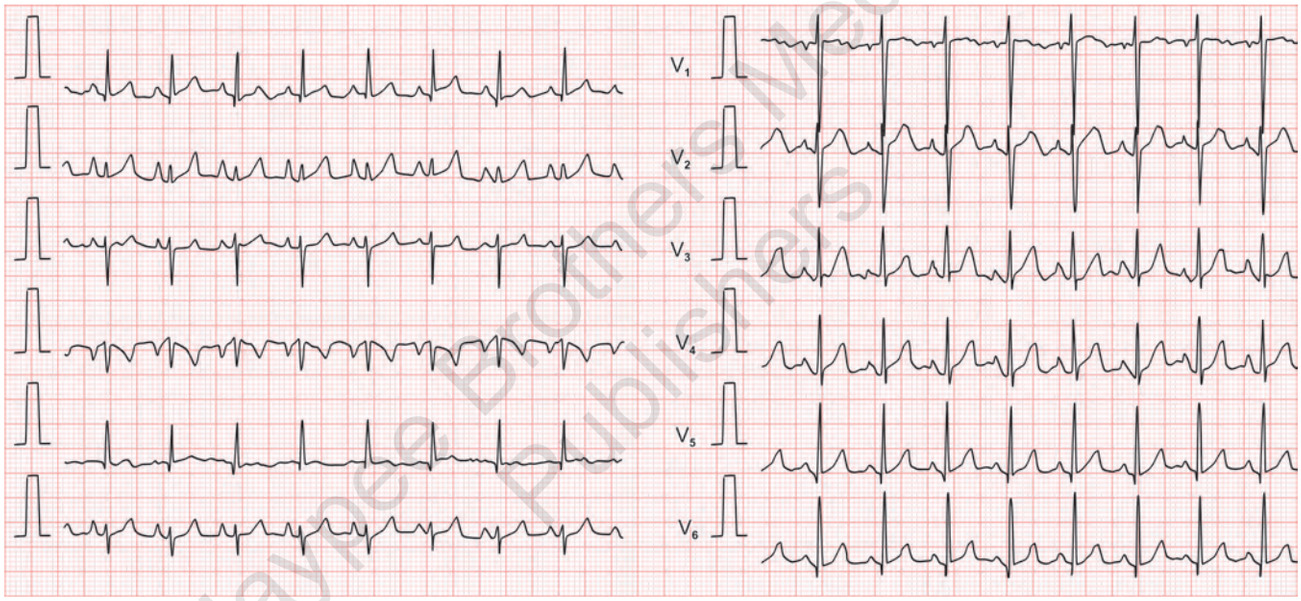

FIG. 14: Tricuspid atresia: Tall P, Q in I, aVL, left-axis deviation, adult transition of QRS in precordial leads seen in infancy.

Double Outlet Right Ventricle

Right ventricle hypertrophies with right-axis deviation are most common features. RV forces are prominent if there is PS. Pronounced increase in LV forces may be evident in restrictive VSD. Biventricular hypertrophy is common if there is increase in pulmonary blood flow. Counterclockwise loop is also known in small substrate.

Single Ventricle

Relation of ventricle and outlet chamber influences QRS morphology. Abnormal initial QRS forces may produce QR in V_1, Q in III, and aVF. In presence of AV canal defect, ECG features are consistent with AVSD.

Post Fontan

Atrial arrhythmia (fibrillation, flutter, re-entrant, sinus node dysfunction, etc.) are on long-term follow-up intracardiac Fontan. After introduction of extracardiac cavopulmonary connection, these entities are uncommon. QRS morphology is consistent with underlying ventricular morphology. ST changes are common on ambulatory monitoring and stress testing which are secondary to ventricular hypertrophy. Possibility of ischemia cannot be ruled out.

X-RAY IN CONGENITAL HEART DISEASE

X-ray chest is a widely available investigation. Though in isolation, X-ray has no diagnostic value in CHD, it can give

valuable information about hemodynamic like lung vasculature and anatomy such as situs, cardiac position, arrangements of cardiac chambers, great vessels, bony thoracic cage, etc. It contributes to understanding of natural history, diagnosis of complications, and management.

Current discussion is mainly about approach to interpretation of X-ray chest in the CHD. PA view is most commonly used. In occasional cases lateral or oblique projections are used. It consists of four important steps:

1. *Technical analysis*: Patient alignment and film quality
2. *Extracardiac structure*: Bony thorax, soft tissue, abdomen, diaphragm, esophagus, and great arteries in mediastinum
3. *Hemodynamic/physiological aspects*: Pulmonary vascularity and lung parenchyma
4. *Anatomy/arrangement of cardiac structure*: Cardiac anatomy must be interpreted in reference to lung vascularity.

Technical Analysis

Alignment

Interpretation of cardiac structure is greatly influenced by any rotation of chest. For proper alignment, distance of medial end of clavicle as well as anterior end of ribs (5th or 6th) should be equidistant from dorsal spine.

Exposure of film: (Under- or overexposed)
Normally lungs should appear gray and the dorsal spine and intervertebral spaces should barely be perceptible through cardiac density (ideally, only first four dorsal vertebral bodies and intervertebral spaces are seen).

Overexposed: In overexposed film more than four vertebral bodies are seen. Pulmonary vasculature (arteries/veins) becomes lost and it looks like decreased vascularity which may in fact be normal.

Underexposed: Less than four vertebral bodies are seen. It leads to overdiagnosis. Normal lung field may have appearance of pneumonia and edema.

Position of diaphragm: Expiratory film may give impression of cardiomegaly, congestion, and infiltration in lung fields. As breathholding is not possible below 4 years of age, it is not possible to comment about cardiomegaly because variations of cardiac size due to respiration are more than those due to pathology.

Bone and Soft Tissue

Signs of previous surgery: (1) *Thoracotomy* may have (a) irregular and ill-defined rib margin are characteristic of rib generation. (b) There may rib crowding or asymmetry in intercostal spaces. (c) Absence of rib, generally 4th rib. (d) Increased density of axilla: seen immediate postoperative period and may persist for a few months. (e) Depressed outer rib sign: Normally, successive rib is sprung further than previous. After thoracotomy, outer margin of involved rim is indented inwards. (f) Thickened pleura **(Fig. 15)**.[10-13]

Sternotomy: (a) Sternal wires may be difficult to detect in PA projection because they lie over dorsal spine and lateral projection may help. (b) Surgical clip in mediastinum. (c) Radiopaque valve prosthesis.

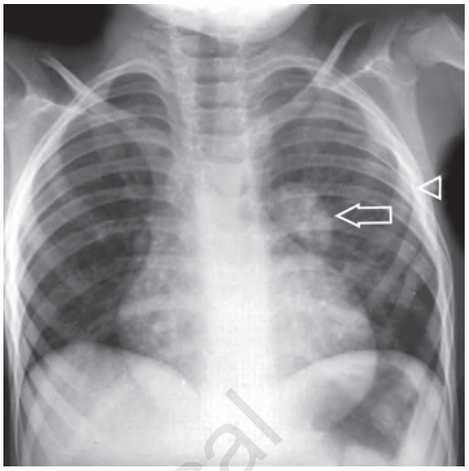

FIG. 15: Crowding of ribs on left side (arrowhead) along with aneurysmal dilatation of left pulmonary artery (LPA) (arrow).

Barrel chest in infants: Large left to right shunt at any level may result in depressed diaphragm, barrel-shaped chest and sprung rib appearance.

Diagnostic Clues from Other Skeletal Abnormalities

- *Hemi/fused vertebra*: VECTERL syndrome → Aortic arch interruption, conotruncal anomalies
- *Cyanosis + skeletal abnormality*: Conotruncal anomalies
- *Bilateral notched rib*: (a) Coarctation of aorta with normal origin of neck vessels. (b) Unilateral rib notching (left-sided): Aberrant right subclavian after origin of coarctation segment. If both subclavian have origin after coarctation segment, there is no rib notching
- *Absent 12th rib/hypersegmented sternum*: Down syndrome
- *Absent Radia/thumb*: Holt-Oram syndrome → OS ASD
- *Polydactyly → Ellis-van Creveld*: Atrioventricular septal defects, OS ASD13

Abdomen

Liver, spleen, and stomach are lateralized organs. Presence of midline liver indicates visceral heterotaxy **(Fig. 16)**. In situs solitus **(Fig. 17)**, stomach bubble is on left side and in situs inversus **(Fig. 18)**, it is on right side. If there is discordance between fundic bubble and cardiac mass, chances of heterotaxy are high **(Fig. 19)**. Dilated azygous vein may mimic a right or left-sided aortic arch. After heterotaxia is ruled out, especially in neonates, presence of aorta and stomach bubble on same side indicates corresponding arrangement of atria, (if in left: situs solitus, and on right: situs inversus).[10-13]

Superior Mediastinum

Aortic arch: Barring 1 in 1,000–2,500, aortic arch is left sided, i.e., it traverses on left side of bronchus or left side of trachea. Signs

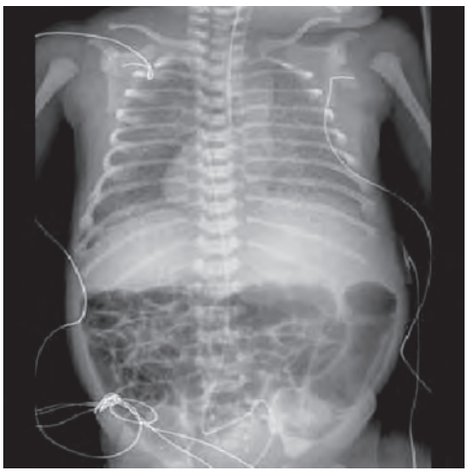

FIG. 16: Midline liver.

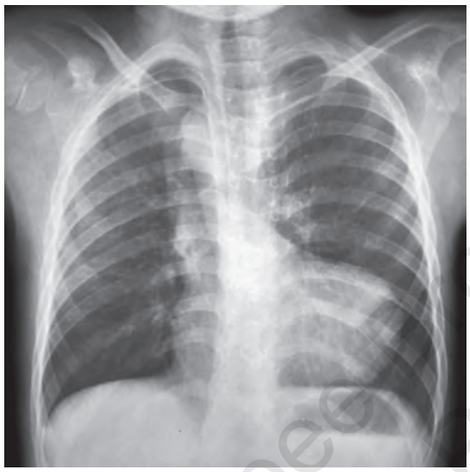

FIG. 17: Left-sided stomach bubble in situs solitus, also note upturned apex, right aortic arch and pulmonary oligemia.

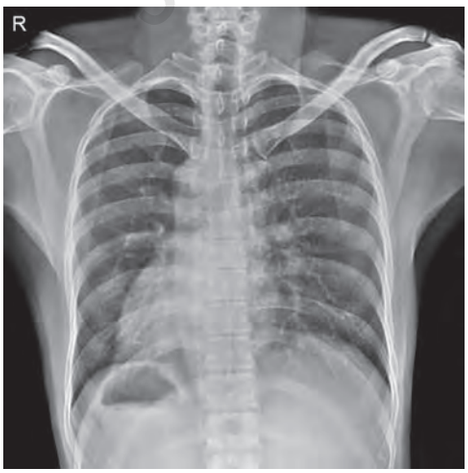

FIG. 18: Right-sided stomach bubble and dextrocardia in a case of situs inversus.

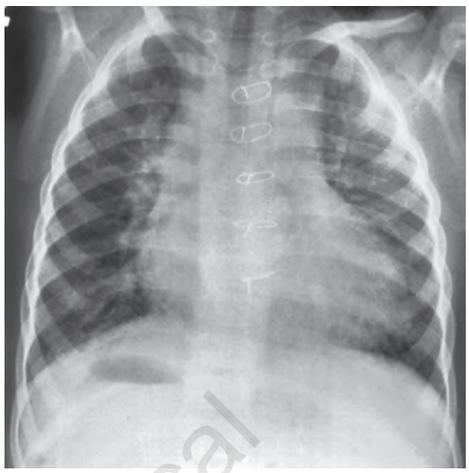

FIG. 19: Polysplenia: Stomach bubble on RT and cardiac apex to left. Also note bilateral symmetrical bronchi.

indicating right-sided aortic arch are **(Fig. 17)**: (1) absence of normal aortic arch/knob in left superior mediastinum, (2) deviation of SVC to right, (3) indentation on right side of trachea and deviation to left side, (4) deviation of esophagus to left.

Main pulmonary artery (MPA)/trunk: Size of MPA is an important indicator of pulmonary pressure and shunt. Large left to right shunt (ASD/VSD/PDA) leads to dilatation of MPA. Pulmonary hypertension irrespective of cause is associated with dilated MPA. A small or absent MPA may be seen in case of pulmonary atresia or severe PS (dysplastic and thick valve). If PS is due to doming valve, MPA may be dilated. Posteriorly placed MPA as in case of transposition does not contribute to cardiac margins.[13]

Tracheobronchial Tree and Central Pulmonary Arteries

Right main bronchus is shorter and more in line with trachea. It is above right MPA, hence called as epiarterial. Left main bronchus is longer, more at angle to trachea (horizontal) and saddle shaped. It is hypa-arteria (below artery). Atrial situs corresponds to bronchial situs. Normally length of left bronchus is twice the right. If the ratio is <1.5 times, possibility of visceral heterotaxia needs to be considered.

Evaluation of Lung Vascularity[10-13]

It is an important marker of hemodynamics and physiology. Pulmonary vascularity evaluation begins with central vessels also called as hila. They are formed by right and left branches of MPA. In infants and teenagers, left hilum is difficult to evaluate in PA view, owing to superimposition of thymus and MPA and it is better seen in left anterior oblique (LAO) view. As lower lobes are in dependent part and anatomically larger than upper lobe, arteries to lower lobe are larger than upper lobe.

Normal pulmonary vascularity: (1) Pulmonary arteries taper from hilum to periphery. (2) Right descending pulmonary artery (RDPA) is normally <14 mm in diameter, (3) Central

(inner) one-third has more vessels than peripheral (outer) one-third → ratio of inner: outer = 5:3 or 5:2, (4) In the first anterior intercostal space below first rib → vessel are <3 mm, and (5) Lower zone vessels are larger than upper zone vessels—ratio lower:upper = 5:1.

Increased vascularity: Shunt lesions.

In case of increased pulmonary blood flow as in a case of shunt lesions, there is dilatation of arteries, arterioles, capillaries, and veins also. Hence, word used is vascularity not just arterial markings. These changes are seen if left to right shunt is >1.5:1. Signs of significant left to right shunt are **(Figs. 20 to 22)**:

- Hilar and proximal pulmonary vessels appear abnormally large and dense.
- End on of vessels seen close to diaphragm. End on pulmonary arteries in parahilar area > 3–5.
- Right descending pulmonary artery diameter. Adults: Upper limit of normal for RDPA diameter is 17 mm. If diameter is <14 mm, a significant shunt is unlikely. In children, in presence of shunt RDPA diameter was more than diameter of his/her trachea.
- Hilar pulmonary artery is larger than accompanying bronchus.
- Vascular markings can be traced to lateral third of lung fields.
- *Waterfall right hilum*: Increased and torrential pulmonary blood flow results in massive dilatation of MPA which, in turn, leads to elevation of right pulmonary artery. It is typically seen in single ventricle with MPA from main chamber.
- First intercostal space vessel diameter > 3 mm.
- Upper and lower lobe vessels have increased blood flow—ratio lower to upper 4:1 or 3:1 (normal 5:1) = shunt vascularity.

Few mimics of above findings are: anemia, pregnancy during 2nd and 3rd trimester, thyrotoxicosis, AV fistula, normal teenagers, well-trained athletes, etc.

Pulmonary Venous Hypertension

Increased in pulmonary venous pressure can be due to (1) pulmonary vein obstruction as seen in infracardiac total anomalous pulmonary venous connection (TAPVC)/postsurgical, (2) left atrium: cor triatriatum, (3) mitral valve: supramitral membrane, mitral stenosis/regurgitation, (4) left ventricle (LV): failure, systolic/diastolic dysfunction, (5) LV outflow tract and beyond: obstruction. Severe aortic stenosis, coarctation of aorta, etc. Increased in pulmonary venous system is freely transmitted into alveolar capillaries and pulmonary arterioles. Changes in X-ray file are directly related to severity and duration of pulmonary venous hypertension (PVH) and not type of lesion. Interstitial edema first occurs away from alveoli, and it collects around vessels, lymphatics, and terminal airways. As interstitial pressure rises with accumulation of fluid, there is flooding into alveoli. Stages of PVH. Stages 1–3 are acute or chronic changes, stage 4 is always chronic.[10-13]

1. *Stage 1 (venous pressure 13–15 mm Hg)*: As there is interstitial edema in lower lobe vessels, there is redistribution of flow to

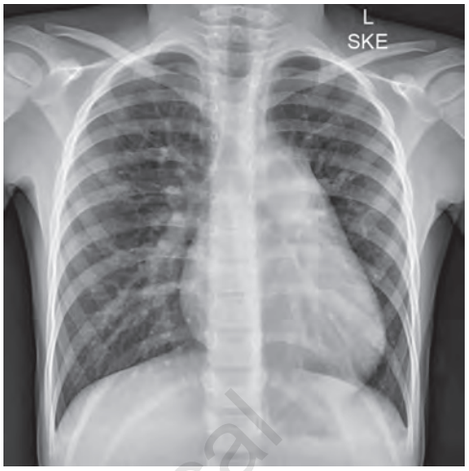

FIG. 20: X-ray in large atrial septal defect. Note dilated main pulmonary artery (MPA) and prominent vasculature.

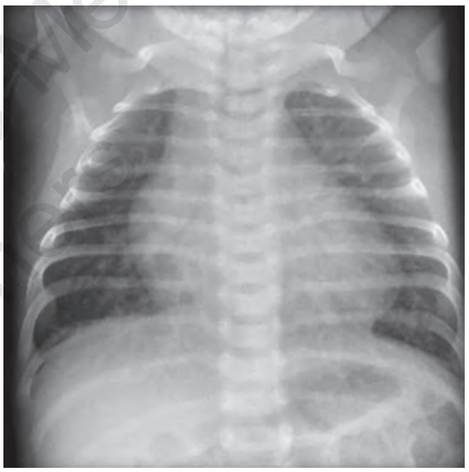

FIG. 21: Large ventricular septal defect (VSD) in an infant. Note increased cardiac size and prominent vessels.

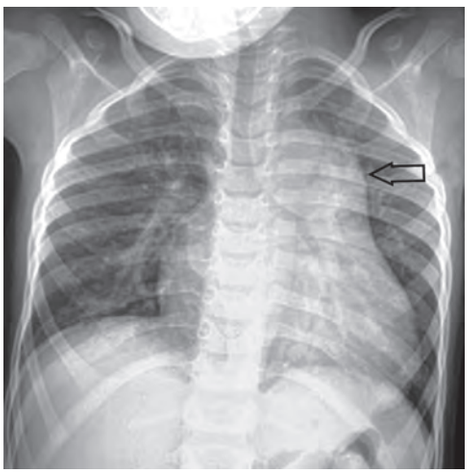

FIG. 22: Dilated main pulmonary artery (MPA) in large patent ductus arteriosus (PDA).

upper lobe vessels. These X-ray changes are seen in upright patient only. Signs are very difficult to pick up and they are: (1) equalization of size of upper and lower lobe vessels, (2) loss of normal hilar angle on right side caused by dilatation of right upper pulmonary vein. (3) Upper lobe vessels distinctly more dilated than lower lobe (15–18 mm Hg).

2. *Stage 2 (venous pressure 18–25 mm Hg)*: It is the stage of interstitial edema. Signs of this stage include: (1) The hila becomes dense and prominent. Outer margin of RDPA is ill-defined and hazy. (2) *Peribronchial cuffing*: edema of bronchial wall with thickening, (3) *Kerley B-line*: When hydrostatic pressure more than colloidal osmotic pressure (22–25 mm Hg), lymphatic of interlobar septa becomes prominent. Fluid in interlobar septa is seen as thin, dense, horizontal streaks (Kerley B lines) **(Fig. 23)**. Similar lines in upper lungs are termed as "Kerley-A lines **(Fig. 24)**. They are best seen in first 24–36 hours. Spiderweb pattern at lung bases is due to superimposition of Kerley-B lines and it is termed as "Kerley-C lines". (4) *Subpulmonary edema*: It represents fluid adjacent to loose alveolar tissue. It mimics thickened interlobar fissures but lower margins are hazy. (5) *Thickened lung fissures*: With severe degree of PVH, fluids form in major and minor fissures of lungs. These are thick dense lines and they remain prominent even after treatment and reabsorption of fluid. (6) *Pleural effusion*: Pleural effusion more on RT side than on left is characteristic sign of PVH. Significant effusion is a sign of RV failure. If effusion is more on left, then possibility of infarction, tumor or Koch to be considered.
3. *Stage 3: Pulmonary edema/Air space edema*: (Mean LA pressure/venous pressure: >25 mm Hg). It manifests as dense poorly defined opacities and must be distinguished from pneumonia or infarction. It is evanescent in character after treatment.
4. *Stage 4*: Effect of longstanding severe PVH—it is characterized by hemosiderosis and ossification of lung. Hemosiderin laden microphages are results of microvascular bleeding into alveoli.
5. *Secondary effects*: (1) Dilated MPA—it is the indicator of moderate to severe pulmonary arterial hypertension (PAH). Along with other signs of PVH, dilated MPA points toward PA pressure > 50 mm Hg. (2) Decreased vascularity in periphery along with prominent upper lobe veins. (3) Typical findings of LA enlargement seen with rheumatic heart disease may not be evident in CHD as it presents earlier and there may not be adequate time for LA enlargement.
6. *Pulmonary venous hypertension (PVH) in neonates*: Findings unique are—(1) absent redistribution of blood flow to apex and air bronchogram. (2) ill-defined reticular vessels throughout lung fields, (3) interstitial fluid in perivascular spaces: pulmonary clouding/interstitial veiling, (4) depressed diaphragm.

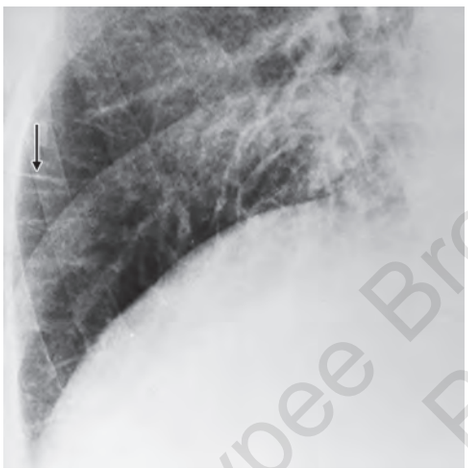

FIG. 23: Kerley's B line indicated with arrow.

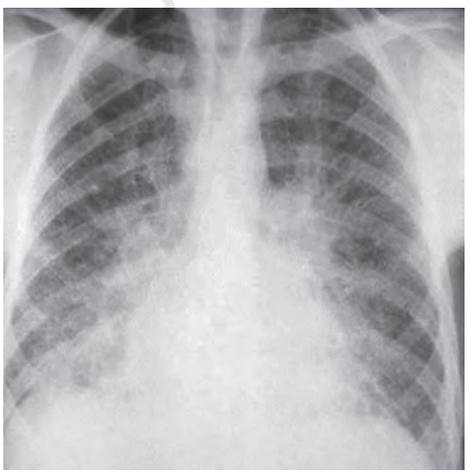

FIG. 24: Kerley's A line.

Precapillary Hypertension

Irrespective of type of shunt lesion, severe irreversible pulmonary hypertension leads to similar changes in X-ray chest. They are similar to pulmonary hypertension due to other etiologies such as cor pulmonale, primary pulmonary hypertension, and chronic thromboembolism. Shunt lesions receive more blood flow before development of severe pulmonary hypertension and thus pulmonary arteries can be more dilated than those seen in nonshunt PAH.[10-13]

Some important signs include: (1) Prominent well-defined central pulmonary artery with tortuosity, (2) Deviation and decrease in size of pulmonary arteries in middle and lateral third of lung fields, (3) Presence of calcium in MPA and proximal pulmonary arteries indicates: (a) longstanding PAH and (b) pulmonary artery pressure equal or greater than systemic pressure **(Fig. 25)**.

The cardiovascular silhouette is usually normal or slightly increased. After development of RV failure and TR, RA and RV dilate along with systemic veins can lead to increase in cardiac size. Calcification of patent arterial duct and snowman heart in TAPVC **(Fig. 26)** are only a few diagnostic clues for cause but beyond this, X-ray may not be useful for etiology.

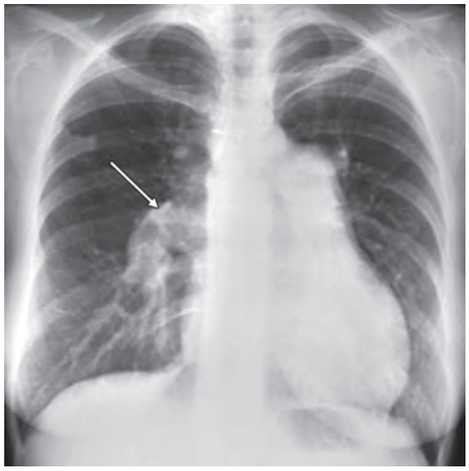

FIG. 25: Note hugely dilated MPA and RPA (arrow), marginally increased cardiac size, very few vessels are seen in middle and lateral third of lung fields.

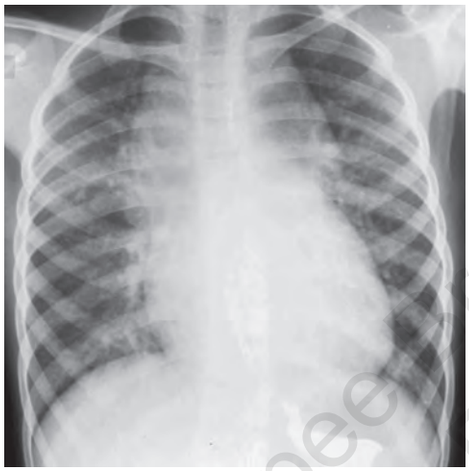

FIG. 26: Supracardiac total anomalous pulmonary venous connection (TAPVC): Snowman or Figure of 8.

It is important to note that small percent of patient with severe precapillary PAH may have essentially normal vascularity. Sensitivity of X-ray chest in detection of precapillary PAH is suboptimal.

Systemic Collateral Arteries[10-13]

It occurs in setting of pulmonary valve atresia with large VSD, common arterial trunk, and major aortopulmonary collaterals. Some diagnostic clues include: (1) MPA may be absent, (2) unequal vascularity of lung fields or right and left lungs, (3) confluence may be absent, (4) vessel pattern though prominent may be disorganized, (5) reticulated appearance, (6) vessels are prominent close to main stem bronchi, (7) *lateral view*: hilar arteries appear disorganized and not large or inapparent.

Decreased Pulmonary Blood Flow[10-13]

Causes of decreased pulmonary blood flow include severe valvar, infundibular or supravalvar stenosis of pulmonary valve or any combination of them in association with intracardiac shunt like VSD or single ventricle. Isolated valvar stenosis may not cause decrease pulmonary blood blow unless associated with RV failure, severe TR, ASD with right to left shunt. X-ray findings include: (1) X-ray film looks like overexposed or emphysema like, (2) hilar and intrapulmonary vessel appear small and less dense, (3) they may not be traced in middle and lateral third of lung fields, (4) lateral vies may be useful to estimate size of branch pulmonary arteries **(Fig. 17)**.

Vascular Pedicle

Pulmonary Trunk[10-13]

Prominent pulmonary trunk is not an uncommon finding and observed in well-trained athletes, idiopathic dilatation, and pulmonary hypertension irrespective of cause (shunt lesions, pre- as well as postcapillary pulmonary hypertension). In PS, though MPA is enlarged, branch pulmonary arteries may be of normal caliber. Small or absent MPA is seen in tetralogy of Fallot (TOF), pulmonary atresia, etc. or if it is posteriorly placed [TGA/congenitally corrected transposition of the great arteries (CCTGA)].

Aorta[10-13]

Evaluation of aortic arch and descending aorta are particularly important in a case of pulmonary venous congestion as it can give important diagnostic clue for LV systolic failure.

Ascending aorta and arch: In older children, lateral border of ascending aorta rarely form part of right margin of cardiac silhouette and it is better seen in LAO projection. Transverse arch forms small, smooth, rounded bulge known as aortic knob seen at uppermost left margin of cardiac shadow.

Aortic arch produces indentation and deviation of trachea. In case of left aortic arch, tracheal indentation is on left and deviation to right and vice versa for right aortic arch.

Prominent ascending aorta: It shows increased curvature on right and anterior. It can be normal finding in adult and old age. In children causes include (1) aortopathy in case of aortic stenosis, coarctation, Marfan syndrome and (2) systemic hypertension.

Transverse Aortic Arch[10-13]

- *Prominence*: Apart from causes mentioned above for dilatation of ascending aorta, PDA can cause prominence of transverse arch which may be apparent, not real.
- *Distortion/alteration/absence of normal curvilinear density of the aortic knob*: Most common cause is coarctation of aorta and other includes: (a) saccular aneurysm (traumatic) of aorta after left subclavian, (b) acute or chronic dissection, (c) interruption of arch, and (d) mediastinal mass.

TABLE 1: Incidence of cardiac anomalies in cardiac malpositions in situs solitus and inversus.

	Levocardia	Dextrocardia
Normal atria	0.8%	75%
Mirror image atria	99.9%	1–2%

- *Prominence and tortuosity of descending aorta*: For adults, common causes in decreasing frequency include: (a) normal finding in elderly, (b) systemic hypertension, (c) severe aortic regurgitation, (d) acute and chronic dissection, (e) systemic AV fistula. In children, it indicates systemic hypertension and aortic regurgitation.
- *Right aortic arch* **(Fig. 17)**: (a) With mirror image branching—the indentation on trachea is on RT and it is deviated to left. If DTA crosses over and descend along left side of spine, it can produce indentation on esophagus (barium swallow) similar to aberrant RT subclavian with left arch, but it is larger. (b) Aberrant left subclavian from DTA: along with findings mentioned above, retroesophageal compression may be similar to its mirror image counterpart.

Special problems in elderly: Degenerative changes and tortuosity may produce pseudo right-sided mediastinal masses as well as aberrant left subclavian may produce pseudomass on left side.

Approach to Dextrocardia and Cardiac Malpositions[10-13]

It is important to know statistics of CHD in various anomalies of situs and cardiac malpositions **(Table 1)**. When atrial situs is opposed to cardiac axis, there are high chances of AV discordance. If there is AV valve atresia, it is generally RT.

Steps:

1. *Confirm*: Heart or stomach or both lie on same side other than left or different sides.
2. *Rule out secondary caused*: (1) Like dextroposition: skeletal deformity, hypoplastic right lung, diaphragmatic hernia on left, eventration, or (2) Dextroconfusion: wrong labeling or positioning.
3. *Evaluate visceral and bronchial situs*: Abdomen, liver, stomach bubble, bronchial situs.
4. In presence of heterotaxia, it is very difficult to determine segmental anatomy and relations.
5. If there is no heterotaxia, ventricular morphology can be determined from counter of heart borders (discussed below) (Left heart border in case of levocardia and right heart border in case of dextrocardia).[13]

Importance of left heart border:

- *Determination on ventricular relation*:[10-13] Normal left heart border has concavity after pulmonary trunk followed by convexity corresponding to LV. In case of CCTGA normal triad of densities (ascending aorta, aortic knob, and MPA) is absent. Left heart border is unusually convex **(Fig. 27)**. If left-sided RV is rudimentary outlet chamber, it produces localized hump along left heart border **(Fig. 28)**.
- *Juxtaposition of atrial appendage*: Right atrial appendage is on left side of arterial trunks. It is seen with single ventricle, double outlet right ventricle (DORV), TGA, and CCTGA. It is generally associated with PS. There is convex bulge produced on left upper border of heart by displaced RA appendage. There is alteration of RA border. There are two types: (1) lower aspect of right heart border is deficient and it does not extend beyond spine. SVC may be deviated to right by transposed ascending aorta. (2) there is flattening of upper right heart border and create impression that apex is deviated to right.

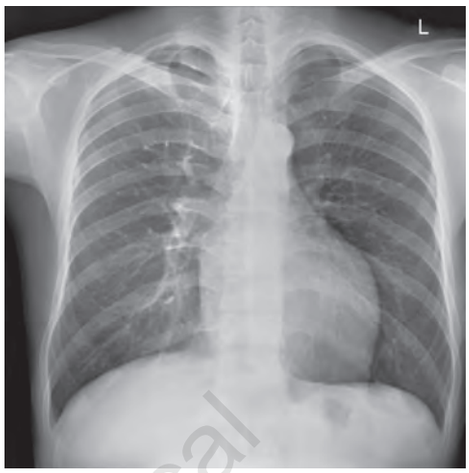

FIG. 27: Convex left heart border in a case of congenitally corrected transposition of the great arteries (CCTGA).

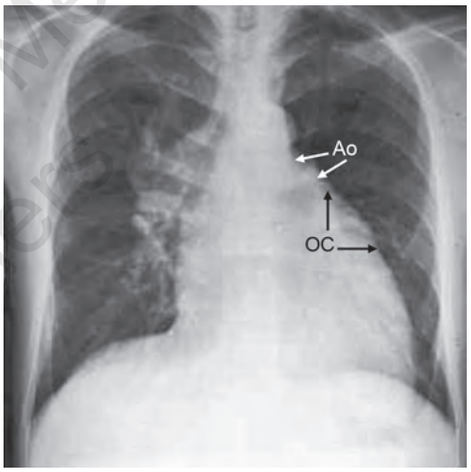

FIG. 28: Left-sided outlet chamber seen as hump.
(Ao: aorta; OC: outlet chamber)

X-ray findings in different cardiac lesions individually or syndromic: Scope of lesion localization—it is important to understand changes in pulmonary vasculature mentioned above, particularly those of shunt lesions and pulmonary hypertension. They help immensely to understand stage of natural history of disease. Small, hemodynamically insignificant lesions may not produce any changes. Discussion hereafter is relevant only of defects which are large and/or hemodynamically significant.

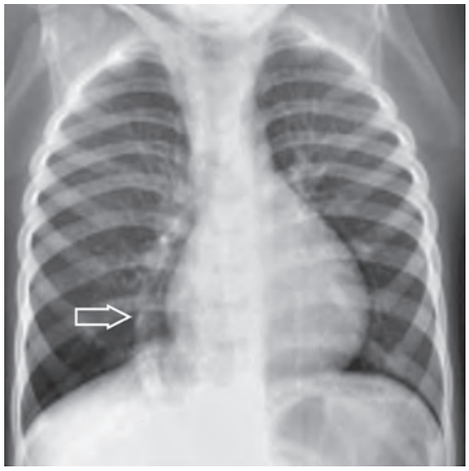

FIG. 29: Arrow indicates drainage of right pulmonary veins below diaphragm.

Shunt lesions: Physiological stage can be understood from lung vascularity. Particularly in infants, large shunt can produce left ventricular failure and pulmonary congestion hence X-ray findings can be similar to PVH in addition to shunt lesions. Refer to section of shunts and pulmonary hypertension for more discussion.

Clues for anatomical localization of shunt ***(Figs. 20 to 22)***:[10-13]

- *Size of left atrium*: Large LA means IAS is intact and shunt is post-tricuspid, or there is significant MR. Small LA rules out post-tricuspid shunt. This sign is relevant only in infancy. Decrease or normal size of LA in case of VSD may suggest (1) decrease in size of VSD and shunt, (2) acquired RVOT stenosis, (3) development of PAH. Small left atrium with dilated right side favors atrial level shunt.
- *Aortic arch*: In VSD and intracardiac shunt, aortic arch is normal size or in apparent. PDA produces convex curvilinear density (bucket handle) between transverse arch and MPA. Aortic arch may be larger than usual.
- Enlarged cardiac silhouette indicates either significant shunt, or in absence of significant shunt (1) significant AR from cuspal prolapse (VSD), (2) ventricular dysfunction, (3) severe tricuspid or MR. Cardiac size decreases with (1) closure of defect, (2) development of pulmonary hypertension and decrease in shunt, (3) complications: RVOT stenosis.
- Cardiomegaly may be absent during neonatal period as shunt is small (PDA/VSD). During late neonatal period or early infancy, as shunt establishes, cardiomegaly may appear on X-ray chest. This can be appreciated on serial X-rays.
- *Partial anomalous pulmonary drainage:* (1) *Scimitar syndrome* ***(Fig. 29)***: Drainage of right pulmonary veins below diaphragm produces characteristic X-ray appearance of Turkish sword. It may be associated with hypoplasia of right lung. (2) *Course of right upper pulmonary vein*: It forms upper limb of right hilum and it is generally oblique. If the course is horizontal, possibility of sinus venous ASD with anomalous drainage to SVC should be suspected. (3) Left-sided upper pulmonary vein drains into innominate and it produces vertical opacity in left upper mediastinum.
- Presence of shunt like vascularity in women generally indicates ASD (Shunt + breast = ASD).

Total Anomalous Pulmonary Venous Connections

Pulmonary vascularity: In unobstructed total anomalous pulmonary venous connections (TAPVC), it is like significant left to right shunt. While, obstructed variety has presentation like left-sided obstruction.

Anatomical Signs

Supracardiac TAPVC to innominate vein via vertical vein and drainage into right SVC: It produces figure of eight or snowman type cardiac shadow **(Fig. 26)**. Upper circle of eight is formed of vertical vein, innominate and right SVC. It may not be apparent at birth and may develop later after decrease in pulmonary vascular resistance. After development of irreversible pulmonary hypertension, there may be decrease in size of vertical vein, innominate and right SVC.

Cardiac TAPVC: (1) *Coronary sinus*: X-ray is similar to large ASD. Indentation produced by coronary sinus on barium-filled esophagus is lower than LA shadow. (2) *Azygous vein*: Rounded opacity in right upper mediastinum. (3) *SVC*: Dilated SVC which is deviated to right. There is no vertical vein shadow.

TAPVC below diaphragm: They are usually obstructive and have signs of PVH in early neonatal period. There is low indentation on barium-filled esophagus produced by low-lying pulmonary vein. Heart is generally not enlarged.

Approach to pulmonary venous hypertension: Localization of lesions.

X-ray chest may offer clue to localization of lesion however in a few cases, pulmonary edema may be seen only very late in natural history.

Obstruction at or proximal to mitral valve: There are signs of LA enlargement. LV is of normal size and configuration.

Diseases distal to mitral valve: There is dilatation of LV and it manifests as concavity on mid left heart border. Important clues for etiology of LV failure in adults on X-ray include: (1) *Aortic valve*: Calcium for aortic stenosis, (2) *Irregular LV border*: Aneurysm, (3) *Unusual convex bulge in young*: Hypertrophic obstructive cardiomyopathy, tumor, etc. (4) *Calcium around aortic valve*: Coronary calcium and ischemic heart disease, (5) *Ascending aorta*: Dilated and calcium → aortic stenosis, aortic regurgitation, syphilitic aortitis, (6) *Transverse aortic arch*: Obliteration of normal counter of aortic knob suggests coarctation of aorta. (7) *Descending thoracic aorta*: Abnormal tortuosity may result from old age, systemic hypertension, aortic regurgitation, dissection, and peripheral AV fistula.

Pulmonary venous hypertension: X-ray in infancy—few causes of PVH in infancy include: (1) LV systolic dysfunction due to

diseases of muscle: Myocarditis, cardiomyopathy, anomalous origin of left coronary from pulmonary artery, storage disorders, (2) Left-sided obstructive lesion leading to LV dysfunction: Aortic stenosis and coarctation of aorta, (3) Hypertrophic obstructive cardiomyopathy, (4) Congenital MR or stenosis, (5) Primary endocardial fibroelastosis.

It is difficult to distinguish one cause from other except for coarctation. Common complication observed in this group is compression of left main bronchus between dilated LA and enlarged pulmonary trunk above. As heart has no room to expand to left, aortic arch pushes trachea more and aggravates bronchial compression and left lower lobe collapse.

Children and young adult: Generally there is overt concavity on mid-left border and unusually convex or rounded left heart border are common findings. Dilatation of ascending aorta is important clue toward diagnosis of aortic valve pathology. Presence of well-formed transverse arch helps to differentiate between aortic stenosis and coarctation. Calcification of aortic valve is very rare in this age group.

Signs of Coarctation of Aorta (Fig. 30)[10-13]

Collateral flow: (1) *Rib notching*: It is due to dilated, tortuous intercostal arteries forming deep grooves on undersurface of ribs and it develops after 5 years of age. It is seen from 3rd or 4th to 8th ribs along inferior margins as irregular scalloped appearance. The first and second/third ribs do not show notching because intercostal arteries arise from thyrocervical trunk which has origin proximal to coarctation. Increased density of inferior rib margin precedes notch sign. (2) *Internal mammary artery*: In lateral view, behind sternum, they appear as irregular, wavy tissue opacities. It is seen exclusively in adults. Occasionally, dilated IMA may be seen on either side of manubrium.

Important anatomical signs: (1) Distortion of normal aortic arch counter, (2) Notched aortic arch: 3 signs, (3) Anterior and rightward displacement of barium-filled esophagus by dilated postcoarctation aorta.

Pulmonary stenosis: Dilated main and left pulmonary artery (LPA) with normal vascularity are important signs of pulmonary valve stenosis. RPA may be normal in caliber. It may present at isolated left hilar mass or tumor due to dilated LPA.

Understanding relationship between ventricles and great arteries (great arteries and left heart border).

Information about relationship of ventricles can be inferred from X-ray relation of great arteries. This is only presumptive and not diagnostic. Ventriculoarterial connection is a different entity from great arterial relationship.[10-13]

There are three densities in a case of normally related great arteries: (1) the ascending aorta, (2) transverse aortic arch and proximal descending aorta, and (3) the pulmonary trunk.

Ascending aorta: There are three basic courses of ascending aorta: (1) Convexity to right (rightward ascending aorta), (2) midline ascending aorta with no convexity to either side, and (3) Leftward ascending aorta. During embryogenesis, truncus develops in such a way that its convexity is toward side of RV. It is irrespective of two or single ventricle anatomy. The ascending aorta having convexity toward the right side means that right ventricle or outlet chamber in single ventricle is on right side. Left-sided convexity is seen in case of corrected transposition with left-sided RV or outlet chamber is on left side in a case of single ventricle.[10-13]

Midline or leftward ascending aorta: When transposed ascending aorta is midline, on PA view, aortic density is usually absent. Aortic knob and descending aorta lie over spine and they are not border forming structures.

Some unique cardiac malformations: Transposition of great arteries and other malformations with posterior and leftward pulmonary trunk ***(Fig. 31)***.[10-13]

As MPA is posterior, it is not a border forming structure along left upper border. In neonates, it is hidden behind thymus and not of value. However, after regression of thymus, absence of pulmonary trunk should arouse suspicion especially in a cyanotic patient. There is hyperinflation of lungs. This results in narrow superior mediastinum. Cardiac silhouette may be

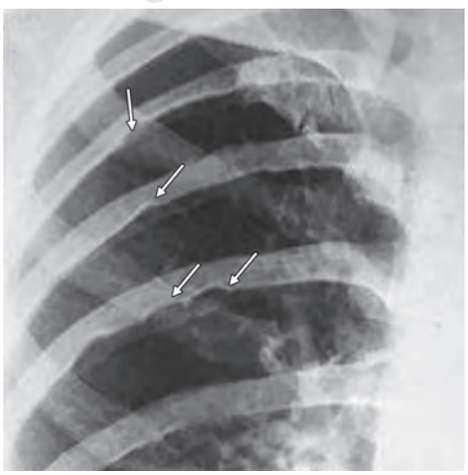

FIG. 30: Rib notching marked by arrows.

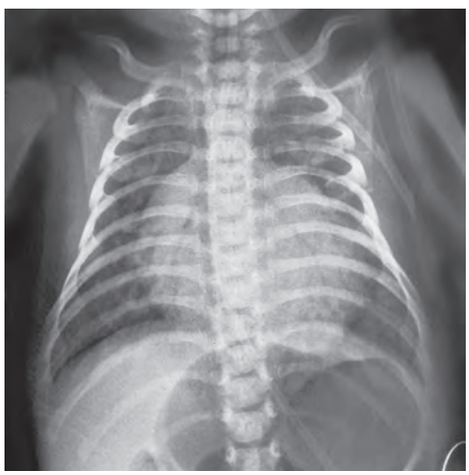

FIG. 31: Egg on side in case of transposition of great arteries (TGA) also note absent thymus.

normal in neonate but enlarges over time and gives impression of egg on string. Right heart border is unusually convex. In absence of thymus in PA view, a dense retrosternal shadow in lateral view suggests anteriorly placed aorta rather than thymus **(Fig. 31)**.

Tetralogy of Fallot (Fig. 17)[10-13]

Overall heart size is generally normal. There is elevation or upturning of apex which is proportional to PS and maximum in atresia (classical description of Coeur en sabot/wooden shoe). Cardiomegaly, if present, is due to anemia, postpalliative large shunt, tricuspid regurgitation (TR) or absent pulmonary valve with severe PR.

Incidence of right aortic arch is 25% in PS and 50% in atresia situation. Pulmonary trunk is generally absent and mid-left heart border is concave. Unoperated cases have decreased pulmonary vascularity. However, hugely dilated pulmonary artery in case of cyanotic patient should arouse suspicion of absent pulmonary valve.

After shunt procedure, along with signs of sternotomy or thoracotomy, lung vascularity may increase. It may be unilateral depending upon shunt flow and PA anatomy. After conventional BT shunt, there may be rib notching from development of collaterals to axillary artery. Anomalous origin of right or LPA may produce differential vascularity.

Tetralogy of Fallot absent pulmonary valve: The MPA and proximal branches are massively dilated. Infundibular dilatation produces leftward hump. Dilated RV forms cardiac apex and RA is dilated.

Interpretation as pseudotruncus: Ascending aorta is dilated and right aortic arch is common. If pulmonary vascularity is not greatly diminished (moderate PS or abundant MAPCAs), it gives impression of truncus arteriosus.

Postcorrective surgery: There are sternal wires. Severe aneurysmal dilatation of infundibulum following transannular patch can be seen as hugely dilated MPA on X-ray. Calcification of conduit can also be appreciated.

Ebstein anomaly: Lung vascularity may be normal to severely diminished depending upon severity of lesion. Dilatation of RA is the most consistent finding and it is not unusual to have hugely dilated RA in cases of extreme forms of Ebstein anomaly. Infundibulum straightens out left heart border or makes a convex bulge. Dilated RA on right and infundibulum of left gives heart box like configuration.

Similar hugely dilated heart can also be found in cases of pulmonary atresia with intact IVS with severe TR and dilated RV **(Fig. 32)**.[10-13]

Tricuspid atresia: In cases of restrictive VSD and normally related great arteries, cardiac borders may be characteristic. Prominent superior counter is caused by dilated RA and appendage. Flat receding right heart border is caused by absent RV. Apex is formed by dilated convex LV and LA is small. Juxtaposition of atrial appendage may produce straightening of left heart border. Ascending aorta is large and lung vascularity may be diminished. If VSD is nonrestrictive, lung vascularity

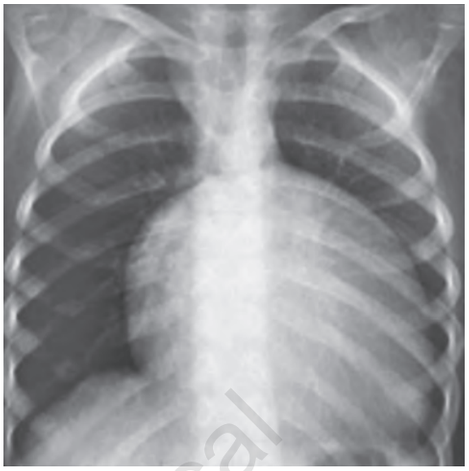

FIG. 32: Dilated heart with BOX like configuration.

is similar to large left to right shunt. In case of associated transposition of great arteries, MPA is posterior and vascular pedicle is narrow.[10-13]

Single ventricle: If outlet chamber is on left side, it produces localized hump on left heart border along with convexity of aorta to left or midline **(Fig. 28)**. Right-sided outlet chamber does not produce any margin, however, aortic convexity is to right. Vascular pedicle is narrow in case of TGA (aorta from outlet chamber and PA from main chamber) and huge flow across MPA and RPA produces waterfall sign. In PS, heart size is normal. If there is increased pulmonary blood flow, heart size is increased, which normalizes after development of pulmonary vascular disease or PA band.

Common arterial trunk: Pulmonary trunk is absent. Dilated LPA may produce left hilar comma which curves upward. Right aortic arch is seen in >50% as well as high transverse arch. Due to significant shunt, there is cardiomegaly. It regresses after development of pulmonary vascular disease. Significant truncal valve regurgitation can produce cardiomegaly and pulmonary venous congestion. Absent pulmonary artery produces reduced vascularity and smaller ipsilateral hemithorax. It is on same side as aortic arch in truncus, while it is on opposite side of aortic arch in case of TOF.

Pulmonary Atrioventricular Fistula (Fig. 33)[10-13]

Generally, there is no cardiomegaly. There are abnormal lung parenchymal densities cast by fistula themselves. Margins of these are sharp, but size may vary. They may be rounded or lobulated. They are connected to hilum by vascular pedicle which can be seen on X-ray. The Valsalva maneuver decreases size of fistula while Müller's maneuver increases it.

Sign of Previous Cardiac Intervention

Device closure:

- *Atrial septal defect* ***(Fig. 34)***: Device in generally retrosternal in position at against 4th to 6th intercostal space. It has two

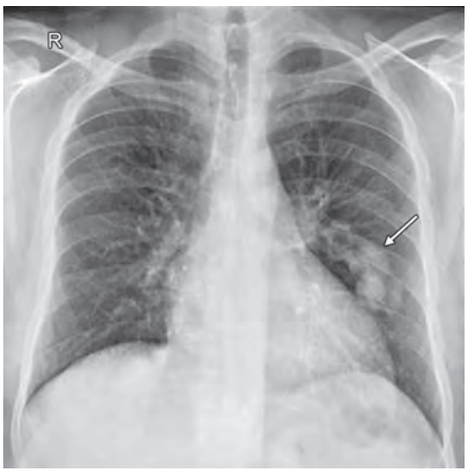

FIG. 33: Arrow indicates shadow produced by fistula.

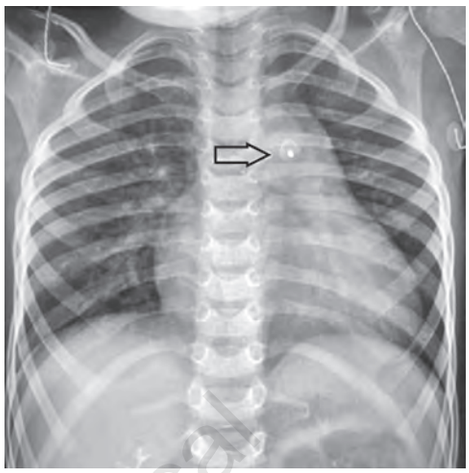

FIG. 35: Arrow indicates position of patent ductus arteriosus (PDA) device.

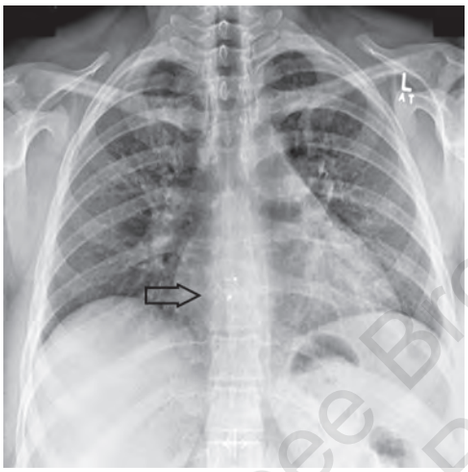

FIG. 34: Arrow marks position of ASD device. Note dense shadow of screw and knob. Mesh can be seen on high penetration image.

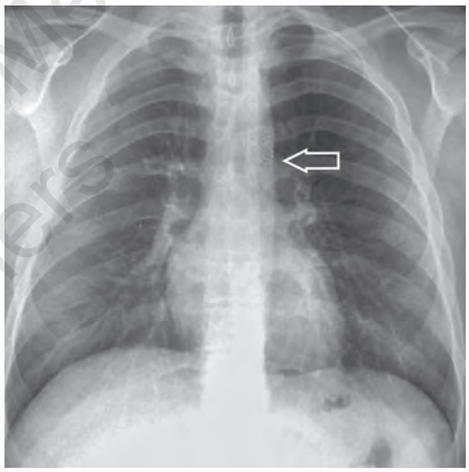

FIG. 36: Coarctation stent.

disks on either side of narrow waist as well as prominent radiopaque markers corresponding to screw and center point of LA disk. If device has embolized: (1) Orientation of device changes and (2) It is found in place like pulmonary artery, right ventricle, RA, or left atrium, etc.

- *Patent ductus arteriosus* ***(Fig. 35)***: Device in left parasternal at 4th vertebral level in a case of left-sided duct. Morphology of device may vary as per make. Embolized device may be found in aorta, branch pulmonary arteries.
- *Ventricular septal defect*: Depending upon type of VSD (perimembranous, mid-muscular or apical muscular), position of device varies.
- *Stents* ***(Fig. 36)***: As per site of implantation, stent can be seen in (1) RV to PA conduit: Left para or retrosternal for levocardia, and right side if dextrocardia, and on lateral film, it is anterior placed, (2) Branch pulmonary artery, (3) Coarctation of aorta **(Fig. 36)**: Left paraspinal against 4–5th vertebral body. In lateral projection, it is posterior structure over vertebral column, etc.

CONCLUSION

In conclusion, the ECG and X-ray provides a wealth of information fundamental to clinical assessment in CHD. Serial ECGs and X-rays may be of value in screening for hemodynamic ramifications of congenital anomalies particularly in obstructive lesions. Moreover, in certain pathologies like tetralogy of Fallot, individual measures and changing parameters provide clinically pertinent prognostic information for risk stratification. Finally, the ECG is also vital in diagnosing and characterizing a broad spectrum of brady- and tachyarrhythmias that are frequently encountered in CHD.

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CHAPTER 3

Approach to Echocardiography in Cyanotic Congenital Heart Disease

Nitin Rao, Suman Vyas, Rajesh Gudipati

ABSTRACT

Echocardiography (Echo) is one of the important tools in diagnosing cyanotic congenital heart disease (CCHD)— A segmental approach with appropriate age-specific probes is recommended. Echo in CCHD helps in diagnosis, planning appropriate surgical repair strategies, and in follow-up. Of late, surgical outcomes in CCHD have vastly improved owing to earlier and accurate diagnosis mainly by Echo. Among the standard views, the subcostal (long- and short-axes) view, apical, and parasternal views outline the outflow tracts, the ventricular septal defects (VSDs), and pulmonary atresia (PA) anatomy. The suprasternal view outlines the arch and descending aorta/collaterals/certain forms of total anomalous pulmonary venous connection (TAPVC). The parasternal short axis view is vital for imaging the right ventricular outflow tract (RVOT)/PA anatomy/malposed great arteries. Additionally, right precordial views in dextrocardia and transesophageal echocardiography (TEE) may also be needed. Additional imaging modalities such as computed tomography (CT) angiography/magnetic resonance imaging (MRI)/cardiac catheterization may be required in planning operability.

INTRODUCTION

Echocardiography (echo) is the mainstay of diagnosis in congenital heart disease (CHD) and is vital in cyanotic heart disease in outlining pulmonary blood flow/admixture lesions/ventricular function/collaterals as well as in planning surgery and in postoperative follow-up.

The incidence of CHD has remained the same over the years but with improved diagnosis and excellent outcomes, we now have quite a few adult survivors operated in childhood–the GUCH (grownup CHD) cases.

SEGMENTAL APPROACH

As with any CHD, the echo approach to any cyanotic congenital heart disease (CCHD) is a segmental approach to the heart. The echo evaluation starts with assessing the situs (visceral + cardiac) and then proceeds to the other levels–venous connections/atria/atrioventricular (AV) valves/ventricles/great arteries and outflow tracts.

There are a few standard views in Pediatric Cardiology and these include: Subcostal (both long and short axes), Apical four chambers, parasternal—long and short axes—and suprasternal views. Transducers are always of a higher frequency, generally >5 Hz.

Subcostal view is very informative, especially in children. We start with assessing the situs and then proceed to a detailed segmental analysis. The subcostal view outlines the venous connections, the AV valves and the outflow tracts very well—especially the right ventricular outflow tract details that may sometimes be obscured in the parasternal short-axis view. The RVOT—valvar, subvalvar, and supravalvar regions—are well outlined in subcostal views, pulmonary venous anomalies, especially the entire findings of an infracardiac total anomalous pulmonary venous connection (TAPVC) may be obtained in a subcostal view itself.

The apical four-chamber view outlines both atria, ventricles, the septae, the outflow tracts, and all AV valve pathologies are well differentiated in this view.

The parasternal short-axis view outlines at different levels—the great artery relationship, the right ventricular outflow tract (RVOT) including the pulmonary valve, main pulmonary artery and branches, and the mitral valve—enface view (especially important in AV canal defects). The parasternal long axis (though relied upon more in adults than in children) outlines the ventricular septal defect (VSD), the left ventricular outflow tract (LVOT), and aortic override in tetralogy of Fallot (TOF) and also the routability of the left ventricle (LV) to the aorta in complex malpositions. Besides, most M mode measurements are recorded in this view.[1]

The suprasternal view is very informative for the aorta—for arch hypoplasia/coarctation/sidedness/double aortic arch/vascular slings, etc. In LVOT obstructions, the gradient across the LVOT is best assessed from the suprasternal view. Occasionally, the left pulmonary artery may be seen better in this view rather than in the parasternal short-axis view. Anomalous venous channels, especially a vertical vein in TAPVC or a persistent left superior vena cava (SVC), are outlined well. Also, BT shunts, the course/origin, insertion, and evidence of narrowing, will be outlined here. In cases with a single ventricle repair strategy (after a Glenn shunt or a Fontan completion), imaging the SVC may be difficult and the probe may have to be angulated more toward the right almost in the supraclavicular area.

Additionally, in cases with dextrocardia, imaging has to be done through right thoracic views.

Of late, transesophageal echocardiography (TEE) has been used extensively in the evaluation of CCHD. Due to the complex anatomic and spatial relationships, high-resolution, 5 and 7.5 MHz biplane or multiplane probes, should be used for adequate assessment. Longitudinal scan planes best delineate the right ventricle (RV) and LV OT and the great arteries. Transverse plane four-chamber views outline the AV septum, AV valves, especially any straddling or commitment to either ventricle. The basal short-axis scans demonstrate the great artery relationships and the proximal pulmonary arteries.

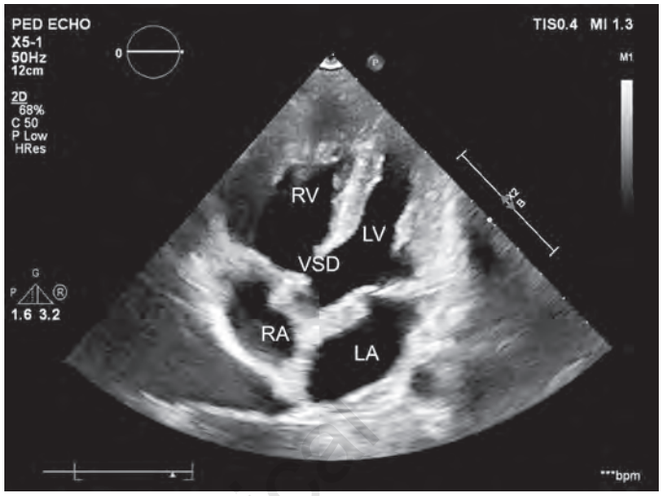

FIG. 1: TOF: Apical four-chamber view showing malaligned VSD and aortic override.
(LV: left ventricle; TOF: tetralogy of Fallot; VSD: ventricular septal defect)

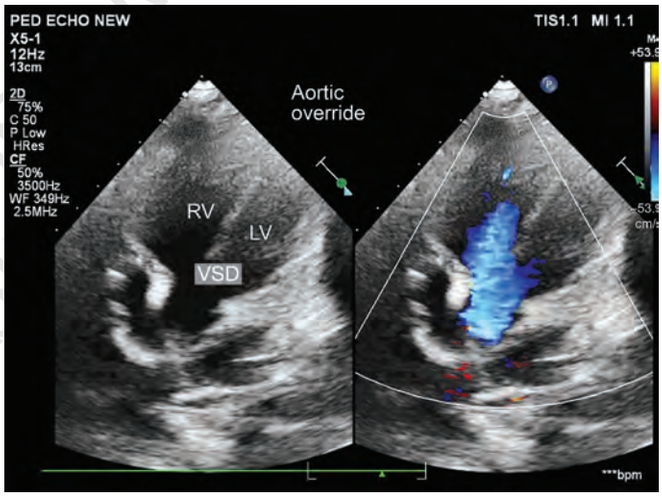

FIG. 2: TOF: Apical four-chamber view showing aortic override with a biventricular origin.
(TOF: tetralogy of Fallot)

SPECIFIC CONDITIONS

Tetralogy of Fallot

Tetralogy of Fallot is the most common CCHD seen across all age groups and it is the CCHD with the longest survival. Over the decades, improved surgical techniques have resulted in excellent outcomes for many adult survivors.

The four essential components of TOF are:

1. Malaligned large nonrestrictive subaortic VSD
2. Overriding of the aorta
3. Right ventricular outflow obstruction—at various levels
4. Right ventricular hypertrophy

The variable features of TOF include: Unbalanced ventricles (smaller LV or RV), additional VSDs, straddling AV valves, discontinuous pulmonary arteries, or branch pulmonary artery stenosis. Other variations include coronary abnormalities and a right aortic arch [arch sidedness is essential information when planning a Blalock–Taussig (BT) shunt]. Also, patent ductus arteriosus (PDA) and other additional sources of pulmonary blood supply [major aortopulmonary collateral arteries (MAPCAs)] usually in extreme TOF cases.[2]

Views

The subcostal and apical four-, five- chamber views outline the ventricles, the large malaligned VSD and the RVOT obstruction **(Figs. 1 to 3)**. Branch pulmonary arteries are better seen on the parasternal short-axis view or sometimes in suprasternal imaging. With branch pulmonary artery stenosis, the probe may have to be angled in superior/inferior direction.

The parasternal long-axis view in TOF demonstrates the large VSD with a bidirectional shunt and aortic override, any associated AR may be delineated **(Fig. 4)**. Tilting the probe inferiorly outlines the tricuspid valve and RV inflow while a superior; cranial tilt outlines the RVOT including the infundibular area, pulmonary valve, and proximal main pulmonary artery.[3]

The parasternal short axis view and subcostal views also outline the RVOT and main pulmonary artery and obstruction at various levels whether infundibular, valvar, or supra valvar **(Figs. 5 and 6)**. In neonates, the RVOT gradient is usually underestimated (due to high neonatal pulmonary vascular resistance and any PDA) and a follow-up echo should be done. The confluence and pulmonary arteries will also be outlined in the parasternal short-axis view with a slight caudal tilt and it is essential to record any bifurcation or branch pulmonary artery stenosis **(Fig. 7)**. Coronary artery crossing the RVOT is also best imaged in the parasternal short-axis view.[4] The origin and course of both coronary arteries should be noted, especially for

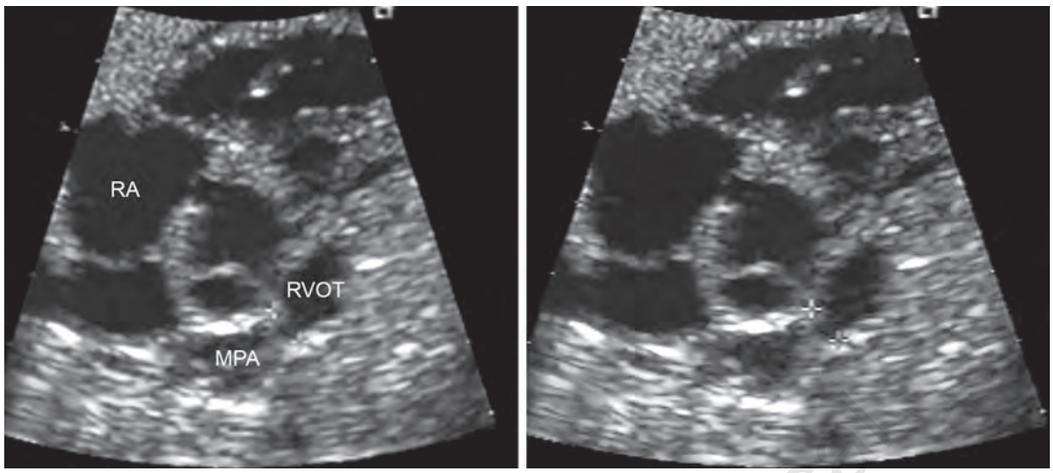

FIG. 3: TOF: Subcostal view showing RVOT obstruction.
(RVOT: right ventricular outflow tract; TOF: tetralogy of Fallot)

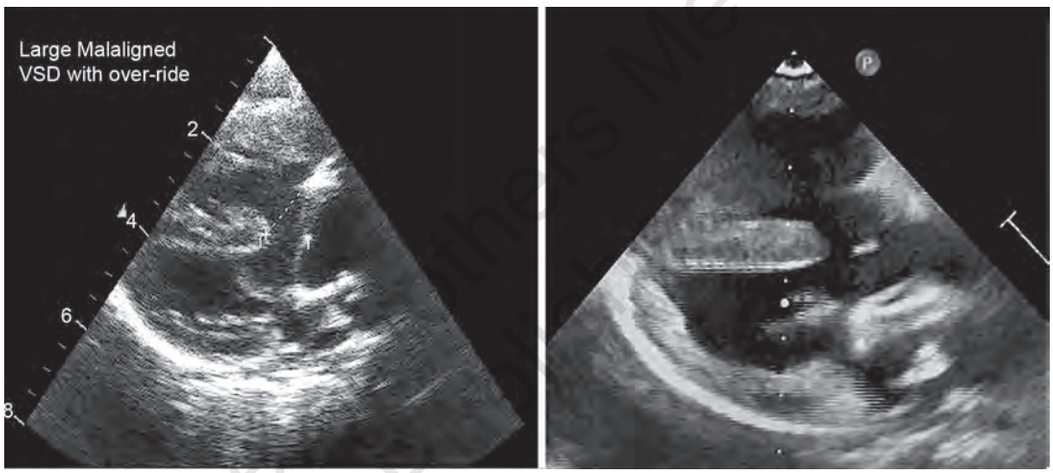

FIG. 4: TOF: Plax views showing malaligned VSD and aortic override.
(TOF: tetralogy of Fallot; VSD: ventricular septal defect)

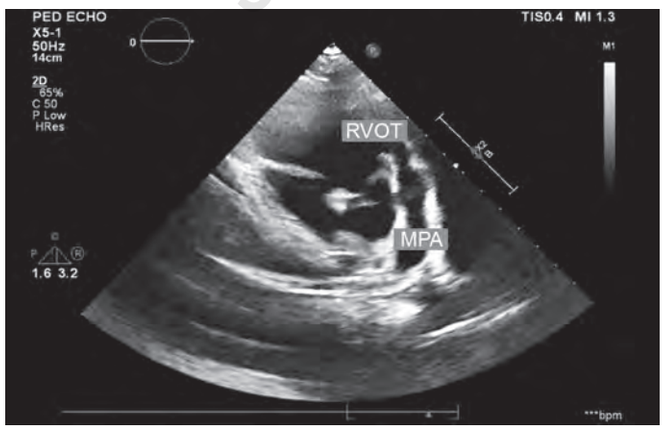

FIG. 5: TOF: Modified short-axis view showing a narrowed RVOT and main pulmonary artery.
(RVOT: right ventricular outflow tract; TOF: tetralogy of Fallot)

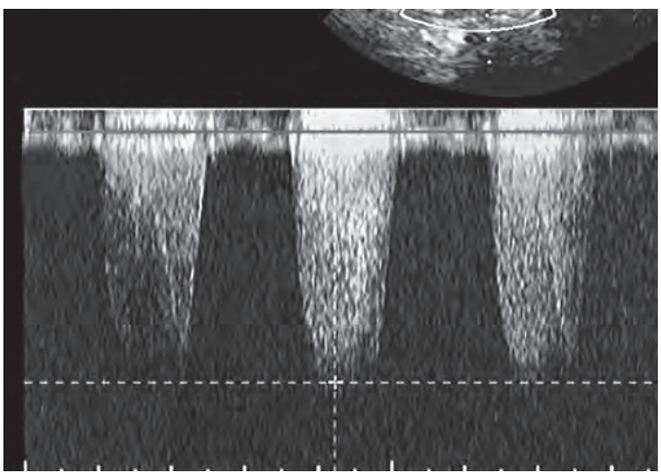

FIG. 6: TOF: RVOT gradient—valvar and infundibular.
(RVOT: right ventricular outflow tract; TOF: tetralogy of Fallot)

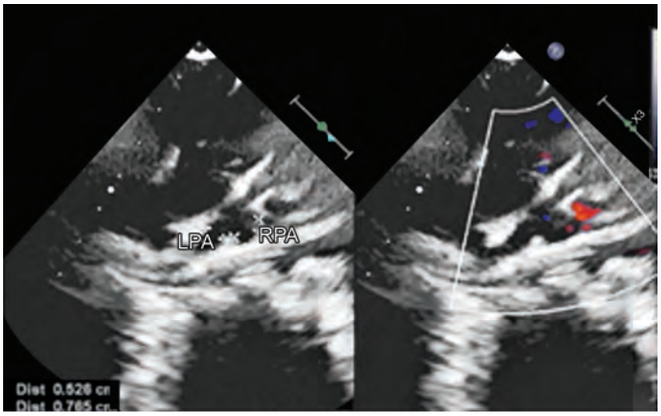

FIG. 7: TOF: Modified short-axis view showing branch pulmonary artery anatomy.
(TOF: tetralogy of Fallot)

any vessel crossing the infundibular area which will preclude placing a transannular patch at the time of intracardiac repair. Echo evaluation has a sensitivity of 82% and a specificity of 99% in detecting coronary anomalies involving the RVOT.

A PDA will be seen in the short-axis or "ductal" view but generally, in TOF, a PDA tends to be more "vertical" (i.e., arising from the inferior surface of the arch of the aorta) more so in cases with severe pulmonic stenosis/PA and this is best seen in the suprasternal view. A BT shunt, if at all, is also seen in this view but it may be necessary to sweep the probe from right to left to profile this shunt.

The high parasternal and suprasternal views outline the pulmonary arteries and aorta, respectively. Size and continuity of the pulmonary arteries should be noted and any additional collateral flows should be looked for, especially a "vertical" PDA. The sidedness of the aortic arch is important, especially when a BT shunt is planned.

In postoperative patients, residual VSDs, RVOT gradients, pulmonary regurgitation, RVOT dilatation, and the branch pulmonary and biventricular function need assessment.

Pulmonary Atresia and Ventricular Septal Defect

This is an extreme form of TOF, and the pulmonary anatomy is more complex than in TOF. PA and VSD accounts for about 2% of all CHDs and is one of the common causes of cyanosis in the neonate. There is a genetic preponderance and mortality in untreated infants is almost 85% at 1 year.

The features include an atretic RVOT (membranous or muscular), a large malaligned VSD, a hypoplastic or atretic main pulmonary artery, hypoplastic branch pulmonary arteries (pulmonary arteries may be of good size if there are large MAPCAs) and PDA or collaterals (MAPCAs) supplying the pulmonary arteries. The pulmonary arteries may be discontinuous also with one branch PA continuing from PDA or MAPCA. Additionally, there may be multiple VSDs, ASD, or sometimes the ventricles may be unbalanced.

Echocardiography usually provides the initial diagnosis but a cardiac catheterization/computed tomography (CT) angiogram is frequently necessary to delineate the pulmonary arterial tree. Two-dimensional echo imaging is similar to that of TOF.

The parasternal long-axis view shows a large aortic valve overriding the malaligned VSD. The infundibular septum is anteriorly malpositioned and fused with the free wall and there is no separate outflow from the RV.

The apical four-chamber view outlines the malaligned VSDs, the large RV, and additional VSDs if any. Tricuspid regurgitation may be significant. The atretic RVOT is visualized as the probe is tilted more anteriorly toward the RVOT.

The parasternal short-axis view demonstrates the RVOT, the main pulmonary artery, the confluence and branch pulmonary arteries (if formed). On color Doppler imaging, flow seen in branch pulmonary artery (probably due to PDA or collaterals) should not be mistaken for forward flow across RVOT. Spectral Doppler will help differentiate forward systolic flow from continuous flow from collaterals.

The suprasternal view and high parasternal windows (both right and left) provide important information about the size and status of the proximal pulmonary arteries. This is difficult when the pulmonary arteries are nonconfluent/ extremely hypoplastic, or when multiple collaterals are present in the area of confluence; in such cases, color flow imaging may enhance the evaluation of PAs and collaterals. Commonly the PDA is "vertical," and this needs detailed evaluation when planning for ductal stenting (whether in line with the left subclavian artery or left common carotid artery while planning a PDA stent). Regardless of Echo data, angiography is required for a complete assessment before a final biventricular repair. An unusual collateral (indirect PDA from neck vessels) may be easily catheterized if there is prior information from echo. The suprasternal view also defines the sidedness and branching pattern of the aortic arch. A right aortic arch is very common in this subset.[5]

Double-outlet Right Ventricle

Double-outlet right ventricle (DORV) encompasses various features with clinical presentation varying from that of VSD to TOF to transposition of the great arteries (TGA). The frequency is approximately 0.09 cases per 1,000 births.

There are four types of VSDs in DORV—subaortic/ subpulmonic/doubly committed and remote (distant from both semilunar valves and may represent a posterior VSD/AV defect VSD/isolated muscular VSD).

There are four types of great artery relationships at the semilunar valve level in DORV: right posterior aorta (NRGA)/ right lateral aorta (side by side relationship)/right anterior aorta (D malposed)/left anterior aorta (L malposed).

Therefore, there are 16 possible types of DORV—depending on the location of the VSD and the relationship of the Great arteries—but the most common types are: DORV, large VSD, unprotected pulmonary blood flow (hemodynamics resembling a large VSD) *or* DORV, large subaortic VSD, pulmonic stenosis (similar to TOF).

Echocardiographic diagnosis in various views (apical four chamber, subcostal, parasternal short- and long-axis, suprasternal views) should profile the great arteries (origin and relation), outflow obstruction, VSD, and associated lesions

(commonly coarctation of the aorta in DORV with unprotected pulmonary blood flow–Taussig–Bing anomaly).
Three observations have been noted for the diagnosis:
1. Origin of both great arteries from the anterior RV
2. Mitral–semilunar valve discontinuity
3. Absence of LV outflow other than the VSD.

A short-axis view from apex to base shows a commitment of great arteries to the RV cavity. The parasternal long axis view shows mitral–semilunar valve discontinuity with the presence of a muscular conus separation. This is seen as a dense echo (fibromuscular) or as a muscular conus separating the two valves). This echo feature differentiates DORV VSD with PS from TOF.

Ventricular septal defect: Typical subaortic or subpulmonic defect can be seen by parasternal or subcostal long- and short-axis views, which also confirm the VSD–great artery relationships. Doubly committed defects appear equally committed to both arteries. Remote defects are usually part of complete AV septal defects (with an inlet VSD), but the defect may also be an isolated one or there may be multiple muscular VSDs. Complete AV septal defects are best outlined in the apical or subcostal four-chamber views.

Double-outlet right ventricle may be associated with multiple AV valve anomalies including complete atrioventricular septal defect (AVSD), isolated anterior mitral leaflet (AML) cleft, and straddling of the left or right AV valves. Apical and subcostal four-chamber views and short-axis views easily demonstrate these abnormalities. It is crucial to accurately delineate the location and points of insertion of the chordae since abnormal insertions and may not allow the LV to be routed to the aorta. Extreme straddling of the AV valves may not permit a biventricular repair. Other associated anomalies such as juxtaposed atrial appendages, atrial septal defect (ASD), anomalous venous connection and coarctation should also be looked for. Multiple views and planes must be used to exclude these associations.

Transesophageal echocardiography (TEE) has been used extensively for diagnosing associated features in complex DORV. Transverse plane four-chamber view/basal short axis and longitudinal scans demonstrate the great artery relationship, outflow tracts, and proximal pulmonary arteries. Also, ASDs and venous anomalies can be picked up.[6,7]

Pulmonary Atresia and Intact Ventricular Septum

This disorder is characterized by striking heterogeneity of the right ventricle, its inlet and its functional size. Besides, many patients have connections between the right ventricle and subepicardial coronary arteries (RV-dependent coronary circulation) and a predisposition for a peculiar coronary artery circulation. Prognosis appears to relate to the nature of the coronary circulation in the RV at high pressure, or alternatively the presence of severe tricuspid regurgitation in the setting of a low-pressure RV. The incidence of PA and intact ventricular septum (IVS) is reported to be 4.1 per 1,00,000 live births.

Echocardiography: Echo and angiocardiography (angiography) both are required for a complete evaluation of this disorder.

An echo should outline the atretic RVOT, the small RV, and the presence of right ventricular to coronary artery connections. This is very important if one is considering establishing the continuity between the RV and the pulmonary circulation. Presently delineation of these connections is difficult on echo and therefore, angiocardiography is essential in all infants prior to ventricular decompression.

It is important to outline the interatrial septum as a neonate relies on obligatory right to left shunting to maintain the cardiac output. The IAS is readily seen in the subcostal view or apical four chamber view with 2D echo imaging or Doppler interrogation. Rarely, the IAS may be aneurysmal.

Tricuspid valve morphology should also be assessed. It may be challenging to detect forward flow across an extreme stenotic, obstructive tricuspid valve and occasionally, tricuspid regurgitation may give a clue about patency.

The right ventricular size, which usually corresponds to the dimension of the tricuspid annulus, can be imaged in subcostal and precordial views. Hypoplasia, if present, may involve all components of the right ventricle. It is important to distinguish anatomic from functional pulmonary atresia (where there is a lack of forward flow due to high pulmonary artery pressure with poor RV function or very severe tricuspid regurgitation—a classic example is Ebstein's anomaly of the tricuspid valve with Severe tricuspid regurgitation and dysfunctional RV, with a minimal forward flow across the RVOT). This differentiation may be possible if Doppler detects systolic regurgitation of the pulmonary valve (caused by the jetting effect of the PDA against the valve). Another technique is Doppler echo during positive-pressure ventilation, which transiently results in the opening of the pulmonary valve and forward Doppler flow.[8,9]

Total Anomalous Pulmonary Venous Connection

Anomalies of the pulmonary veins vary widely in anatomy and clinical presentation and are influenced by other associated cardiac lesions too. Surgical outcomes for TAPVC have now improved tremendously, especially with early prenatal diagnosis. In TAPVC, all four pulmonary veins drain anomalously to the right side of the heart either individually or through a common chamber that drains via a vertical vein to some right cardiac chamber. Consequently, the right chambers are dilated with a very small left atrium. Other associated cardiac lesions (VSD and coarctation) may complicate the clinical course.

The incidence of TAPVC in various studies ranges from 0.4 to 0.5%. There is a marked male preponderance in cases of infracardiac TAPVC-draining to the portal vein but not with other types and connections. The classification of TAPVC, proposed by Darling and others, as per the site of drainage is as follows:

- *Type I TAPVC (supracardiac)*: The pulmonary veins form a venous confluence that usually drains via a vertical vein to the left innominate vein (LIV). Other drainage sites include the SVC and azygos veins (AZs).
- *Type II TAPVC (cardiac)*: The pulmonary veins connect to the heart, either individually or through a confluence either to the right atrium (RA) directly or to the coronary sinus (CS) **(Figs. 8 and 9)**.

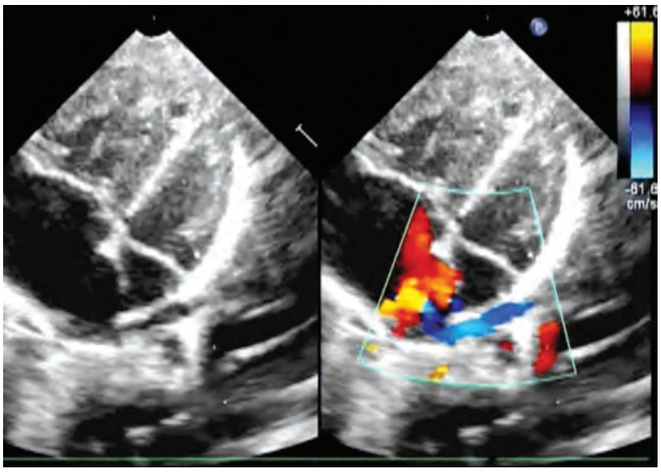

FIG. 8: Cardiac TAPVC: Apical four-chamber view showing a small LA, dilated RA, and common chamber draining into RA.

(LA: left atrium; RA: right atrium; TAPVC: total anomalous pulmonary venous connection)

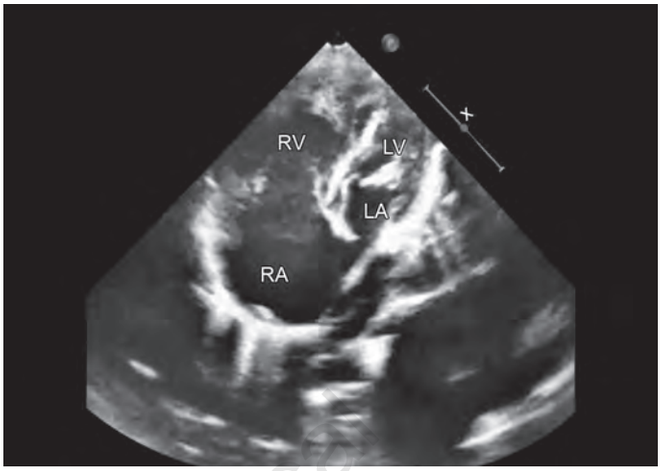

FIG. 10: TAPVC: Apical four-chamber view showing a small LA and dilated RA/RV.

(LA: left atrium; RA: right atrium; RV: right ventricle; TAPVC: total anomalous pulmonary venous connection)

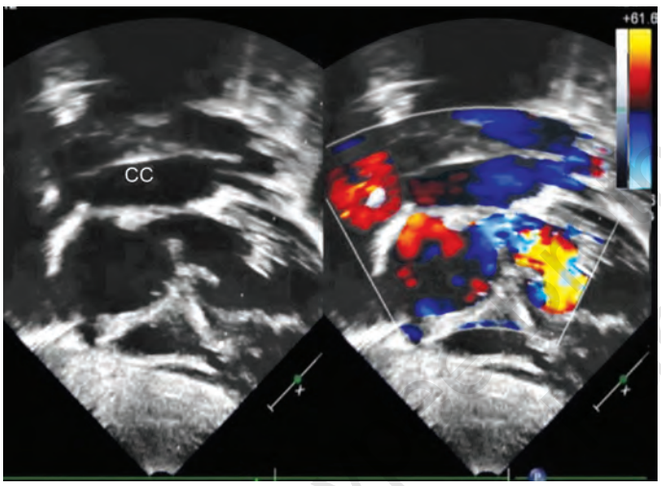

FIG. 9: TAPVC: Apical four-chamber (inverted view) showing a common chamber behind the LA.

(LA: left atrium; TAPVC: total anomalous pulmonary venous connection)

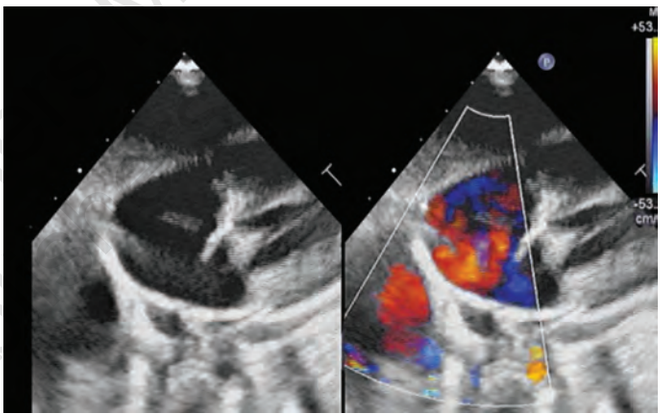

FIG. 11: TAPVC: Subcostal four-chamber view showing a small LA, dilated RA, and ASD shunting right to left.

(ASD: atrial septal defect; LA: left atrium; RA: left atrium; TAPVC: total anomalous pulmonary venous connection)

- *Type III TAPVC (infracardiac)*: The anomalous connection occurs at the infracardiac level below the diaphragm and drains into the portal veins, ductus venous, hepatic veins, or inferior vena cava (IVC).
- *Type IV TAPVC (mixed pattern)*: The pulmonary veins drain at least two different locations.

Total anomalous pulmonary venous connection may be obstructed or nonobstructed and this will influence the clinical presentation, the management strategy, and the surgical outcome. Obstruction could be extrinsic or intrinsic. Common sites of obstruction include compression of the ascending vertical vein between the left bronchus and left pulmonary artery (hemodynamic vise common in supracardiac TAPVC) or compression of the descending vertical vein at the level of the diaphragm (infracardiac TAPVC). There may be other levels of obstruction too, as at the portal vein, at the site of drainage in the innominate vein or SVC, or at times, just a small, restrictive ASD/patent foramen ovale (PFO) could be a potential site. Rarely, the individual pulmonary veins may be inherently stenotic.[10]

Echocardiographic Imaging in TAPVC

The essential features to note in a TAPVC are:

Small-sized left artery (LA), dilated RA, pulmonary veins not draining to the LA and an ASD shunting right to left **(Figs. 10 and 11)**.[11,12] Occasionally, a dilated CS in a cardiac TAPVC may be mistaken as a primum ASD shunting left to right. However, the additional ASD/PFO with a right-to-left shunt will clinch the diagnosis.

The SVC, IVC, or coronary sinus will be dilated depending on the site of drainage of the pulmonary veins, common chamber, or the confluence.

It is essential to identify the site of drainage of the pulmonary veins, the adequacy of the ASD/PFO, tricuspid regurgitation jet

and pulmonary hypertension, ventricular function (especially right ventricular) and possible obstruction in the vertical vein/portal vein/SVC drainage/confluence or even individual pulmonary vein stenosis **(Figs. 12 to 14)**.

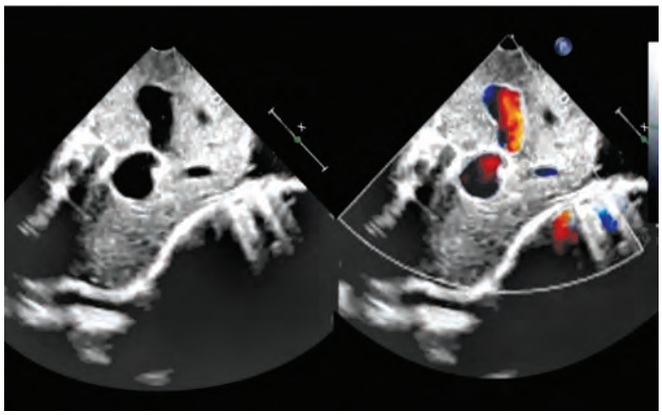

FIG. 12: Infracardiac TAPVC: Multiple "lakes" in the liver.
(TAPVC: total anomalous pulmonary venous connection)

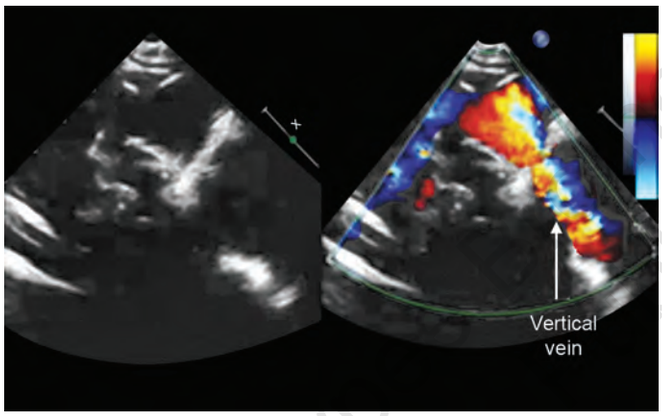

FIG. 13: Supracardiac TAPVC: Suprasternal view showing left-sided ascending vertical vein.
(TAPVC: total anomalous pulmonary venous connection)

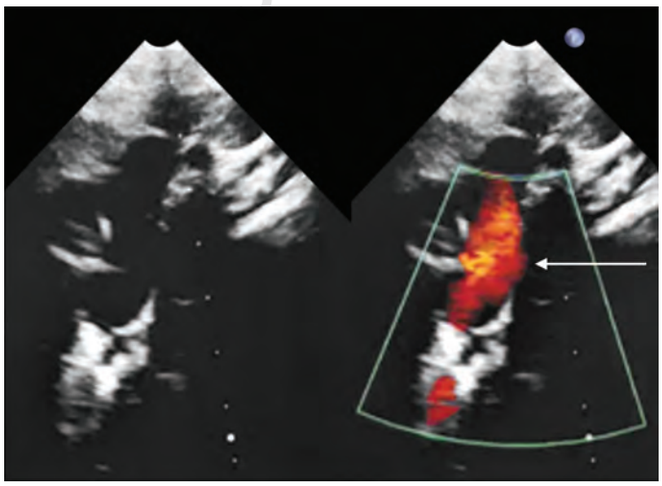

FIG. 14: TAPVC : Suprasternal view showing right-sided ascending vertical vein.
(TAPVC: total anomalous pulmonary venous connection)

In supracardiac TAPVC, the SVC will be dilated with a torrential flow, whereas the IVC will be equally dilated in an infracardiac TAPVC. These subtle clues help in identifying potential sites of drainage.

If the subcostal view shows three blood vessels at the level of the diaphragm, it is usually a descending vertical vein (of an infracardiac TAPVC) in addition to the IVC and aorta. Infracardiac TAPVC is invariably obstructed and the dilated vertical vein/IVC and portal vein radicles give a characteristic appearance of "multiple lakes" in the liver that is easily distinguished.

The individual pulmonary veins should be identified as far as possible, and they should be traced to the common chamber, or vertical vein and sites of drainage should be sought. The vertical vein course may sometimes be tortuous (or meandering) and every attempt should be made to trace the vein to either SVC or IVC.

Right atrium/RV will be dilated with severe tricuspid regurgitation and pulmonary hypertension.

A checklist for TAPVC echo imaging:

- Identify each pulmonary vein and its connection/drainage—partial or total and any obstruction. Note the diameter of each pulmonary vein, the smallest diameter of the pulmonary venous confluence and its proximity to the left atrium.
- Adequacy of ASD and the direction of the interatrial shunt
- RV volume overload features—tricuspid valve annulus diameter, diastolic septal flattening, and RV size.
- RV pressure—tricuspid regurgitation and pulmonary regurgitation jet velocity, systolic septal configuration
- LA and LV volumes
- Associated cardiac anomalies—PDA/VSD/anomalies of the AV valves or semilunar valves/anomalies of the aortic arch and systemic venous anomalies

Postoperative follow-up echo should record any gradient at the anastomosis site/ tricuspid regurgitation, pulmonary hypertension and consequently RV function/individual pulmonary vein stenosis if discernible/LV function/pericardial effusion/other associated anomalies.[13]

D-transposition of Great Arteries

D-transposition of great arteries (D-TGA) is a commonly encountered CCHD with excellent outcomes if operated in time.

The essential feature is ventriculoarterial discordance, i.e., the left ventricle gives rise to the pulmonary artery while the aorta takes origin from the right ventricle. The posterior ventricle (LV morphology) gives rise to the pulmonary artery, which acutely angulates toward the lungs, and the aorta originates from the anterior ventricle (RV morphology). The great arteries course in parallel alignment (normally they cross each other). Their course can be profiled in different views. Other variable features include VSDs (single/multiple)/PDA/outflow tract obstruction/hypoplasia of the aortic arch/straddling AV valves/unbalanced ventricles, etc.

A detailed segmental analysis is the key to a diagnosis of TGA:

- Venous connections/atrial septum for interatrial communication, AV valve morphology and function, determination of biventricular size/function and detailed

evaluation for VSD—single or multiple defects/location and size/restriction to flow/direction of flow, etc. Ventriculoarterial connections should be profiled in detail the relation of the great arteries at the level of the semilunar valves, semilunar valve anatomy and function (e.g., stenosis or regurgitation), determination of presence and severity of outflow tract obstruction; if present, mechanism of obstruction. Coronary artery anatomy, presence of a PDA and evaluation of the aortic arch for sidedness, and arch hypoplasia/coarctation are essential.

- *Assessment of the atrial septum and ductus arteriosus*: IAS is outlined in the subcostal (subxiphoid) view to assess the presence, size, and adequacy of the defect and the PDA can be examined from parasternal and suprasternal views.
- *Characterization of coexisting anomalies*: VSD number, size, location, and type of VSD/LV outflow tract obstruction—severity and level—/aortic arch-sidedness and presence of coarctation/evaluation of AV valves/semilunar valves—morphology and function
- *Delineation of coronary artery anatomy*: Coronary artery anatomy in patients with TGA is highly variable, and this can affect surgical outcomes. In the "usual" arrangement, the right coronary artery (RCA) arises from the right sinus of Valsalva and the left main coronary artery from the leftward sinus, which then branches into the left anterior descending (LAD) and circumflex (Cx) arteries. Occasionally, the Cx arises from the RCA , in which cases it courses behind the pulmonary artery or there may be a single RCA. Rarely other anatomic patterns are encountered.
- *Assessment of chamber size, systolic function, and determination of left ventricular preparedness*

In infants with simple transposition, the common echocardiographic parameters considered to ensure the likelihood of a good outcome after the arterial switch operation (ASO) are LV muscle mass >35 g/m^2 and posterior wall thickness > 3.5 mm. Also, the shape of the IVS is indicative, the LV is considered prepared for an ASO if it is circular with the convexity of the IVS toward the RV on short-axis imaging of the ventricles. Besides, the presence of a PDA or LVOT obstruction helps preserve LV morphology.[14,15]

Imaging Transposition of Great Arteries

In the subcostal view, the transducer is swept in an oblique coronal plane to demonstrate the venous connections, the atrial septum, AV and ventriculoarterial connections and alignments, and the great vessels.

As the transducer is swept from posterior-inferior to superior-anterior, the main pulmonary artery is seen originating from the LV and further anteriorly, the aorta from the rightward and superior aspect of the RV. Coronary artery origin from the aortic root helps to identify the aorta. Rotating the transducer clockwise ~90° to the ventricular short axis (oblique sagittal plane) demonstrates the superior-inferior and anterior-posterior relations of the cardiovascular structures. The transducer is swept from right to left, beginning at the bicaval view and ending at the level of the ventricular apex. This sweep outlines the connection of the right upper pulmonary vein to the left atrium, the atrial septum, and the anatomy of the atrioventricular valves and their attachments and the outflow tracts of both ventricles. In TGA, this view demonstrates the parallel course of the great arteries **(Fig. 15)**. Color Doppler interrogation outlines the septae, valve function, outflow tract obstruction, and the PDA. Evaluation of the atrial septum outlines the location and size of interatrial communications and the direction and velocity of blood flow. In most patients, atrial level flow is from left to right.

The apical four-chamber which outlines the ventricular inflow/outflow tracts/IVS and is ideal for assessing the AV valve morphology and function **(Figs. 16 to 19)**.

In the parasternal long-axis view, the parallel course of the great arteries can be imaged longitudinally in the same plane (similar course of arteries in double-outlet right ventricle and congenitally corrected TGA). This view also demonstrates the fibrous continuity between the mitral and pulmonary valves. The aortic valve is seen anterior to the pulmonary valve and is supported by an infundibulum.[14,15]

The parasternal short-axis view shows the relationships between the semilunar valves and great vessels. Most commonly,

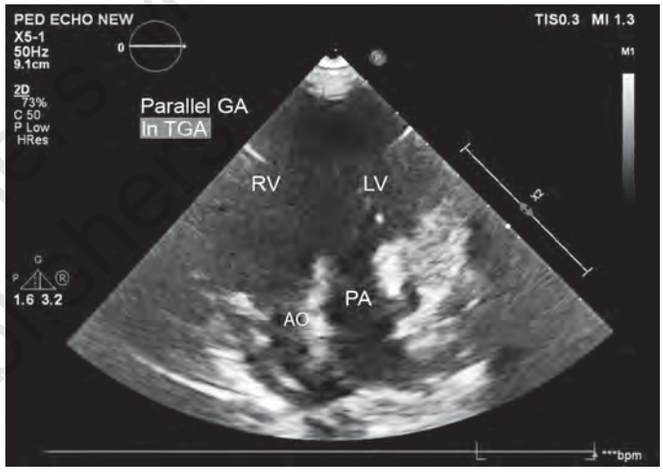

FIG. 15: DTGA: Parallel great arteries, D-transposed.
(DTGA: dextro-transposition of great arteries)

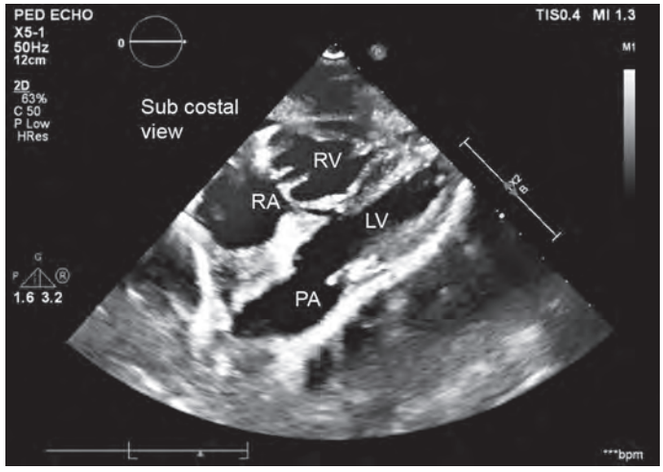

FIG. 16: D-TGA: Subcostal view showing pulmonary artery arising from LV.
(DTGA: dextro-transposition of great arteries; LV: left ventricle)

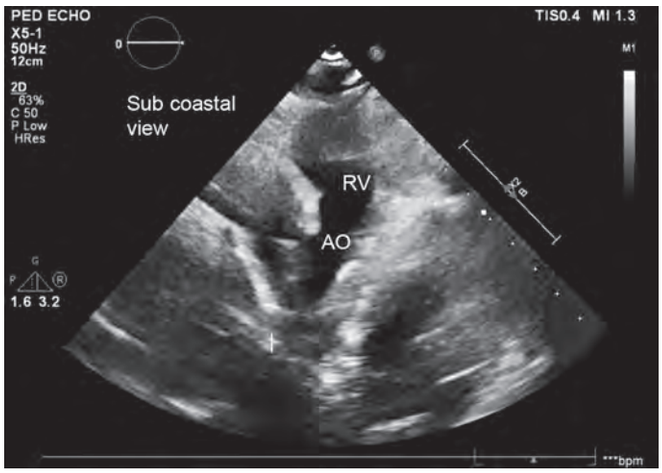

FIG. 17: D-TGA: Subcostal view showing AO arising from RV.
(AO: aorta; DTGA: dextro-transposition of great arteries; RV: right ventricle)

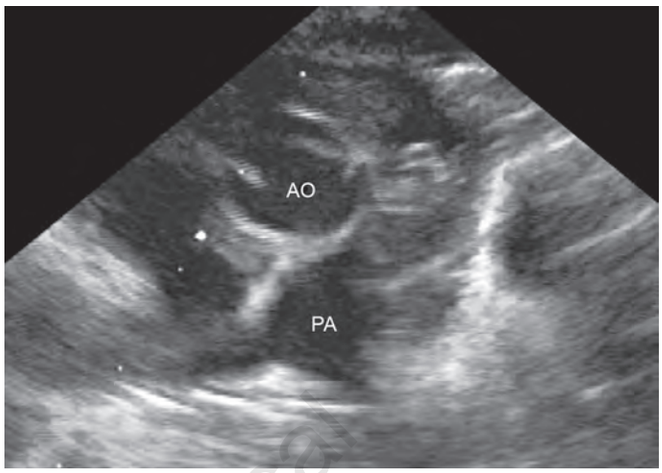

FIG. 20: D-TGA: Parasternal short-axis view showing AO to the left and anterior to pulmonary artery.
(AO: aorta; DTGA: dextro-transposition of great arteries)

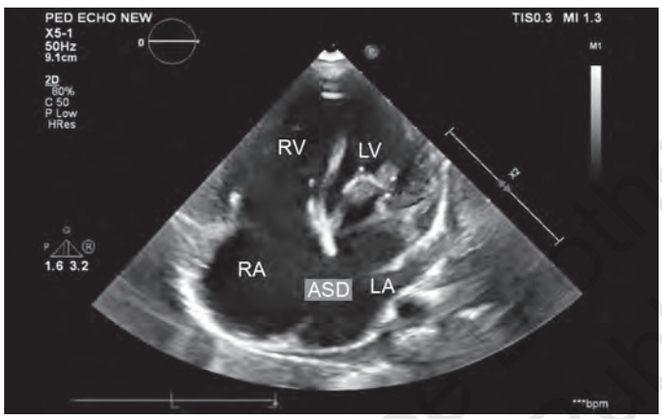

FIG. 18: D-TGA: Apical four-chamber view showing large ASD.
(ASD: atrial septal defect; DTGA: dextro-transposition of great arteries)

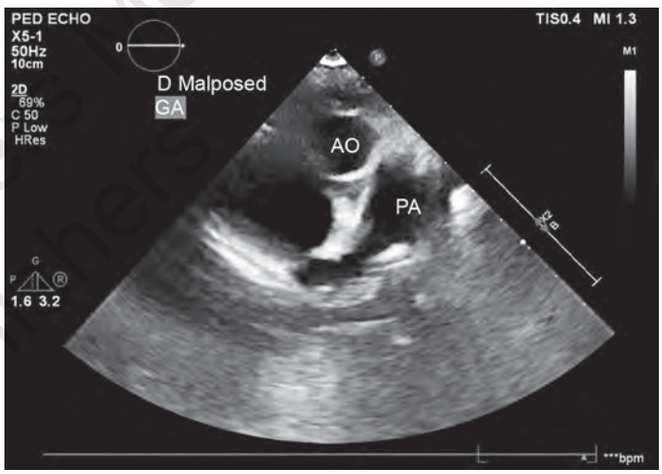

FIG. 21: D-TGA: Parasternal short-axis view showing AO to the left and anterior to pulmonary artery.
(AO: aorta; DTGA: dextro-transposition of great arteries)

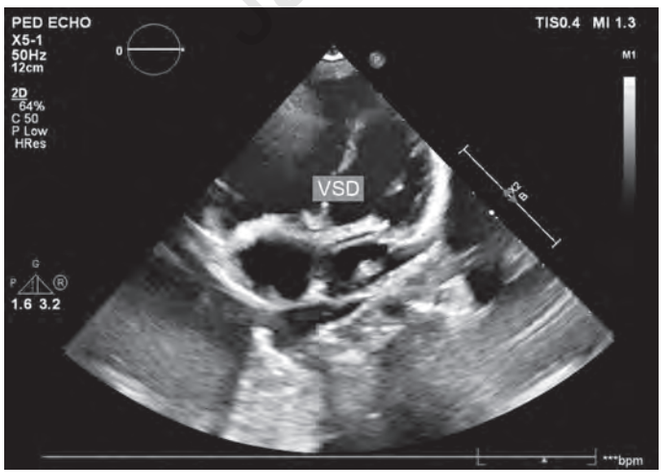

FIG. 19: D-TGA: Apical four-chamber view showing VSD.
(DTGA: dextro-transposition of great arteries; VSD: ventricular septal defect)

the aortic valve is anterior and to the right of the pulmonary valve but other relationships (e.g., side-by-side, anterior, leftward) are possible. A high left parasternal position often optimizes this view **(Figs. 20 and 21)**. In most patients, it is possible to obtain an image where the commissures between aortic and pulmonary valve leaflets can be viewed simultaneously. This is useful for assessing commissural alignment between the valve leaflets—surgical implications for coronary transfer during the ASO.

Assessment of biventricular size and function is essential (in multiple views) and this includes ventricular dimensions, wall thickness, and systolic and diastolic performance measures.

On follow-up after ASO, patients should be monitored for biventricular function, outflow tract obstruction (especially at the anastomosis) and semilunar valve regurgitation, mainly aortic.

Univentricular Hearts

This group includes all patients with unbalanced ventricles—tricuspid atresia, mitral atresia, PA, IVS, AV canal defect with unequal ventricles, double-inlet LV with small outlet chamber. In these cases, a biventricular repair cannot be achieved. Therefore, a single ventricle repair strategy is followed wherein the dominant ventricle becomes the systemic ventricle and systemic venous return is directed toward the pulmonary arteries by passing the cardiac chambers. These patients usually undergo a bidirectional Glenn shunt at 6–9 months and a Fontan completion [total cavo pulmonary connection (TCPC)] after 3 years of age. Prior to 6 months of age, a BT shunt or a PA band may be needed to optimize the pulmonary blood flow till a Glenn shunt is feasible.

Tricuspid atresia is a common CCHD characterized by an atretic tricuspid valve and a smaller RV. Variable features include VSD (single, multiple, restrictive, or large), Great artery relation and the presence of RV outflow obstruction. Tricuspid atresia is classified as Type I (normally related GA) or Type II (D malposed) and Type III (L malposed). These types are further subclassified as:

- Pulmonic atresia
- Pulmonic stenosis
- Unprotected pulmonary blood flow

The atretic tricuspid valve, the hypoplastic RV, dilated atria, and VSD are all seen well in the apical four-chamber view or subcostal view. The RV outflow and the great artery relation will need to be imaged in the parasternal short-axis views **(Figs. 22 and 23)**.

The subcostal and apical four-chamber views outline the atretic tricuspid valve, the dilated RA/LA/RV and smaller RV. The VSD, commonly perimembranous, is easily seen in the apical view, but an anterior tilt may be needed to outline additional VSDs. Pulmonic stenosis and the RVOT can be seen in a modified parasternal short-axis view and the branch pulmonary arteries can be imaged in a high parasternal window. Any PDA flow can also be seen in the short-axis view. The suprasternal view is not very informative in tricuspid atresia except for outlining a left SVC or in postoperative evaluation.

At postsurgical follow-up, a PA band and PA anatomy should be imaged in the parasternal short-axis and subcostal views. The Glenn shunt is best profiled in the suprasternal and subcostal views while a lateral tunnel (post Fontan) can be seen as a circular structure in the RA in apical four-chamber and subcostal views.

At follow-up, all single-ventricle repair patients should be imaged for patency of the circuits (Glenn/Fontan), adequacy of interatrial and interventricular communication, ventricular function, AV valve regurgitation and the presence of any intracardiac thrombi or spontaneous echo contrast in the cardiac chambers. Also, a fenestration if present, should be profiled.[16]

Univentricular Atrioventricular Connection

This includes all hearts where the AV connection is completely or predominantly to a single ventricular chamber. This includes three types of AV connections—double inlet (like DILV), single inlet (single AV connection), and common inlet (common AV valve to a single ventricle). The ventricle may be either left or right depending on respective morphology and the presence of an infundibulum which identifies with the RV. The other ventricle is usually a hypoplastic outlet chamber.

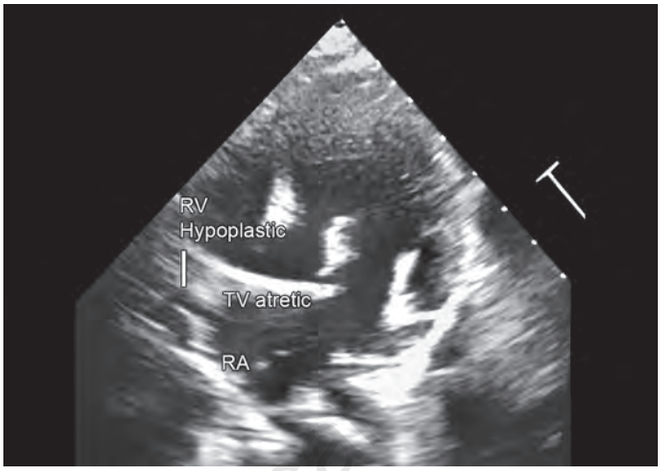

FIG. 22: Tricuspid atresia: atretic TV, HYPOPLASTIC RV.
(TV: tricuspid valve; RA: right atrium; RV: right ventricle)

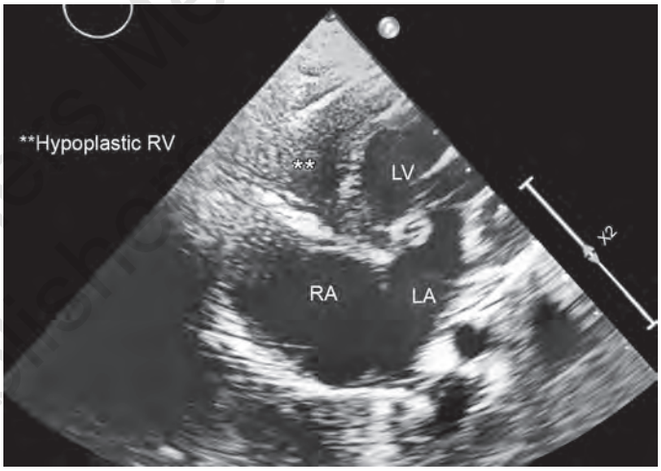

FIG. 23: Tricuspid atresia: Atretic TV, small RV, dilated RA, LA, LV.
(LA: left atrium; RA: right atrium; LV: left ventricle; RV: right ventricle; TV: tricuspid valve)

Univentricular AV connection limits the characterization and localization of the AV valves as mitral or tricuspid. Therefore, AV valves should be described simply as right or left AV valve. Overriding of AV valves results from malalignment of the atrial and ventricular septae. Annular, rather than chordal, features are used to determine AV connections. More than 50% annular commitment to a ventricular chamber establishes the AV valve connection to that ventricular chamber. If >75% of a common AV valve empties into a ventricular chamber, a common inlet ventricle pertains. Straddling and overriding AV valves may occur independently and commonly coexist.

Additionally, patients with two adequate ventricles may also undergo a single-ventricle repair strategy when a biventricular

repair may not be feasible, e.g., straddling AV valves, Inlet VSD with malposed great arteries, which will not permit the LV to be easily routed to the aorta without damaging the tricuspid valve, etc.

Echo Features

Diagnostic features of univentricular AV connections are detailed from the apical view delineating the crux of the heart showing the AV connections and status and commitment of the AV valves. The apical four-chamber view demonstrates the basic type of univentricular connections (double inlet, single inlet, and common inlet). Parasternal short view and subcostal four-chamber view are important for describing the features of the AV valves, the location of the hypoplastic outlet or rudimentary chambers and the location, commitment, and relationships of the great arteries. The short-axis view also outlines the pulmonary valve, pulmonic stenosis, and PA anatomy.

Apical and subcostal four-chamber views should demonstrate AV valvular abnormalities, including atresia or stenosis and annular override or valve straddling.

Parasternal long- and short-axis views will outline the size and location of VSD, outlet chambers, and outflow tracts. Subaortic obstruction is observed frequently in patients with double-inlet left ventricle following pulmonary artery banding. Doppler interrogation of the ascending aorta from the high left parasternal view estimates the subaortic gradient.[17]

Truncus Arteriosus

This is another not uncommon CCHD that requires close monitoring and may need multiple surgeries. Truncus arteriosus is classified as follows (Collet Edwards classification):

- *Type I*: Common trunk gives rise to the main pulmonary artery (that usually arises posteriorly) which later bifurcates into right pulmonary artery and left pulmonary artery. The trunk usually continues as the aorta.
- *Type II*: Both right pulmonary artery and left pulmonary artery arise from the common trunk separately but both origins are close to each other, reconstructive surgery is easier than type III.
- *Type III*: Both right pulmonary artery and left pulmonary artery arise separately, usually posteriorly, and the origins are far apart. Surgical repair may be a bit difficult at times.

Apical four-chamber view, subcostal view and parasternal long-axis views demonstrate a single great vessel with a biventricular origin and a large nonrestrictive VSD. The pulmonary arteries are seen arising from this trunk **(Figs. 24 and 25)**.

The short-axis view will also show the origin/bifurcation of the pulmonary arteries. In type III, TA the probe may have to be posteriorly angulated to profile the individual pulmonary arteries. The short-axis view will also profile the truncal valve—whether bicuspid, tri-leaflet (most common), or quadricuspid. It is vital to look for and quantify any truncal stenosis/regurgitation that may adversely impact long-term prognosis since the truncal valve is the future aortic valve.[18-20]

Fetal echo and antenatal diagnosis: In recent years, most cases have been diagnosed antenatally. This lesion can be detected easily owing to a distinctive single great artery of biventricular origin which also gives rise to the pulmonary artery. A VSD is also outlined **(Figs. 26 and 27)**.

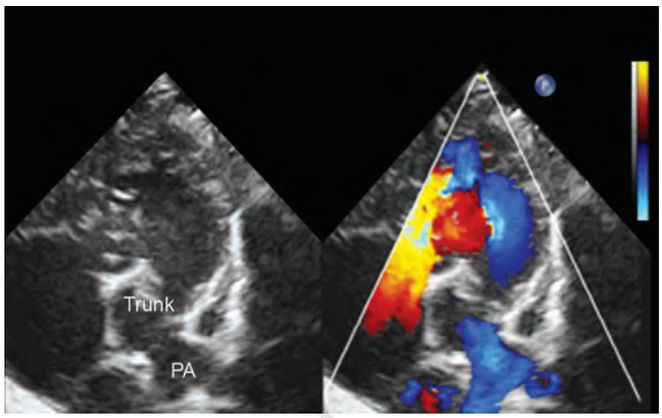

FIG. 24: Truncus arteriosus: Subcostal view, type I truncus.

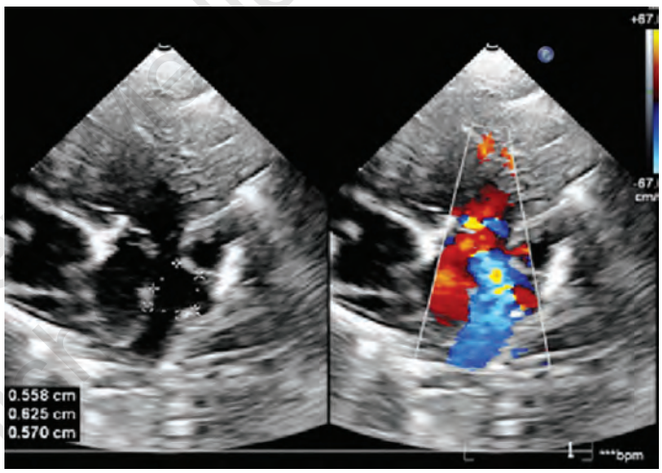

FIG. 25: Truncus arteriosus: Apical four-chamber view, type I truncus.

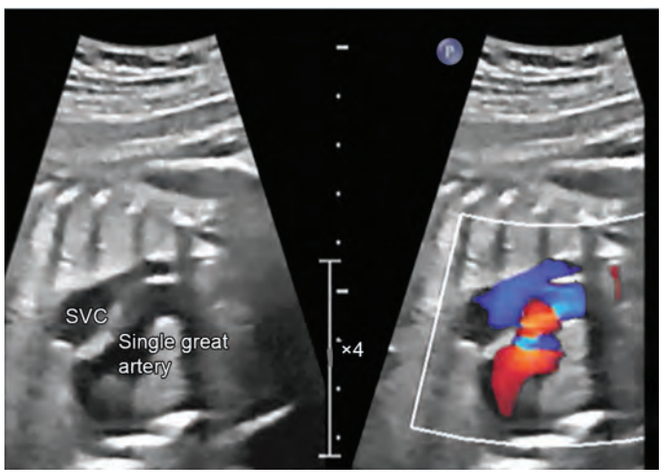

FIG. 26: Truncus arteriosus: Fetal echo showing single great artery.
(SVC: superior vena cava)

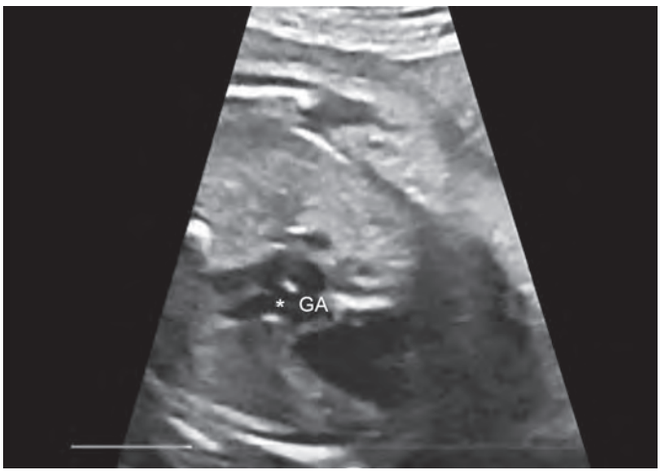

FIG. 27: Truncus arteriosus: Fetal echo showing pulmonary artery arising from trunk (GA).
(GA: great artery)

Surgery involves VSD closure, routing the LV to the aorta and a right ventricle to pulmonary artery conduit/homograft that may need revision later. At follow-up, a note should be made of the RVOT gradient/pulmonary arteries and ventricular function. Most patients will require a Redo conduit in later years and therefore, a progression of RVOT gradients should be recorded.

Ebstein's Anomaly of the Tricuspid Valve

The following features characterize: (1) Caudal displacement of the septal tricuspid leaflet, (2) A sail-like anterior tricuspid leaflet, and (3) A small functional RV and dilated RA (native RA + atrialized RV).

Variable features include PA (functional/organic), ASD, and VSD. Most important in evaluation is the 2D echocardiogram. Echo identifies the lesions, the degree of displacement of the septal tricuspid leaflet (STL), RV assessment, and tricuspid regurgitation assessment. *The internal cardiac crux, as imaged in the apical four-chamber view is the most consistent imaging landmark.* The apical four-chamber view outlines the septal hinge points of the mitral and tricuspid leaflets. The most sensitive and specific diagnostic feature in Ebstein's anomaly is the displacement of the hinge point of the septal leaflet- caudal displacement of the septal tricuspid leaflet. A displacement index of *8* mm/m^2 is the reliable feature to distinguish Ebstein's from other forms of RV volume overload. (Displacement index = distance between the AML and STL hinge points divided by body surface area in square meters). In severe cases, the hinge point of STL may not be seen in the four-chamber imaging plane because the STL is rotated anteriorly into the RVOT. In these cases, the displacement index is considered infinite.

The apical four-chamber and subcostal views demonstrate the displaced tricuspid valve, tricuspid regurgitation, RV size, ASD, and biventricular function. It is essential to evaluate for the functional RV (to plan surgical management—single ventricle repair vs. tricuspid valve repair/replacement). The degree of tricuspid regurgitation or stenosis should be assessed accurately. Quantification of tricuspid regurgitation in Ebstein's anomaly may not be simple – since the regurgitation jet may appear deceptively laminar and underestimate the severity, valve leaflets may have multiple fenestrations, and most importantly, the orientation of the valve leaflet is not normal. Therefore, the tricuspid regurgitation jet is best evaluated in a modified RVOT view rather than an apical four-chamber view. The Celermajer index, proposed in 1992, allows for assessing the size of the right atrium and prognostication of Ebstein's severity. This index is computed by dividing the area of the right atrium and the atrialized RV (area above the tricuspid valve coaptation) by the combined area of the right ventricle (below the level of coaptation) + left atrium area + left ventricular area. An index exceeding 1.0 is a poor prognostic factor.[21]

Preoperative echo can also help predict the possibility of a surgical tricuspid valve repair (monoleaflet approach). If at least half of the anterior tricuspid leaflet is mobile and free of tethering, it can freely coapt with the ventricular septum after surgical repair.[22,23]

Lastly, associated lesions namely PFO/ASD, pulmonary stenosis or functional pulmonary atresia, VSD, and patent ductus arteriosus should be checked for.

Fetal echo and antenatal diagnosis: In recent years, most cases have been diagnosed antenatally. This lesion can be detected easily owing to the distinctive tricuspid valve displacement. The presence and prognostic features of the abnormality can be assessed **(Figs. 26 and 27)**. Fetal hydrops is an ominous sign.[24]

Hypoplastic Left Heart Syndrome

The incidence of hypoplastic left heart syndrome (HLHS) is 1.4–3.8% of all CHD. HLHS causes 22% of cardiac deaths during the first week of life and 15% of all cardiac deaths within the first month. There is a male preponderance and small recurrence risk in the family affected—possibly an autosomal recessive inheritance—also there is a 12% prevalence of left ventricular outflow tract abnormalities among first-degree relatives of patients with HLHS.

The term HLHS includes any lesion with a dominant RV and a systemic outflow obstruction that are not amenable to two-ventricle repair. These morphologies may include aortic valve atresia with mitral atresia, aortic valve atresia with a patent mitral valve, and aortic stenosis with a patent mitral valve (this blends smoothly into critical aortic stenosis). All of these result in underdevelopment of the left ventricle + aorta complex, with an intact ventricular septum. The ascending aorta is hypoplastic. Blood flow in the arch is retrograde, and, in aortic atresia—the ascending aorta serves only as a conduit for the retrograde flow of blood into the coronary arteries. A localized coarctation of aorta is present in 80% of the patients. Corresponding changes on the right side include dilated RA, RV, pulmonary artery, and tricuspid valve annulus. Abnormalities of the tricuspid valve are identified in ≤35% of patients with HLHS. Tricuspid valve dysplasia is more common in patients with a patent mitral valve, occurring in 50% of patients in this subgroup. Volume overload of the RV and resulting annular dilation may further worsen the tricuspid regurgitation and RV subendocardial ischemia may also contribute.

In the present era, many cases of HLHS are detected antenatally and this allows for timely parental counseling regarding continuation of pregnancy and a planned delivery at a tertiary center.

Echo diagnosis is easy—multiple imaging views of the heart with Doppler assessment. The parasternal long-axis view shows a small muscle bound left ventricular chamber that does not extend to the cardiac apex. The endocardial surface of the LV is often echogenic and bright indicating areas of fibro elastosis. The left atrium is usually small but may be dilated when the ASD is restrictive. The ascending aorta is usually small (2–3 mm in diameter): the aortic valve may or may not be patent. The mitral valve is often imperforate but when patent, the leaflets are thickened with short or absent papillary muscle chordal attachments. A VSD is rare in the presence of aortic atresia but ventriculocoronary arterial connections may be seen. A left ventricular cross-sectional area <1.5 cm^2 is often found in most infants with HLHS, as well as a left ventricular end-diastolic inflow dimension <25 mm (measured from hinge point of PML to LV apex) and a mitral annulus <6 mm in diameter.[25]

The parasternal short-axis view shows the LV size, function, mitral valve, papillary muscles, and aortic valve anatomy. The main pulmonary artery, pulmonary valve and branch pulmonary arteries, and PDA are seen in this view.

The apical four-chamber view shows a small LV and a large RV forming the cardiac apex. There may be RV dysfunction in the neonate due to ductal closure and acidosis. Also, the mitral valve apparatus should be evaluated.

Subcostal view outlines the hypoplastic left heart structures/atrial septal anatomy/pulmonary venous anatomy and drainage. Anomalous pulmonary venous anatomy and/or drainage occurs in about 5–10% of HLHS patients. The pulmonary veins normally connect to the left atrium. However, especially in cases of an intact atrial septum, there may be a levoatrial cardinal vein that originates directly from the left atrium (decompressing LV)and drains either all pulmonary veins (total) or some (partial) to a variable location.

The suprasternal view is important for the arch anatomy. The transverse arch and the descending thoracic aorta are best seen from this view. Doppler interrogation shows retrograde systolic flow from the ductus toward the transverse arch, indicative of a ductal dependent systemic circulation and implies that the LV may not support a biventricular repair. Also, coarctation of aorta and interruption of the arch may be outlined in this view.

CONCLUSION

A detailed echo is essential in the diagnosis of CCHD and a systematic segmental analysis remains the cornerstone. Multiple views including modified views and TEE should be imaged. A detailed echo assessment helps in planning management as well as surgical strategies, whether palliation/single stage or multiple corrections and the feasibility of a single ventricle versus a two-ventricle repair strategy. Multiple examinations may be required in special cases. Other imaging modalities such as computed tomography angiography (CTA)/MRI/cardiac catheterization complement the information from echo and are increasingly relied upon.

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CHAPTER 4

Approach to Cyanosis from Newborn to Adult: Hemodynamics and Management Strategies

Sakshi Sachdeva, Anita Saxena

ABSTRACT

Cyanosis is a clinical sign referring to bluish discoloration of skin, nails, and mucosa. It can be central cyanosis or peripheral cyanosis depending on the presence or absence of mucosal involvement. Central cyanosis can have many etiologies ranging from cardiac, pulmonary, hematologic, or neurologic causes. Clinical history, physical examination, and specific investigations, as described in the chapter, help in reaching to a specific etiology. Etiology of cyanosis differs across different age groups. For cardiac causes of cyanosis, examination followed by electrocardiogram (ECG) and chest radiograph should lead to a broad clinical categorization before embarking upon echocardiogram. Oxygen saturation could be measured in both preductal and postductal regions. Saline contrast echocardiography should be done in suspected cardiac causes of cyanosis with apparently normal echocardiogram to detect occult right-to-left shunts. Management is directed toward the cause. In neonates with cyanosis and shock, prostaglandin E1 (PGE1) may be life-saving till a definitive diagnosis is reached.

INTRODUCTION

The term cyanosis is derived from Greek word *kyanos*, which means dark blue. Cyanosis refers to bluish discoloration of skin, nail beds, or mucosa. Cyanosis is easily appreciated in areas with minimal melanin pigment and abundance of capillaries such as lips, oral mucosa, tongue, conjunctiva, nail beds, palms of hand, and soles of foot. Cyanosis is of two types, namely peripheral cyanosis and central cyanosis. Peripheral cyanosis (also called acrocyanosis) involves bluish discoloration of extremities, that is, nail beds, tip of nose, and ear lobes. This occurs specially during cold exposure, shock, or peripheral vascular disease due to slowing of blood flow and enhanced oxygen extraction from the capillary blood. It is a benign phenomenon that resolves with the restoration of normal circulation. In contrast, central cyanosis involves bluish discoloration of extremities as well as the mucosa. Etiology of central cyanosis could be cardiac, respiratory, neurological, hematologic, or metabolic causes.

Cyanosis occurs due to increase in deoxyhemoglobin >5 g% in capillary blood, or >7 g% in arterial blood, or >15 g% in venous blood. Abnormal hemoglobin (other than deoxyhemoglobin) can also result in visible cyanosis, namely methemoglobin. Cyanosis depends on the absolute concentration of deoxyhemoglobin and not on the ratio of deoxyhemoglobin to oxyhemoglobin. Hence, the presence of anemia may mask cyanosis because the absolute amount of deoxyhemoglobin is also less. Conversely, polycythemic patients may appear cyanotic even with minimal desaturation.

CO-RELATION BETWEEN CYANOSIS, PO_2, AND OXYGEN SATURATION OF HEMOGLOBIN

An oxygen–hemoglobin dissociation curve is shown in **Figure 1**. The ratio of fetal to adult hemoglobin varies in different age groups, and proportions of each hemoglobin determine the oxygen saturation resulting at any PO_2. Oxygen saturation is measured by two techniques—pulse oximetry and arterial blood gas (ABG) analysis.[1] ABG analysis is the gold standard for measuring oxygen saturation. Oxygen saturation is the percentage of total hemoglobin sites available for binding to oxygen that is occupied with oxygen. It is calculated by formula: SO_2 = oxyHb/oxyHb + deoxyHb.

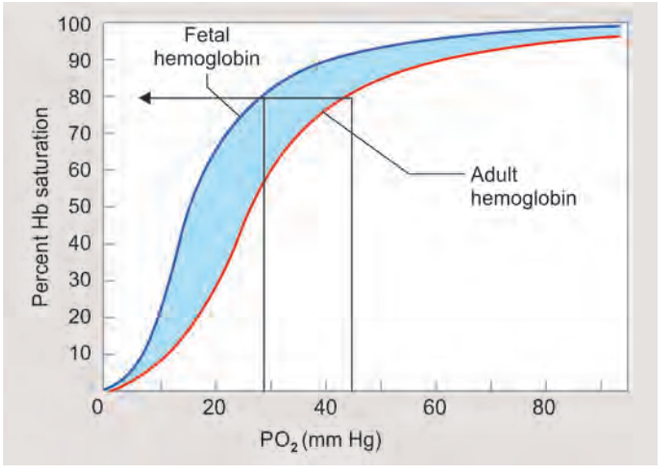


FIG. 1: Oxygen–hemoglobin dissociation curve.

There are two forms of functionally redundant hemoglobin in blood, namely carboxyhemoglobin and methemoglobin. In healthy people, they constitute <5% of total Hb. But in carbon monoxide poisoning and methemoglobinemia, the oxygen-delivering capacity of blood is reduced and there is tissue hypoxia. But the oxygen saturation is normal. Co-oximetry is a technique of ABG analysis based on spectrophotometry, where the light absorption characteristics of four different types of Hb (oxyHb, deoxyHb, MetHb, COHb) are utilized to directly measure oxygen saturation of hemoglobin. Pulse oximetry, on the other hand, measures oxygen saturation in the pulsatile signal of the arterial blood, by analyzing the unique absorption spectra of different wavelengths of light by oxyhemoglobin and deoxyhemoglobin.

CYANOSIS DUE TO HEART DISEASES

Cardiac conditions can lead to cyanosis by various mechanisms:

- Intracardiac right-to-left shunt [admixture physiology, ventricular septal defect with pulmonary stenosis (VSD/PS) physiology]
- Abnormal streaming of blood (transposition physiology)
- Severe pulmonary venous hypertension (PVH) and pulmonary edema

In intracardiac right-to-left shunt lesions, there is shunting of deoxygenated systemic venous blood into the systemic arterial circulation due to mixing at the systemic venous level [total anomalous pulmonary venous connection (TAPVC), total anomalous systemic venous connection (TASVC)], atrial level (tricuspid atresia, common atrium), ventricular level [double outlet right ventricle (DORV), tetralogy of Fallot (TOF), single ventricle], or great vessel (truncus arteriosus) level. Lesions that have reduced pulmonary blood flow (PS physiology) have deeper or much more evident cyanosis due to less quantity of oxygenated blood returning from pulmonary venous circulation. In transposition physiology, there is either discordant atrioventricular or ventriculo-arterial connection leading to poor mixing or there is abnormal streaming of deoxygenated blood into the aorta (DORV with D-malposed great vessels) leading to cyanosis. In conditions such as acute mitral regurgitation with acute severe PVH culminating in pulmonary edema, the oxygenation is hampered due to interstitial edema at the respiratory membrane. Patients with cardiac etiology of cyanosis have exertional breathlessness, secondary polycythemia, and clubbing. Unless concomitant congestive heart failure (CHF) is present, tachypnea and respiratory distress are relatively less as compared to a patient having similar saturation to respiratory etiology.

CYANOSIS DUE TO PULMONARY DISEASES

Pulmonary conditions can lead to cyanosis by the following mechanisms:

- Reduced partial pressure of oxygen within the alveoli
- Inability of respiratory membrane to facilitate oxygen transport across it
- Intrapulmonary right-to-left shunting

Airway obstructions limit the amount to air and thus oxygen reaching the alveoli. Obstructions can occur at one or multiple levels, namely nasal polyp, choanal atresia, micrognathia, Pierre Robin sequence, adenoid enlargement, laryngomalacia, vocal cord palsy, subglottic stenosis, tracheal stenosis, complete tracheal rings, airway hemangioma, neck masses, vascular rings, and slings. Important arch anomalies presenting as vascular rings include double aortic arch, circumflex aortic arch with contralateral ductus arteriosus, aberrant subclavian artery with Kommerell diverticulum, and early origin of innominate artery from the ascending aorta causing anterior tracheal compression. The patients would present with either stridor or apneic spells. In adults, the common causes could be chronic obstructive pulmonary disease (COPD) or chronic bronchitis.

Despite patency of airways and normal partial pressure of oxygen in the alveoli, in certain conditions, the oxygen transport (across the respiratory membrane) from alveoli to the hemoglobin in capillaries is affected. These conditions include pneumonia, diaphragmatic hernia, bilateral phrenic nerve palsy (common in postcardiac surgery situations), pulmonary sequestration, lung hypoplasia, congenital or acquired emphysema, chest deformity (extreme kyphoscoliosis), interstitial lung diseases, which are common in adults, and scleroderma, asbestosis, berylliosis, and sarcoidosis. At high altitudes, there is reduced partial pressure of oxygen in the inhaled air; hence, cyanosis can occur. High-altitude pulmonary edema is another cause of cyanosis. Patients with a respiratory cause of cyanosis are sicker compared to a similar degree of desaturation with a cardiac disease.

In pulmonary arteriovenous malformation (PAVM), depending upon the shunt fraction, a patient will present with mild to deep cyanosis. The deoxygenated pulmonary venous blood is transported directly to pulmonary veins bypassing the pulmonary capillary bed. Osler–Weber–Rendu syndrome or hereditary hemorrhagic telangiectasia is a common association. PAVMs occur in patients with Abernethy malformation (extra-hepatic portal vein to systemic vein shunt), liver disease, and post-Glenn surgery for single ventricle palliation. Pulmonary

artery to left atrium fistula (PA–LA fistula) has the same pathophysiology of cyanosis as PAVM.

NEUROLOGICAL CAUSES OF CYANOSIS

Reduction of central respiratory drive or neuromuscular disorders result in alveolar hypoventilation. Various causes include raised intracranial pressure, brainstem tumors, cervical spine injury, Guillain–Barré syndrome, spinal muscular atrophy (SMA), myopathies and muscular dystrophies (Duchenne and Becker's), myxedema, drugs (narcotics, sedatives), and primary alveolar hypoventilation.

HEMATOLOGIC/METABOLIC CAUSES OF CYANOSIS

Abnormal hemoglobin present in blood can cause cyanosis. Presence of methemoglobin concentration >2 g% and sulfhemoglobin >0.5 g% in blood leads to cyanosis. Methemoglobin is an oxidized form of hemoglobin with a half-life of 55 minutes and is unable to transport oxygen. It is reduced to deoxyhemoglobin by NADH Cytochrome-b5 reductase. With mutations of the gene coding, this enzyme results in elevated levels of methemoglobin. Exposure to higher doses of certain drugs such as sulfonamides, nitroprusside, and aniline group of drugs leads to production of oxidative metabolites resulting in methemoglobinemia. Similarly, sulfhemoglobinemia can result from sulfur binding to hemoglobin.

APPROACH TO A PATIENT WITH CYANOSIS

Out of the multiple causes of cyanosis discussed above, determining the cause in a particular patient needs a comprehensive approach including detailed history, physical examination, and investigations. Determination of etiology of cyanosis needs meticulous history taking about the time when it was noticed, comprehensive physical examination of all four limbs and oral mucosa, search for clubbing, determination of SpO_2 in at least 1 upper limb and 1 lower limb and obtaining an arterial blood gas. History-taking and examination are focused toward the causes, which may present in a particular age group. Work-up for causes is determined taking leads from the history and physical examination.

Newborn with Cyanosis

Majority of causes of cyanosis in a newborn are respiratory conditions followed by cardiac conditions. History taking should start from the antenatal history of maternal exposure to drugs, infections [toxoplasma, rubella, cytomegalovirus, herpes (TORCH), specially rubella], and diabetes mellitus, which would increase the risk of congenital heart disease (CHD). Maternal diabetes can lead to increased risk of CHD along with transient tachypnea of newborn, and hyaline membrane disease. History of prolonged rupture of membrane may indicate sepsis and pneumonia in a neonate. Difficult delivery may lead to neonatal trauma and Erb's palsy (along with phrenic nerve palsy) producing respiratory distress and cyanosis. In preterm and low birth weight (LBW) babies, bronchopulmonary dysplasia (BPD) can develop with cyanosis. Asking for family history of CHD is important.

The timing of onset of cyanosis and respiratory distress is an important indicator toward etiology. Meconium aspiration syndrome, respiratory distress syndrome, and congenital diaphragmatic hernia will be symptomatic at birth. Neonates with cyanotic heart disease usually develop cyanosis and respiratory distress from few hours to 1–2 days after birth. The baby should be examined in a warm and quiet environment. Core and peripheral temperature and capillary filling time (CFT) should be checked to rule out acrocyanosis. Tachypnea, nasal flaring, and chest retractions indicate respiratory disease. Choanal atresia is ruled out by passing a nasogastric tube. Examine for any birth trauma or stridor. Auscultation of lung fields is important. Pulses should be felt in all four limbs and SpO_2 should be checked in pre-ductal and post-ductal regions (right arm and one leg). A difference in SpO_2 ≥4% between upper and lower extremity indicates presence of right to left shunt at PDA level. Cardiovascular (CV) examination should include identifying the cardiac impulse, auscultation for second heart sound, and murmurs.

Cyanosis in Older Children and Adults

Unlike neonatal and early infantile age groups, where pulmonary diseases are the most common causes of cyanosis, cardiac diseases are the most common cause of cyanosis beyond this age group. The onset of cyanosis in early life should point toward the diagnosis of transposition physiology. Presentation with gradually increasing cyanosis should point toward VSD/PS physiology. History of failure to thrive (FTT) and breathing difficulties points toward a cyanotic CHD (CCHD) with increased pulmonary blood flow. History of cyanotic spells and deep cyanosis points toward TOF physiology.

HYPEROXIA TEST

In patients (specially neonates), when it is difficult to differentiate a cardiac cause of cyanosis from a respiratory cause, hyperoxia test is carried out. The principle behind this test is that, in the absence of intracardiac shunt lesions, 100% oxygen given for 10 minutes will increase alveolar PO_2 and thus pulmonary venous and systemic arterial PaO_2. Little or no increase is expected in CCHD. However, it may be false positive in newborns with TAPVC, where torrential pulmonary flow may increase the PaO_2 despite an intracardiac right-to-left shunt. In newborns with persistent pulmonary hypertension of newborn (PPHN), it may be false negative due to a ductal right-to-left shunt. **Table 1** shows the steps to differentiate a cardiac disease from pulmonary disease.

APPROACH TO A PATIENT WITH CYANOTIC CONGENITAL HEART DISEASE

Once the cause of cyanosis is suspected to be cardiac, all attempts should be made to identify the defect. Knowing exact anatomy

TABLE 1: How to differentiate respiratory versus cardiac cause of cyanosis?

	CCHD	Pulmonary disease
Onset	Neonatal age or early childhood; if occurs later, onset is gradual	Usually later, may be acute
Clubbing	Present	May be present if chronic condition
Polycythemia	Present	Usually mild
Associated symptoms	Spells, CHF	Stridor, wheeze, crepitations
SpO_2	May be same or different in four limbs	Same in all four limbs
Hyperoxia test	Saturation does not improve with oxygen	Saturation improves with oxygen
Chest radiograph	Abnormal cardiac silhouette, pulmonary plethora/oligemia	Abnormal lung shadows, hyperinflation, rib-cage deformities
Electrocardiogram	Abnormal, characteristics specific to a CHD	Usually normal, RVH due to PAH may be seen
Echocardiography	Structurally abnormal heart	Structurally normal heart

(CCHD: cyanotic congenital heart disease; CHD: congenital heart disease; CHF: congestive heart failure; PAH: pulmonary artery hypertension; RVH: right ventricular hypertrophy)

may not be possible, but deciding whether it is an increased or reduced pulmonary blood flow situation or a critical duct-dependent lesion (specially in neonates) is important. Features of heart failure (HF), such as rapid breathing, feeding difficulty (suck–rest–suck cycle), feeding diaphoresis, FTT, and recurrent lower respiratory tract infections (LRTIs) point toward CCHD with increased pulmonary blood flow. Cyanosis in these situations is generally milder. Patients with reduced pulmonary blood flow have deeper cyanosis with significant clubbing. They are generally comfortable at rest without respiratory distress. They present with history of irritability while crying, cyanotic spells, or exertional worsening of cyanosis and dyspnea in older children. Occurrence of stroke and brain abscess is common in these patients. **Table 2** shows hemodynamic classification of CCHD.

Some patients with CCHD and increased pulmonary blood flow are not recognized in infancy or early childhood, and they may first present with deep cyanosis and dyspnea in late childhood or adolescent age, as they develop severe pulmonary artery hypertension (PAH) or Eisenmenger syndrome. On the other hand, some patients with acyanotic CHD and increased pulmonary blood flow may first present with cyanosis only in adolescent age group once they have developed Eisenmenger syndrome. History about symptoms and timing of onset of cyanosis is important to differentiate all these hemodynamic subtypes. **Table 3** shows differences between CCHD with reduced pulmonary blood flow (TOF physiology) and Eisenmenger syndrome.

EXAMINATION OF A PATIENT WITH SUSPECTED CYANOTIC CONGENITAL HEART DISEASE

Assessment of vital signs is the most important initial step. Examine for temperature, respiratory rate and signs of respiratory distress, perfusion status by CFT, pulse volume, and blood pressure. Pulses should be checked in both preductal and postductal locations and SpO_2 measured. Similarly, blood pressure should be checked in all four limbs. Examine for tachycardia, tachypnea, and hepatomegaly. Examination for situs abnormalities and cardiac position is important. Palpation for parasternal pulsations, type of apical impulse, and right ventricle (RV) or left ventricle (LV) dominance may point toward a diagnosis. Examination of second heart sound and presence or absence of third heart sound are important to differentiate the hemodynamic groups of CHD. Cardiac murmurs are important to identify, but some critical neonatal CHDs do not have any murmur.[2]

Certain findings may point to a specific type of CHD. Clues to diagnosis of a CCHD are mentioned in **Table 4**. LV-dominant impulse points toward tricuspid atresia or single ventricle or atrioventricular septal defect (AVSD) with LV as the dominant ventricle. Dextrocardia or mesocardia may point toward congenitally corrected transposition of great arteries (CCTGA) or Scimitar syndrome. A heaving parasternal impulse indicates the presence of atrial septal defect (ASD)/PS physiology or Hoffman variant of TOF (with restrictive VSD). **Table 5** shows differentiating features between VSD/PS and ASD/PS physiology. A systole–diastolic murmur at the left base (sawing wood murmur) indicates TOF with absent pulmonary valve syndrome. In TOF, the intensity of murmur is inversely proportional to the severity of cyanosis. However, in a patient with deep cyanosis along with a loud murmur, TGA/VSD/PS or DORV/VSD/PS with malposed great vessels should be suspected. Presence of low heart rate or cannon waves in jugular venous pulse (JVP) should indicate CCTGA as heart blocks are associated with this CHD. Presence of pan-systolic murmur at left lower sternal border indicates AVSD with concomitant atrioventricular valve regurgitation (AVVR). Presence of continuous murmur in a cyanotic patient may indicate pulmonary atresia with patent ductus arteriosus (PDA), TOF with major multiple aortopulmonary collaterals (MAPCAs), PAVMs, or surgical aortopulmonary shunts. Presence of such findings is helpful in older children and adults.[3]

TABLE 2: Hemodynamic classification of cyanotic congenital heart disease (CCHD).

Hemodynamic subset	Lesions	
	Neonatal and early infancy	Any age group (common beyond infancy)
Reduced pulmonary blood flow with low PA pressure	• Critical PS • Pulmonary atresia with IVS • VSD with pulmonary atresia • TGA/VSD/PS	VSD/PS physiology • TOF • DORV/VSD/PS • TGA/VSD/PS • AVSD/PS • Tricuspid atresia/VSD/PS • Single ventricle/PS • CCTGA/VSD/PS
Increased pulmonary blood flow with high PA pressure	Transposition physiology • TGA/intact IVS • TGA/VSD/PDA • Taussig–Bing (DORV/ subpulmonic VSD/PAH)	Admixture physiology • Systemic venous or right atrial level admixture ○ TAPVC ○ Mitral atresia • Left atrial level admixture ○ TASVC ○ Tricuspid atresia • Ventricular level admixture ○ Single ventricle ○ Double outlet right atrium; maligned interatrial septum ○ AVSD with straddling of tricuspid valve ○ DORV • Great vessel level admixture ○ Truncus arteriosus
Pulmonary venous hypertension	• Obstructed TAPVC • HLHS/Mitral atresia with restrictive ASD	
Normal pulmonary blood flow with normal PA pressure	Ebstein anomaly	• LSVC to LA PAVM • Ebstein anomaly
Reduced pulmonary blood flow with high PA pressure	PPHN	Eisenmenger syndrome

(ASD: atrial septal defect; AVSD: atrioventricular septal defect; CCTGA: congenitally corrected transposition of great arteries; DORV: double outlet right ventricle; HLHS: hypoplastic left heart syndrome; IVS: intact ventricular septum; LA: left atrium; LSVC: left superior vena cava; PA: pulmonary artery; PAH: pulmonary artery hypertension; PAVM: pulmonary arteriovenous malformation; PDA: patent ductus arteriosus; PPHN: persistent pulmonary hypertension of newborn; PS: pulmonary stenosis; TAPVC: total anomalous pulmonary venous connection; TASVC: total anomalous systemic venous connection; TGA: transposition of great arteries; TOF: tetralogy of Fallot; VSD: ventricular septal defect)

TABLE 3: Differences between tetralogy of Fallot (TOF) physiology and Eisenmenger physiology.

Examination	TOF physiology	Eisenmenger physiology
Growth, weight gain	Normal	H/O failure to thrive
History of heart failure	No	Yes
Squatting	Yes	No
Syncope	+	+++
Hemoptysis	+	+++
Chest pain/angina	No	Yes
Onset of cyanosis	Variable	Late
Degree of cyanosis	Variable	Generally mild
'*a*' wave in JVP	In older patients	Yes
Left parasternal lift	Grade I	Grade I
Heart size	Normal	Normal
Systolic thrill	May be present	Always absent
Second heart sound	Single	Single, narrow, wide
Ejection click	Yes, aortic	Yes, pulmonary
Ejection systolic murmur	Yes, intensity-related to cyanosis	Not >grade II
Early diastolic murmur	No	May be (in PDA)

(JVP: jugular venous pulse; PDA: patent ductus arteriosus)

TABLE 4: Clues to diagnosis of congenital heart disease (CHD) by clinical examination.

Physical finding	Likely underlying CCHD
Prominent '*a*' wave in JVP	• ASD with PS (Triology of Fallot) TOF in adulthood • Tricuspid atresia
LV type of apical impulse	• Tricuspid atresia • Single ventricle of LV morphology DORV with restrictive VSD
Pulsation in second LICS (L posed aorta)	Corrected TGA, single ventricle
Parasternal heave	• ASD with PS • TOF with restrictive VSD
PSM of AV valve regurgitation	AVSD, CCTGA
EDM of AR at LUSB	Truncus arteriosus with regurgitation
See-saw murmur at LUSB	TOF with absent pulmonary valve
Complete heart block	Corrected TGA, heterotaxy syndrome
Ejection systolic murmur out of proportion to severity of cyanosis	Transposition/Admixture with VSD and PS

(AR: aortic regurgitation; ASD: atrial septal defect; AV valve: atrioventricular valve; AVSD: atrioventricular septal defect; CCHD: cyanotic congenital heart disease; CCTGA: congenitally corrected transposition of great arteries; DORV: double outlet left ventricle; EDM: end diastolic murmur; JVP: jugular venous pulse; LICS: left intercostal space; LUSB: left upper sternal border; LV: left ventricle; PS: pulmonary stenosis; PSM: pan-systolic murmur; TGA: transposition of great arteries; TOF: tetralogy of Fallot; VSD: ventricular septal defect)

TABLE 5: Differences between ventricular septal defect (VSD)/pulmonary stenosis (PS) and atrial septal defect (ASD)/PS physiology.

	Tetralogy of Fallot VSD/PS physiology	Triology of Fallot ASD/PS physiology
JVP	Usually normal	Raised prominent 'a'
Left PSH	Absent	Present
S2	Single S2	Widely split, may be single
S4	Rare	May be present
Ejection click	Aortic	Pulmonary
Level of stenosis	Infundibular + valvular	Valvular
Murmur	Loud ESM in left 3/4 ICS (inversely proportional to severity of cyanosis)	Loud ESM in left second ICS (directly proportional to severity of stenosis)
Right heart failure	Rare	Common
ECG	Early transition in V_2. T-wave inversion very rare	RVH with T-wave inversion
CXR	No cardiomegaly, pulmonary bay	Cardiomegaly, dilated PA segment

(CXR: chest radiograph; ECG: electrocardiogram; ESM: ejection systolic murmur; ICS: intercostal space; JVP: jugular venous pulse; PA: pulmonary artery; PSH: parasternal heave; RVH: right ventricular hypertrophy; S2: second heart sound; S4: fourth heart sound)

TABLE 6: Cause of unequal saturation in limbs.

Finding	Causes
Differential cyanosis Postductal saturation lower than pre-ductal	• PDA with PPHN • PDA with Eisenmenger syndrome • Severe coarctation with PDA and PAH • Arch interruption with PDA in absence of VSD
Reverse differential cyanosis Preductal saturation lower than post-ductal	• TGA/PDA with PPHN • TGA/PDA and Eisenmenger syndrome • TGA/PDA with severe coarctation of aorta • TGA with arch interruption • Supracardiac TAPVC with severe PAH and PDA with unfavorable streaming of SVC blood to RV, and IVC blood to LA
Desaturation in isolated upper limb	Isolation of subclavian artery or brachiocephalic artery with PDA and severe PAH
One upper limb saturation better than other three limbs	Isolation of subclavian artery in TGA with PAH

(LA: left atrium; IVC: inferior vena cava; PAH: pulmonary artery hypertension; PDA: persistent ductus arteriosus; PPHN: persistent pulmonary hypertension of newborn; RV: right ventricle; SVC: superior vena cava; TAPVC: total anomalous pulmonary venous connection; TGA: transposition of great arteries; VSD: ventricular septal defect)

Role of Pulse Oximetry

Pulse oximetry provides continuous assessment of oxygen saturation noninvasively.[1] It is a part and parcel of physical examination of a patient with cardiac disease. Oximeter does not measure PaO_2, for which ABG analysis should be done. In neonates, umbilical artery catheters are in situ, and samples are taken from them. It needs to be highlighted that umbilical artery is a branch of iliac artery and hence provides postductal parameters. Simultaneous measurement of preductal and postductal saturation should be done. The right arm should be used to measure preductal saturation as the left subclavian artery may be preductal or postductal in origin. Sometimes, other arch vessel abnormalities may give variable saturations in upper limbs as listed in **Table 6**.

Chest Radiograph

Evaluation of chest radiograph is important in identification of respiratory or cardiac cause of cyanosis. Segmental approach should be utilized to review a radiograph. Determination of situs is done by identifying the location of liver position and stomach air bubble. Also, identification of bronchial morphology helps in determining situs. The right bronchus is shorter, straighter, and early branching. The left bronchus is longer, more oblique, and late branching. In isomerism, the morphology of both bronchi is identical. Presence of bronchial stenosis may be indicated by unilateral hyperinflation (ball-valve mechanism) or lung collapse (tight pinhole stenosis). Presence of lung collapse, consolidation, honey-combing pattern (BPD), coin-shaped lesions (PAVM), or diaphragmatic hernia may be identified. Ground-glass appearance of lungs indicates severe PVH due to obstructed TAPVC or mitral atresia with restrictive ASD. Pulmonary vascular markings are useful to identify CCHD with increased or reduced pulmonary blood flow.[4]

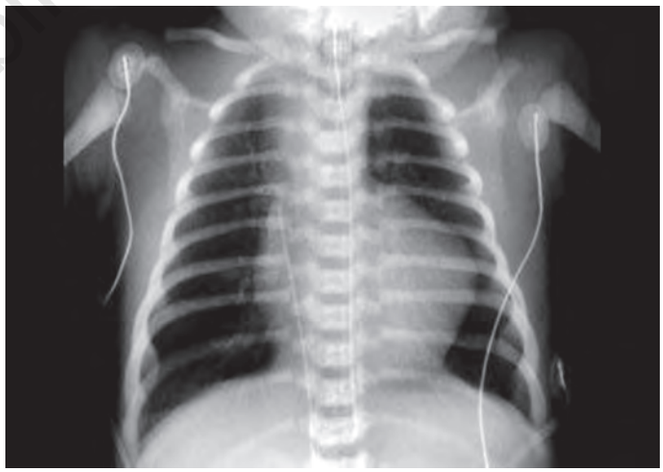


FIG. 2: X-ray of chest showing a boot-shaped heart in a patient with tetralogy of Fallot.

Cardiac silhouette has characteristic appearance in certain CHDs such as boot-shaped heart (TOF) **(Fig. 2)**, egg on side appearance (TGA), box-shaped heart (Ebstein anomaly), and

figure of eight appearance (supracardiac TAPVC) **(Fig. 3)**. It is not a sensitive finding because such characteristic shapes are seen only in 10% of such lesions and are mostly seen in older children. CCHD with cardiomegaly include TAPVC; truncus arteriosus; TGA, DORV, single ventricle, and tricuspid atresia (without PS); AVSD Eisenmenger syndrome; ASD Eisenmenger syndrome; Ebstein anomaly; critical PS **(Fig. 4)**; TOF with absent pulmonary valve syndrome; TOF with MAPCAs; and PAVM with large shunt fraction. CCHD with relatively normal-sized heart include TOF, TGA/VSD/PS, DORV/VSD/PS, tricuspid atresia/PS; TASVC; obstructed TAPVC; and Eisenmenger syndrome with VSD/PDA/arterioportal (AP) window. **Flowchart 1** depicts evaluation of chest radiograph in suspected CCHD.

Electrocardiography

Evaluation of origin of rhythm is important as it may be low atrial rhythm in AVSD. Complete heart block (CHB) is seen in CCTGA. Most cyanotic heart diseases have right-axis deviation and right ventricular hypertrophy. Sudden transition of QRS from pure R wave in V_1 to RS complex in V_2 is hallmark of TOF **(Fig. 5)**. Patients with AVSD and tricuspid atresia have left-axis deviation. Northwest axis is seen in DORV. Left ventricular hypertrophy is seen in tricuspid atresia and DORV with restrictive VSD. Isomorphic QRS complexes are seen in single ventricle. Presence of Q waves in V_1 is a feature of CCTGA. Himalayan P waves and fractionated QRS complexes are seen in Ebstein anomaly **(Fig. 6)**. **Table 7** provides the clues to diagnosis on electrocardiogram (ECG) in a patient with CCHD.[5]

Before proceeding toward echocardiography, a provisional diagnosis should be synthesized based on history, physical examination, ECG, and chest radiograph. Sometimes, a patient has cyanosis but other examination findings suggest ASD; **Table 8** shows causes of cyanosis in a patient with clinically suspected ASD.

Echocardiography

Based on clinical suspicion, echocardiography should be done to diagnose the exact anatomy and plan the management. Neonates with suspected duct-dependent lesions or transposition of great vessels need urgent echocardiography.

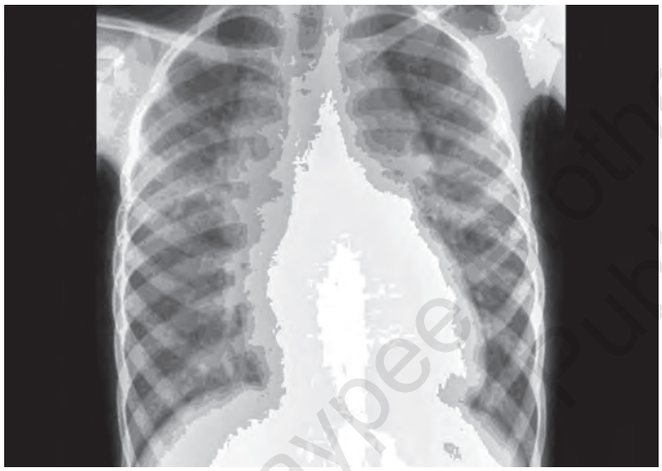


FIG. 3: X-ray of chest in a patient with supracardiac total anomalous pulmonary venous connection showing Snowman appearance.

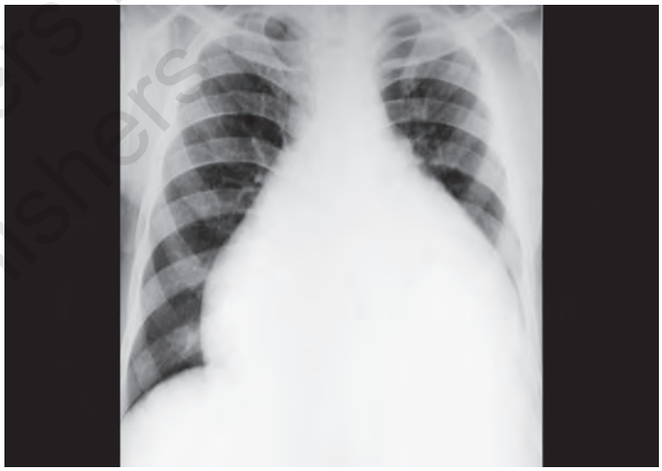
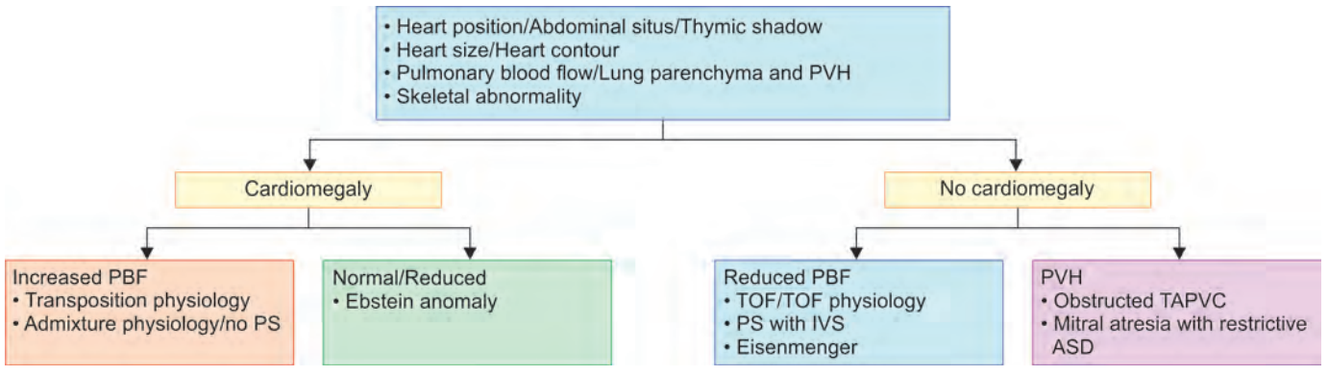


FIG. 4: Chest radiograph of a patient with critical valvular pulmonary stenosis showing cardiomegaly and pulmonary oligemia.



FLOWCHART 1: Interpretation of chest radiograph in cyanotic congenital heart disease (CCHD).

(ASD: atrial septal defect; IVS: intact ventricular septum; PBF: pulmonary blood flow; PS: pulmonary stenosis; PVH: pulmonary venous hypertension; TAPVC: total anomalous pulmonary venous connection; TOF: tetralogy of Fallot)

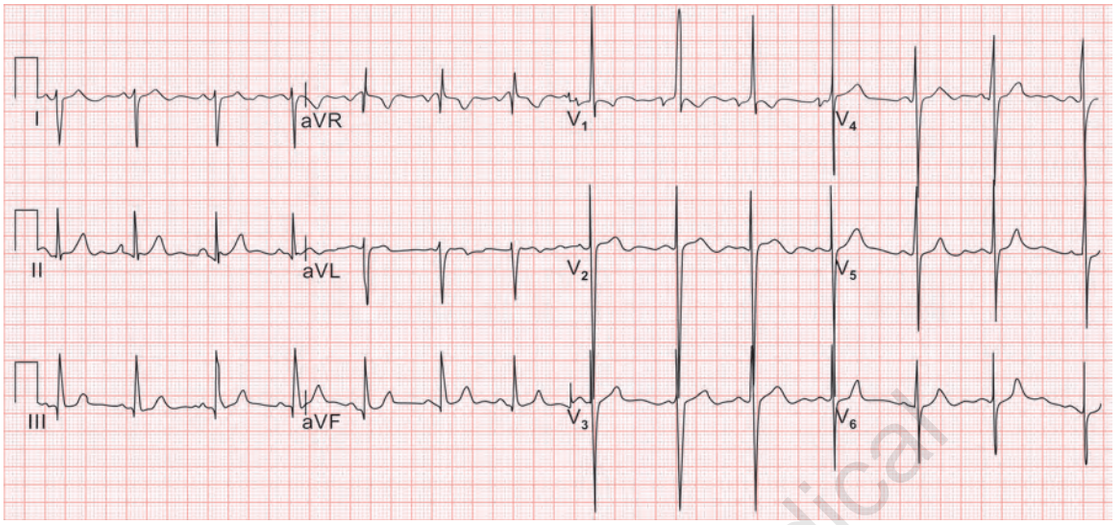


FIG. 5: Electrocardiogram (ECG) of a patient with tetralogy of Fallot showing right-axis deviation and right ventricular hypertrophy with early transition of QRS in V_2.

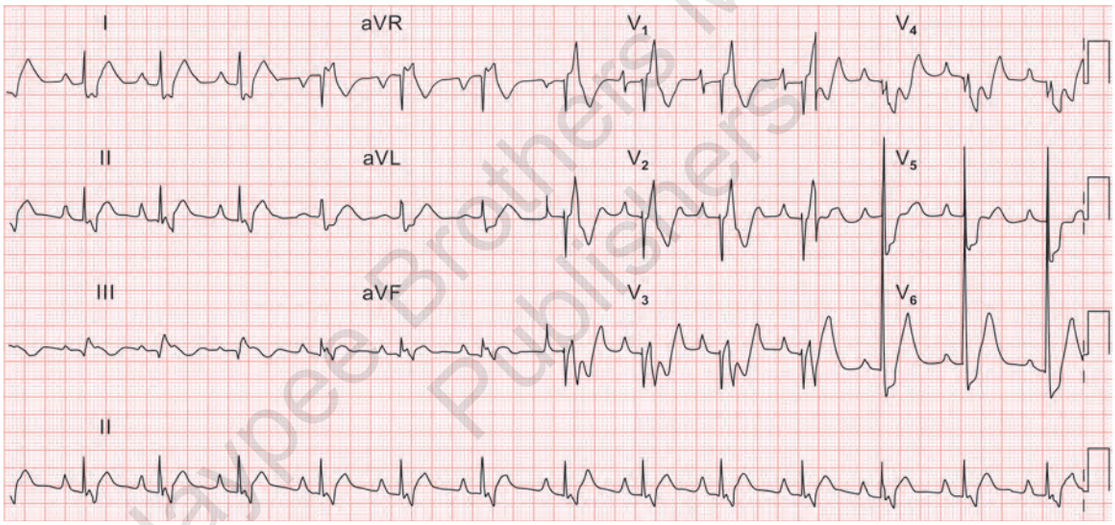


FIG. 6: Electrocardiogram (ECG) of a patient with Ebstein anomaly showing tall P waves, full PR interval, and fractionated QRS complexes.

In patients with apparently normal echocardiogram, saline contrast evaluation should be done to evaluate occult shunts such as left superior vena cava to LA with unroofed coronary sinus (CS) and PAVM.

Other Investigations

Important investigations in a patient with cyanosis include complete blood count (CBC), red blood cell (RBC) indices, iron studies, serum creatinine, and uric acid.

MANAGEMENT

The causes of cyanosis are variable according to different age groups. The patients presenting with cyanotic heart disease and having stable hemodynamics may be evaluated sequentially with all the investigations and then management planned accordingly. Some common measures to be advised are prevention and treatment of iron deficiency, and maintaining adequate hydration and dental hygiene. However, in neonatal and early infantile age groups, the patients may present with shock or cyanotic spell and would need emergent management. In sick patients, metabolic stabilization is must. Establish normothermia, normoglycemia, treatment of acidosis, and other metabolic abnormalities. Assisted ventilation should be provided in patients with severe respiratory distress.[6]

In neonates presenting with deep cyanosis and acidosis, two important differential diagnoses are duct-dependent circulation and TGA. Both present with deep cyanosis without a murmur. In duct-dependent pulmonary circulation, cyanosis dominates, while in duct-dependent systemic circulation, shock and hypotension are the predominant findings. After metabolic management and fluid resuscitation, prostaglandin E1 (PGE1)

TABLE 7: Electrocardiogram (ECG) clues to diagnosis of cyanotic congenital heart disease (CCHD).

ECG finding	Likely CCHD	Remarks
RVH/RAD	• TOF/PS or VSD/ pulmonary atresia • DORV/VSD/PS • L TGA/VSD/PS • Critical PS • D TGA/IVS • TAPVC • DORV/Subpulmonic VSD	• Rapid R to S transition • Counter-clockwise loop • Absent septal q in V_5–V_6 qR V_1, RV strain
RVH/LAD	AVSD with PS	
BVH/LAD	AVSD with straddling AV valve unroofed coronary sinus	
Dominance LV, LAD or normal axis	• Tricuspid atresia • Pulmonary atresia/IVS ~ HRHS • DORV with restrictive VSD	Poor RV forces
Biventricular hypertrophy	• D TGA with VSD/PDA • DORV/subaortic VSD • Truncus arteriosus • Single ventricle/PS	Monomorphic QRS V_1–V_6
IRBBB	Ebstein anomaly	Polyphasic QRS complexes

(AV: atrioventricular; AVSD: atrioventricular septal defect; BVH: biventricular hypertrophy; DORV: double outlet right ventricle; HRHS: hypoplastic right heart syndrome; IRBB: incomplete right bundle branch block; IVS: intact ventricular septum; LAD: left-axis deviation; PS: pulmonary stenosis; RAD: right-axis deviation; RV: right ventricle; RVH: right ventricular hypertrophy; TAPVC: total anomalous pulmonary venous connection; TGA: transposition of great arteries; TOF: tetralogy of Fallot; VSD: ventricular septal defect)

TABLE 8: Causes of cyanosis in a patient with clinically suspected atrial septal defect (ASD).

Mechanism	Conditions
Admixture of systemic and pulmonary venous blood	• Common atrium • Very large ASD • Totally anomalous pulmonary venous connection
Anomalies of systemic venous connection	• Partial or complete unroofing of coronary sinus • LSVC to LA • RSVC to LA • IVC to LA • Total anomalous systemic venous connection to LA
Abnormal streaming of systemic venous blood to LA	• Long Eustachian valve • SVC/IVC straddling across ASD • TR jet directed toward LA
Reduced RV compliance	• Severe PAH • Severe pulmonary stenosis • RV cardiomyopathy • RV myocardial infarction • RV dysfunction—systolic or diastolic
Elevated RA pressure	• Tricuspid stenosis • RA myxoma • Pericardial constriction • Positive pressure ventilation
Abnormal orientation of atrial septum (orthodeoxia)	• Elongated aorta compressing on RA • Aortic aneurysm • Loculated pericardial effusion • Post-right pneumonectomy
Intermittent elevation of RA pressure	Atrial flutter

(IVC: inferior vena cava; LA: left atrium; PAH: pulmonary artery hypertension; RA: right atrium; RV: right ventricle; SVC: superior vena cava; TR: tricuspid regurgitation)

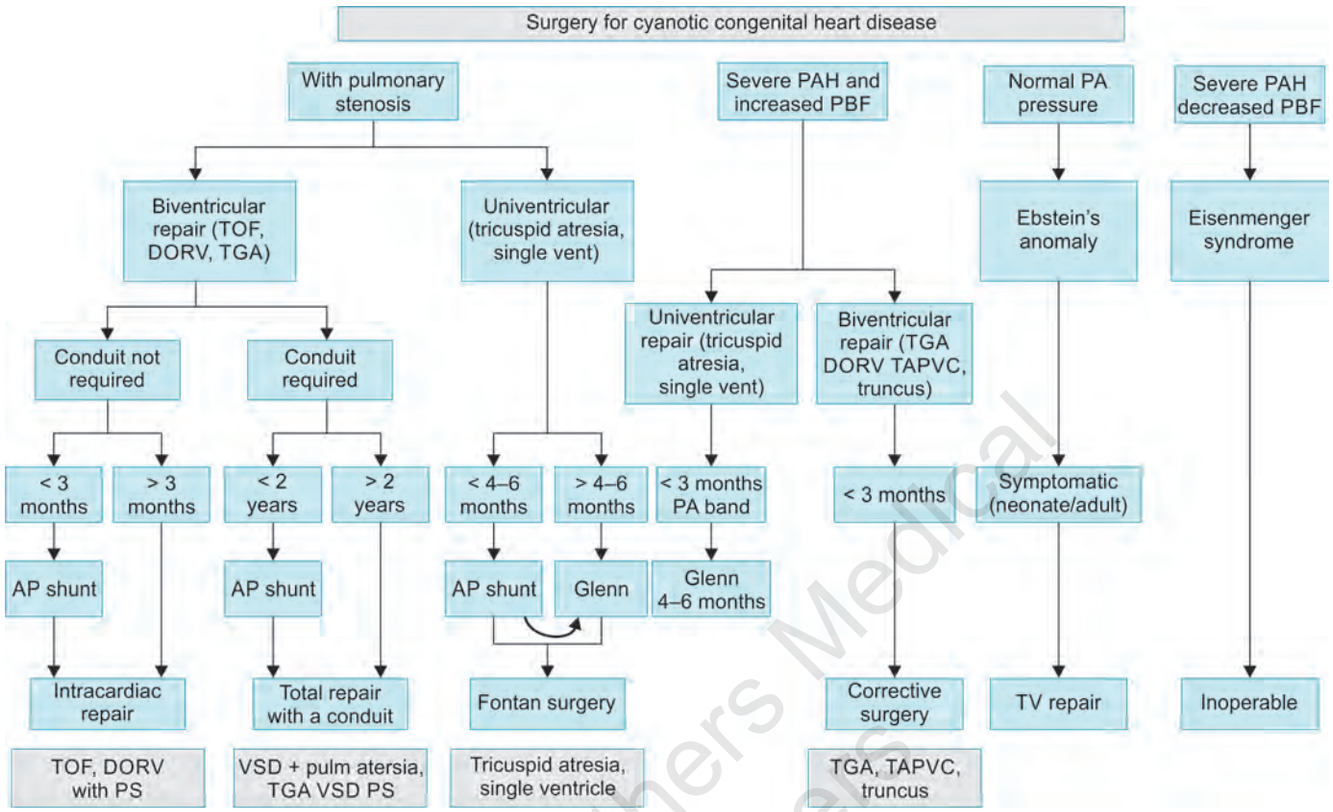
Source: Adapted with permission from Gupta SK, Sachdeva S, Juneja R. Atrial flutter: yet another cause of arterial desaturation in atrial septal defect. Cardiol Young. 2021;31:1027-9

infusion should be initiated (especially if the presenting age is in between 1 and 3 weeks). It is given as a continuous infusion with the dose range between 10 and 400 ng/kg/min. The starting dose is generally 50 ng/kg/min and it can be down-titrated or up-titrated depending on the response. A significant side effect is apnea, which if develops happens in the first 6 hours of infusion.

A cyanotic spell should be managed by knee–chest positioning, fluid bolus, subcutaneous morphine, intravenous metoprolol, sodium bicarbonate infusion, and injection phenylephrine. If uncontrolled, urgent surgical or transcatheter intervention is required. Oxygen administration helps by improving the dissolved oxygen in blood and is helpful in CCHD with reduced pulmonary blood flow conditions presenting with deep cyanosis. Duct-dependent lesions may develop ductal constriction at high FiO_2, so it may be harmful. In conditions with CCHD and increased pulmonary blood flow oxygen, administration can worsen the symptoms by reducing the pulmonary vascular resistance (PVR) and increasing the pulmonary blood flow. However, if required, 40–60% FiO_2 should be administered.[6]

CONCLUSION

The definitive treatment is decided by the underlying anatomical diagnosis. **Flowchart 2** depicts the management pathway of such patients. Supportive measures include iron supplementation, avoiding dehydration, phlebotomy if symptomatic polycythemia (only after ruling out iron deficiency), advocating good oro-dental hygiene, advising antenatal folate supplementation, and fetal echocardiography at 18-week period of gestation to mothers for future pregnancies.



FLOWCHART 2: Definitive management plan for cyanotic congenital heart disease (CCHD).

(AP: arterioportal; DORV: double outlet right ventricle; PA: pulmonary artery; PAH: pulmonary artery hypertension; PBF: pulmonary blood flow; PS: pulmonary stenosis; TAPVC: total anomalous pulmonary venous connection; TGA: transposition of great arteries; TOF: tetralogy of Fallot; TV: tricuspid valve; VSD: ventricular septal defect)

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CHAPTER 5

Relevance of Stethoscope in Contemporary Cardiology

Satyavan Sharma, Vishal Patil

ABSTRACT

Ever since its discovery over 200 years ago by the French physician, Laënnec, the stethoscope has been at the center of patient care and a symbol of doctor-patient relationship. A lot of advances occurred in stethoscope technology from monaural, binaural, and electronic to advanced digital versions. The art of cardiac auscultation developed remarkably during the 19th century and stethoscopes occupied the place of pride in clinical diagnosis. The traditional clinicians still maintain that there is no substitute for auscultation training as it remains an essential skill which can facilitate prompt management and avoid unnecessary investigations.

A lot of concern has been expressed recently about the decline in auscultatory skills and overreliance on echocardiography and advanced imaging techniques. The future will answer the debate about whether to continue investing in teaching medical students about auscultation or to abandon it for advanced diagnostic technology. The use of simple, easily available, cheap, and time-honored stethoscopes should continue. The emphasis should be to improve training in auscultation by introducing digital teaching modalities and not allow this fine art to die out.

INTRODUCTION

Over 200 years have elapsed since the prominent and iconic invention of the stethoscope. The name is derived from Greek literature where the word "Stethos" means chest and "Skopian" means to explore. Over the years, the "Stethoscope" has become a proud symbol of the medical profession and wearing it around the neck continues to be a cherished moment. It represents a connection that patients and doctors have experienced over the years. In addition to intimacy, a stethoscope provides immediate information and paves the way for judicious management. The stethoscope is used across the specialties for listening to heart, chest, bowel sounds, and blood flow patterns in arteries and veins. It is also routinely used in association with the sphygmomanometer to assess blood pressure (BP) by listening to blood flow sounds.

There is a growing debate about the decline in competent cardiac auscultation skills and the fate of the stethoscope. The topic will be discussed under the following heads:

- Discovery of the stethoscope
- Advances in stethoscope technology
- Rise and decline of auscultation
- Auscultation or echocardiography?
- Stethoscope in coronavirus disease 2019 (COVID-19) era
- Future of the stethoscope

DISCOVERY OF THE STETHOSCOPE

During the Hippocratic period (460–370 BC), physicians practised auscultation by the direct application of the ear to the patient's chest, abdomen or back, a process known as immediate auscultation (Latin auscultare = to listen). French physician, Rene Theophile Hyacinthe Laënnec (Laënnec), is credited for the historical discovery of the stethoscope in 1816.[1,2] The inspiration came from two children playing and transmitting tapping sounds by putting their ears at the ends of a wooden bar. Laënnec applied this observation while examining a young woman whose gender and age prohibited immediate auscultation. In 1819, he introduced the first stethoscope which consisted of a wooden tube, similar to an ear trumpet (used for better hearing) and introduced a practical method of bedside examination known as "mediate auscultation".[1,2]

ADVANCES IN STETHOSCOPE TECHNOLOGY

Throughout the "stethoscope's 200 years journey", there have been significant developments from the use of monaural earpieces to the binaural stethoscope followed by electronic and digital versions **(Table 1)**. Dr David Littman, a distinguished cardiologist and Harvard professor, is credited with developing the ideal stethoscope and improving its acoustic performance.[3]

TABLE 1: Evolution of stethoscope technology.

Scientist	Years	Design modification
Laënnec	1816	First rolled paper cone, then a wooden tube
Priorry	1828	Funnel-shaped bell, a lightened stem, and thinner earpiece
Williams	1843	First binaural stethoscope with lead pipes for earpieces
Marsh	1851	Stethoscope chest piece with a flexible membrane
Cammann	1855	Binaural stethoscope with flexible tubing
Bianchi	1894	First stethoscope with a rigid diaphragm—"phonendoscope"
Bowles and Sprague	1925	Combination of bell and a rigid diaphragm chest piece
Rappaport, Sprague and Groom	1945–1946	Various designs to determine ideal properties for the modern binaural stethoscope
Leatham, Littman and others	1956 onward	Modern stethoscopes using the same principles described by Rappaport, Sprague, and Groom

Source: Roguin A. Rene Theophile Hyacinthe Laënnec (1781–1826): the man behind the stethoscope. Clin Med Res. 2006;4(3):230-5.

In 1963, Littman patented the stethoscope and founded "Cardiosonics" which was acquired by 3 M, a US company selling electromechanical, medical, and pharmaceutical products. The basic components of the stethoscope are a headset, tubing, and a chest piece that incorporates a diaphragm and a bell into one known as multifrequency stethoscopes. The diaphragm is used to listen to high-pitch sounds and the bell, mid- and low-pitch sounds. These sounds are transmitted as sound energy through hollow tubing which is usually 18–26 inches in length. The hollow tubing splits into a binaural which is attached to a pair of earpieces **(Fig. 1)**. When a physician uses a stethoscope to auscultate, he/she closes a circuit where sound energy is transmitted with a bit of energy loss from the patient's chest to the physician's ear for interpretation. The sound quality can be affected by a number of variables including a thick chest, obesity, break in the circuitry, and pericardial or myocardial disorders. At present, several commercial stethoscopes are available with excellent acoustical features are sturdy, lightweight, and convenient to use in day-to-day clinical practice. Special stethoscopes are available for examining children and newborns. The limitations of the acoustic (conventional) stethoscope include the inability to record and process the acoustic signal, reduce noise, and enhance the murmurs or sounds. Another drawback is the inability to transmit sounds and murmurs to multiple listeners during teaching sessions.

Electronic stethoscopes were designed long back to overcome the deficiencies of conventional stethoscopes and upgrade their functionality.[4] The progressive models have integrated features such as ambient noise reduction, heart sound amplification, and bluetooth transmission to external devices. The acoustic signals are converted to electronic signals to allow volume accentuation and frequency selection for optimal listening. Modern electronic stethoscopes offer better sound quality than an acoustic stethoscope, allow the visual display of sounds in both standard waveform and spectral formats and allow the development of computer-assisted programs. Electronic signals can be further processed and digitalized to a laptop or personal computer for teaching, competency testing, and for comparison with previous or future recordings. The results of comparative studies are disappointing but data exists regarding the better performance

FIG. 1: Parts of stethoscope.

of electronic stethoscopes in special circumstances. In a study of 219 patients, an electronic stethoscope provided superior quality sounds in 65% of patients as compared to an analog stethoscope.[5] The use of the electronic stethoscope in clinical practice is still limited though physicians with hearing loss or the elderly may find them useful.

The future digital stethoscope will include the application of machine learning (ML) and artificial intelligence (AI) allowing analysis of complex data of heart sounds, murmurs, and abnormal heart rhythm.[6] Smartphones have the potential to integrate these new stethoscope technologies and integrate them into our daily practice.

Another advance is the development of a miniaturized, battery-operated, real-time handheld ultrasound imaging device, also called an "ultrasound stethoscope".[7] It is easy to use with good imaging capabilities and has been found to be useful in emergency rooms, intensive care units, outpatient clinics, and screening programs. Currently, the role of these devices in individual practice versus conventional stethoscopes and comprehensive echocardiography is uncertain.

RISE AND DECLINE OF AUSCULTATION

Laënnec's contribution to cardiac auscultation is in the revolutionary discovery of the stethoscope and a scientific approach to clinical examination. Major advances in the understanding of mechanisms, significance and prognostic implications of heart sounds and murmurs occurred in the 20th century with the advent of fluoroscopy, chest X-ray, right and left heart catheterization, angiography, external and internal phonocardiography, and echo-phonocardiography. The outstanding contributions of distinguished physicians across the globe including Paul Wood, Aubrey Leatham (both UK), Samuel Levine, W Proctor Harvey, J Willis Hurst, Joseph K Perloff, and Michael Criley (all USA) ushered a scientific era of auscultation.[8]

Auscultation became a dominant part of physical examination in the19th century because of the high incidence of rheumatic heart disease (RHD) globally. Stethoscope proved to be of unparalleled value and often the competence of a cardiologist was judged by his skills in auscultation. This period is often referred to as the "Golden Era of the Stethoscope". The scenario changed in the late 1990s with the epidemiological shift to coronary artery disease (CAD), the advent of echocardiography, Doppler, other imaging techniques, and the loss of important teachers who were the gold standard of teaching. All these developments resulted in a decrease in interest and diminution of the physical examination.

During cardiology training and in practice, auscultation is considered the most important component of the physical examination which is difficult to master. The individual auscultatory proficiency is highly variable with a considerable amount of subjectivity. Competent cardiac auscultation skills are declining among students, residents, and physicians and the deficiency begins in medical schools.[9-11] Several studies have been done to assess the diagnostic value of auscultation using echocardiography with or without Doppler interrogation.[11-13] Despite criticisms surrounding the design, merit and scientific value of these studies, certain conclusions can be drawn: (1) The interobserver agreement of auscultation is moderate to poor. (2) There is low sensitivity for diagnosing diastolic murmurs and gallop sounds. (3) Sensitivity and specificity improve with the increasing experience of the clinician. (4) In serious valve lesions, the sensitivity was 100% and correlated with the severity of the pathological changes. In clinical practice, poor auscultatory skills often lead to a delayed diagnosis and treatment as well as unnecessary potentially expensive and harmful investigations.

AUSCULTATION OR ECHOCARDIOGRAPHY?

A sensational news item published in the Washington Post[14] claimed that the "stethoscope is having a crossroad moment". This article ignited a debate about technologies, their impact on basic auscultation skills, and the demise of the stethoscope. Studies have demonstrated superior diagnostic accuracy of echocardiography in detecting subtle cardiac disorders as compared to auscultation alone.[15-18] However, the proponents of point of care acknowledge the relatively high risk of misdiagnosis among in-experienced operators with ultrasound.[18] Narula and colleagues advocate incorporating selective use of bedside ultrasound (insonation) as the fifth component of clinical examination.[19] They argue that seeing pathologies through imaging might improve interest in a physical examination in the trainees.

Dr Valentin Fuster vehemently argues in favor of physical examination using a stethoscope and cautions that echocardiography systems are not and will never be able to eradicate the stethoscope, as it is not possible for every physician to possess a handheld echocardiography in the United States of America or elsewhere.[20] Fuster quotes several clinical situations where even the experienced echocardiography operator misses cardiac pathologies which can be detected by a stethoscope. One example is a febrile patient with pericarditis without effusion where echocardiography remains normal but a pericardial rub can be detected by a stethoscope. Pulmonary hypertension without detectable tricuspid regurgitation is often missed on echocardiogram and diagnosed by stethoscope. The existence of better tests does not negate the stethoscope but pushes to understand the value alongside the cardiac auscultation.

STETHOSCOPE IN CORONAVIRUS DISEASE 2019 ERA

During the COVID-19 pandemic, a number of articles/viewpoints appeared about the fate, hygiene, modified versions, and replacement of the stethoscope.[21-25] An expert group published a logical viewpoint entitled "COVID-19 outbreak: less stethoscope, more ultrasound".[25] The reasons to abandon the stethoscope during the pandemic were many including the safety of the medical professionals and the difficulty to use conventional stethoscopes after wearing the protective clothing.

An excellent paper entitled "Do not throw away the stethoscope!" from a large military hospital in China discussed the value of stethoscopes over ultrasound equipment.[22] A

simple substitute to the traditional stethoscope was prepared by using a sterilized paper tube around an empty potato chip cylindrical packet. This can be kept on each bed and was found to be economical, safe, and none of the personnel involved in using this version got severe acute respiratory syndrome related coronavirus-2 (SARS-CoV-2) infection. This contactless stethoscope utilizes a built-in bluetooth drum and earplugs. The earplugs can be inserted into the ear before wearing the protective equipment. The authors discuss the value of human care, drawbacks of ultrasound physicians (vis-à-vis clinicians), the potential of spreading infection by the ultrasound probe, the utility of auscultation in the examination of lungs, and logistics and cost with the use of this substitute stethoscope.

FUTURE OF THE STETHOSCOPE

The time-honored stethoscope despite its limitations is a patient-friendly, effective, and economic equipment in medical practice. It is feared that stethoscopes will soon be degraded from a valuable diagnostic instrument to a token unless serious attempts are made to improve the efficiency in auscultation.[26] New innovations are required to train students, physicians, and healthcare professionals in cardiac auscultation to avoid misinterpretation. The future seems to be in incorporating multimedia applications (computers and smartphones), audio CDs, and patient stimulators into auscultatory teaching. The online platforms and phone-based applications offer a low cost, flexible, and effective medium for evidence-based auscultatory techniques. The American College of Cardiology (ACC) and teaching heart websites offer online auditory training programs. Modern techniques may revive interest in auscultation, and avoid unnecessary diagnostic tests and costs. Late Dr Carolyn Reed summarized that modern tests, machines, and procedures cannot supplant listening, experience, and intuitiveness.[10] Let us hope that the serious and irreparable loss of losing the stethoscope is avoided by future generations.

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CHAPTER 6

Approach to Chest Pain: The New Perspective

Vijay Bang, Mustafa Taskeen

ABSTRACT

Chest pain is one of the notorious symptoms that baffle the physician and the patient in the office and emergency department. It is imperative to distinguish the myriad of etiologies of chest pain to prevent life-threatening complications, including death. The challenge lies in discriminating between life-threatening cardiac causes of chest pain from noncardiac causes. If missed, the diagnosis of acute coronary syndrome (ACS) leads to substantial consequences and early mortality. On the other hand, low-risk patients for "ACSs" should invariably be treated conservatively, considering the cost of admission, unnecessary procedures, and investigations having a low probability of improving patient outcomes. This chapter is being written to simplify the algorithm for prognosticating the symptoms of chest pain with the help of recently published guidelines by the American College of Cardiology (ACC).

INTRODUCTION

Among the given population of patients undergoing evaluation of chest pain in the emergency departments, 10–15% have "acute myocardial infarction" or "unstable angina".[1] A small percentage of patients have life-threatening complications such as "pulmonary embolism" or "acute aortic dissection".[2] However, most leave the emergency department without a diagnosis or with a diagnosis of a noncardiac-related condition.[2] The noncardiac conditions include musculoskeletal syndromes, disorders of the abdominal viscera, and psychological ailments.[2]

CAUSES OF ACUTE CHEST PAIN

Myocardial Ischemia or Infarction

It is the most common serious cause of acute chest discomfort caused due to myocardial—oxygen demand and supply mismatch secondary to atherosclerosis or coronary spasm.[3] It manifests as chest heaviness, squeezing, burning to feel, choking, or difficulty breathing.[3] According to the recent American College of Cardiology (ACC) guidelines, chest pain means pain, pressure, tightness, or discomfort in the chest, arms, shoulders, neck, back, upper abdomen, or jaw, shortness of breath, and fatigue. All above symptoms should be considered anginal equivalents.[4] The natural history of angina is altered in women, the elderly, and diabetics.[4]

Some essential characteristics of noncardiac chest pain are as follows:

- Pleuritic pain (Sharp pain aggravated with respiratory movements)
- Sole location of discomfort arising from the middle or lower abdominal region
- Pain localized by the tip of one finger
- Constant pain persisting for hours unrelated to exertion or very brief, lasting for a few seconds or less.[5]

High-sensitivity cardiac troponins are the preferred standard in establishing a biomarker diagnosis of acute myocardial infarction, permitting more accurate detection and exclusion of myocardial injury.[5]

Pericarditis

Noninfectious causes involve the visceral pericardium and hence do not cause chest pain. It is an infectious cause that leads to sharp pleuritic pain associated with breathing, coughing or changes in position. The pain of pericarditis is frequently in the shoulders and neck as it is a referred pain from the diaphragm. Pericarditis occasionally mimics the crushing type of pain seen in myocardial infarction.[6]

Vascular Disease

"Acute aortic dissection" leads to sudden onset, excruciating ripping type of pain.[7] The anterior aortic dissection tends to manifest in the anterior aspect of the chest, while posterior descending aortic dissection leads to cause pain in the back of the chest.[7] Aortic dissections are rare and are associated with connective tissue disorders such as Marfan's syndrome and Ehlers–Danlos syndrome, or bicuspid aortic valve, hypertension, and pregnancy.[7]

"Pulmonary embolism", if massive, cause severe substernal chest pain commonly attributed to pulmonary artery dissection. Extreme case scenarios lead to sudden onset of dyspnea, tachycardia, hypotension, and right heart failure. Smaller emboli cause pulmonary artery infarction leading to a pleuritic type of chest pain.[2]

Pulmonary Conditions

Pulmonary conditions cause dyspnea, and pleuritic type of chest pain—tracheobronchitis causes midline burning type of pain, whereas pneumonia causes pain over the involved lung. The pain of pneumothorax is sudden in onset and rapid in progression. Primary pneumothorax occurs in tall thin individuals, while secondary pneumothorax is seen in the setting of chronic obstructive pulmonary disease (COPD), asthma or cystic fibrosis.[2]

Gastrointestinal Conditions

Reflux esophagitis causes a burning type of chest pain exacerbated by spicy meals, alcohol, and aspirin which gets aggravated by assuming a recumbent position and relieved after acid relieving therapies. Mallory-Weiss tear in the esophagus occurs in patients with continuous vomiting. Peptic ulcer disease often causes pain in the epigastric region radiating to the shoulder and chest—excessive vomiting against closed glottis results in Boerhaave syndrome with mediastinitis. Very unusually, cholecystitis causes chest pain radiating to the back.[2]

Musculoskeletal Disorders

Chest pain arising from musculoskeletal disorders involves the chest wall, i.e., costochondritis, or conditions affecting the nerves of the chest wall such as herpes zoster or cervical disk disease. The pain is elicited by direct pressure over the affected area or the patient's neck movements.[2]

DIAGNOSTIC CONSIDERATIONS

Clinical Evaluation

When a patient with chest pain comes to the emergency department, clinicians should address a series of issues related to prognosis and immediate treatment. Clinical decision pathways have to be applied based on clinical stability and the immediate prognosis of the patient. If the risk of a life-threatening illness is low, whether to discharge the patient for outpatient management or further testing and observation is required needs to be ascertained.[8]

Initial Assessment

It involves history, physical examination, and investigations. History should include the quality, location, nature of onset, and duration of chest pain in either setting.[9] The pain arising from myocardial ischemia is gradual, radiating to the jaw, bilateral arms, back or shoulders, associated with tightness or heaviness in the chest, which gets aggravated on exertion and relieved after rest. A well-localized pain, unrelated to the effort, dull aching in character with no electrocardiograph (ECG) changes should usually be safely regarded as noncardiac chest pain.[10] Accompanying symptoms such as nausea, shortness of breath, giddiness, diaphoresis, and palpitations are dominant characteristics of cardiac chest pain.[10] According to the latest ACC/American Heart Association (AHA) guidelines, "Atypical" terminology for chest pain is out as it is misleading; noncardiac should be used if heart disease is not suspected.

Physical Examination

A focused cardiovascular examination should initially be performed to diagnose acute coronary syndrome (ACS) or other potentially severe causes of chest pain such as aortic dissection, tension pneumothorax, pulmonary embolism, or esophageal rupture. It includes evaluating blood pressure in both arms and pulses in both legs. Unequal blood pressures and pulses indicate aortic dissection. Chest auscultation may reveal diminished breath sounds, a pleural rub or evidence of pneumothorax, pulmonary embolism, pneumonia, or pleurisy. Tension pneumothorax causes deviation of the trachea away from the side of the pneumothorax. The cardiac examination should seek pericardial rubs, systolic and diastolic murmurs and third or fourth heart sounds.[11]

Investigations

An ECG is essential to test for patients with acute chest discomfort and an imperative investigation to delineate cardiac from noncardiac causes of chest pain. The new ACC guidelines recommend obtaining serial ECGs to detect potential ischemic changes, especially when the clinical suspicion for ACS is high. It is also prudent to get posterior leads v_7 to v_9, and right-sided chest leads ECG to rule out right ventricular infarction and posterior wall myocardial infarction, respectively. The presence of electrocardiographic changes is consistent with ischemia or infarction. Thus, such patients should immediately be admitted to a unit with ECG monitoring with a capacity to respond to cardiac arrest. The absence of changes does not exclude acute ischemic heart disease, but the risk of life-threatening complications is low if ECG is normal. Such patients are often candidates for early exercise stress testing.[12]

A chest radiograph is helpful to evaluate other possible causes of chest discomfort, such as pericardial disease, aortic dissection or aneurysm. Markers of myocardial injury have proven to be a very effective tool in evaluating the etiology of chest discomfort.[13] High sensitive Troponin I (hsTropI) is the preferred biomarker enabling more rapid detection or exclusion of myocardial injury and increasing diagnostic efficacy.[14] Provocative testing is inappropriate in patients with ongoing

chest pain. Rest myocardial perfusion scans or CT angiography in such patients are an emerging alternative diagnostic strategy. The warranty period for a standard CT coronary angiography (CTCA) report is 2 years, while that of a standard stress test is 1 year, beyond which retesting is advisable.

THE CLINICAL DECISION PATHWAY FOR ACUTE CHEST PAIN

The clinical decision pathways for chest pain in emergency and outpatient settings are routinely applied. The previous testing, when available, is incorporated into clinical decision making. It is reasonable to exclude myocardial injury for a patient with acute chest pain having a normal ECG, with symptoms mimicking ACS beginning at least 3 hours prior to casualty arrival with a single hsTrop I report being below the level of detection.[15] According to the latest ACC guidelines, the clinical decision pathway incorporates three cohorts of patients, i.e., low-risk, intermediate-risk, and high-risk patients with stable chest pain and with or without preexistent coronary artery disease (CAD).[16-20]

A low-risk patient has acute chest pain with a 30-day risk of death or major adverse cardiac event being <1%. It is reasonable to discharge such patients without admission or urgent cardiac testing.[21-25] An intermediate-risk patient with acute chest pain requires transthoracic echocardiography as a rapid bedside tool to establish the ventricular and valvular function, evaluate wall motion abnormalities, and rule out pericardial effusion. Such patient requires admission to an observation unit to shorten the length of stay and cost relative to inpatient admission.[26-31]

The latest ACC guidelines recommend CTCA in patients with intermediate-risk with no known CAD to rule out atherosclerotic plaque and obstructive CAD.[32-41] If there is moderate to severe ischemia documented in current or prior stress testing (<1 year) with no known CAD established by prior anatomic testing, the latest guidelines recommend invasive coronary angiography (ICA).[42-51] Also, suppose the intermediate-risk patient with acute chest pain has a history of prior CAD; in that case, fractional flow reserve (FFR) CT is reasonable for diagnosing vessel-specific ischemia and aids in decision making regarding coronary vascularization.[52-57] Exercise ECG, stress echocardiography, stress myocardial perfusion imaging (MPI), or stress cardiac MRI are beneficial for diagnosing myocardial ischemia in eligible intermediate-risk patients with no known prior CAD.[58-63]

High-risk patients include those with new ischemic changes on electrocardiography, troponin-confirmed acute myocardial injury with new-onset left ventricular (LV) systolic dysfunction or newly diagnosed moderate to severe ischemia on stress testing.[64-66] ICA is an absolute indication in such patients.[67,68]

For patients with acute chest pain with prior coronary artery bypass graft procedure, coronary CT angiography (CCTA) is an effective tool for evaluating graft stenosis and myocardial ischemia.[69-75] If CCTA or stress testing are indeterminate, ICA is helpful.[76] Another advantage of CT angiography is that it is the investigation of choice for pulmonary embolism and aortic dissection. Hence, triple rule out CTA can evaluate PE, aortic dissection, and CAD.[77,78]

THE CLINICAL DECISION PATHWAY FOR STABLE CHEST PAIN

Low-risk patients with stable chest pain having no known CAD should undergo coronary artery calcium scoring and exercise stress testing to exclude calcified plaque and the likelihood of obstructive CAD.[79-84]

For intermediate-high-risk patients with stable chest pain and with no known CAD, CCTA is adequate for diagnosing CAD, risk stratification, and guiding treatment decisions.[34,36,37,85] Transesophageal echocardiography (TTE) is effective when there are pathological Q waves with signs and symptoms of heart failure, complex ventricular arrhythmia or a heart murmur with an unclear diagnosis.[86-88] ICA is reasonable if stress testing and CCTA both are inconclusive, but there is a high suspicion of CAD.[89-91]

In patients with known obstructive CAD with stable chest pain, optimization of guideline-directed medical therapy (GDMT) is always a reasonable option.[92-94] If the pain is persistent in such patients despite optimized medical treatment, then ICA is the next step for therapeutic decision making.[94] These patients will thereby benefit from FFR or instantaneous wave-free ratio. Supposedly such patients undergo CCTA, then ICA effectively guides therapeutic decision-making when there is either CCTA defined >50% stenosis in the left main coronary artery or obstructive CAD with FFR < 0.80 or critical stenosis in all three vessels.[95-97]

Coronary microvascular dysfunction (CMD) is a new emerging notion that explains the onset of chest pain in patients with suspected ischemia but no obstructive epicardial CAD.[98,99] Stress positron emission tomography (PET)-MPI with myocardial blood flow reserve is a reasonable noninvasive investigation to diagnose CMD. Coronary flow reserve (CFR) and index of microcirculatory restriction (IMR) are two significant indices of ICA to diagnose CMD. CFR < 2 with IMR > 25 coupled with ECG changes is indicative of CMD.[100,101]

Ultimately, the traditional trifecta of a clinician's assessment of the prior probability of cardiac chest pain, the nature of acute episode coupled with physical examination and more objective data, which includes serial ECGs, rapid biochemical testing and imaging, helps in the optimization of patient triage.

CONCLUSION

A thorough history, physical exam, and the use of predictive tools and diagnostic modalities are critical in diagnosing chest pain using a systematic approach. Importantly, life-threatening causes should be ruled out and treated, since these etiologies progress quickly.

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CHAPTER 7

Heart Sounds and Murmurs

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ABSTRACT

Despite all the advances in diagnostic imaging and biomarkers, cardiac auscultation lies at the heart of cardiac diagnosis. Normal first heart sound (S1) occurs with the onset of left ventricular (LV) contraction coinciding with the upstroke of carotid impulse. The intensity and splitting of the two components of second heart sound (A2 and P2) aid in differentiating many close cardiac diagnoses. The third heart sound (S3), heard during rapid filling phase of ventricular diastole, usually suggests an overloaded ventricle of heart failure patients. Similarly, the fourth heart sound (S4) is a diastolic sound corresponding to atrial filling phase of ventricular diastole and usually suggests a stiff ventricle as in hypertrophy or ischemia. The presence of systolic and/or diastolic murmur is often the first pointer toward valvular heart disease (VHD). Murmur characteristics to be noted during examination include: Location, timing, intensity (loudness/grade), pitch (frequency), duration, configuration, quality, radiation, etc. In this chapter, we describe normal and abnormal heart sounds, their timing, genesis and clinical significance. In addition, various physiologic and pathologic causes of murmurs are reviewed in detail with special emphasis on accompanying physical examination and echocardiographic findings.

INTRODUCTION

We recall from the physics of sound waves that "amplitude" or the maximum displacement from the equilibrium position corresponds to the "loudness" of a sound wave, i.e., louder sounds have a larger amplitude and vice versa. The "frequency" [the number of oscillations per second, measured in hertz, (Hz)] correlates with the "pitch" of a sound wave, i.e., higher frequency implies higher pitch and vice versa. Human ears can appreciate sounds with frequencies between 20 and 20,000 Hz with frequencies of 1,000–5,000 Hz being heard the best (the usual human conversations are in this range). Most heart sounds and murmurs are in frequency range of 30 and 1,000 Hz, which therefore requires careful auscultation. We can appreciate two sounds as being distinct if they are at least 20 ms apart. First and second heart sounds (S1 and S2) are examples of relatively high frequency (pitch) sounds while third and fourth heart sounds (S3 and S4) are low frequency (pitch) sounds.

In this chapter, we will review the normal and abnormal heart sounds as well as murmurs, highlight their genesis as well as clinical implications.

HEART SOUNDS

First Heart Sound

Genesis and timing: The most commonly accepted idea is the one popularized by Leatham, according to which, the S1 has two high frequency components that arise from the closure of mitral (M1) and tricuspid (T1) valve leaflets respectively at the onset of ventricular contraction.[1] The two components of S1 are separated only slightly (20–30 ms apart) which makes their clinical appreciation slightly difficult. The closure of mitral valve normally precedes closure of tricuspid valve, hence M1 preceded T1. The mean time from the QRS onset to M1 was 60 ± 3 ms while that between QRS onset to T1 was 90 ± 2 ms.[2] The two components of S1 (M1 and T1) are best heard in the mitral (apex) and tricuspid (lower left sternal border) area respectively. An entirely different viewpoint on the mechanism of S1 is put forth by Luisada and colleagues who believe that closure of atrioventricular (AV) valves contribute only minimally to the genesis of S1.[3] They highlight the fact that both AV valves are already closed at the time of S1 or onset of ventricular contraction. S1

occurs due to tensing of the ventricular walls and mitral valve apparatus producing the acceleration and deceleration of blood column and vibration of cardiohemic system. The opening of aortic valve also contributes to the second component of S1 and that tricuspid valve closure is not related to genesis of S1.[3] S1 occurs with the onset of left ventricular (LV) contraction following the QRS onset on ECG by 60–90 ms. S1 coincides with the upstroke of carotid impulse.

Intensity/loudness: Normally, S1 is louder than S2. M1 is louder than T1 and usually radiates to all precordial areas. T1 is best appreciated at left lower sternal border or the tricuspid area. Several factors determine the intensity of S1 including the state of the valve leaflets (integrity, calcification, mobility, etc.), rate of closure of valve leaflets and ventricular contraction, and cardiac cycle length. Inadequate leaflet coaptation as in mitral regurgitation (MR) leads to reduced intensity of S1 or soft S1. Similarly, increased calcification and hence decreased leaflet mobility produces a soft S1. The rate of rise of ventricular pressure and hence rate of closure of mitral valve affects intensity of S1. Exercise, inotropes, or hyperdynamic states increase the intensity of S1, while LV dysfunction decreases the intensity of S1. The intensity of S1 also varies inversely with the PR interval. At shorter PR intervals, the mitral valve leaflets are widely separated at the onset of LV contraction and hence produce a higher intensity sound on closure. Lastly, the characteristics of surrounding structures and the chest wall also affect the intensity of S1, e.g., hyperinflated lungs and pericardial or pleural effusion or thick body wall in obese adults decrease the intensity of S1 **(Box 1)**.

Splitting of S1: M1 normally precedes T1 by 20–30 ms and can be appreciated at left lower sternal border.[1] The mitral component is louder than tricuspid component, and the latter is heard mostly in left lower sternal area or tricuspid area **(Box 2)**.

Second Heart Sound

Genesis and timing: S2 has two components, which arises from the closure of aortic (A2) and pulmonic (P2) valves respectively.[1] The closure of aortic valve cusps coincides with the A2 and the dicrotic notch of aortic pulse. S2 coincides with the downslope of carotid pulse.[7] A2 and P2 are best heard over left second intercostal space using diaphragm of the stethoscope. A2 is transmitted to all precordial auscultatory areas, while P2 is heard best only at upper left sternal border.

Intensity/loudness: The determinants of A2 intensity include structural integrity and mobility of aortic leaflets, size of aortic root, and aortic pressure. Similarly, the intensity of P2 depends on structural integrity and mobility of pulmonary valve leaflets, pulmonary pressures, and size of the pulmonary artery **(Box 3)**.

Splitting of S2: During inspiration, there is increased venous inflow into the right heart and consequently, prolongation of right ventricular (RV) ejection time and delay in pulmonary valve closure. Hence, the splitting of S2, i.e., P2 delayed in comparison to A2 during inspiration. The degree of splitting varies between 20 and 60 ms. Another explanation for inspiratory splitting of S2 is based on decrease in impedance of pulmonary vascular bed during inspiration.[8]

BOX 1 Factors affecting intensity of S1.

Increased intensity or loud S1 (If S1 is louder than S2 over left or right second interspace):

- *Increased transmitral gradient*: Mitral stenosis (with mobile leaflets) and left atrial myxoma
- *Increased transtricuspid gradient*: Tricuspid stenosis and right atrial (RA) myxoma
- Increased transvalvular flows, e.g., left to right shunt lesions such as atrial septal defect (ASD), ventricular septal defect (VSD) or patent ductus arteriosus (PDA), and high outflow states
- *Short diastole*: Tachycardia and short cycle lengths in atrial fibrillation
- *Short PR interval*: Preexcitation syndrome

Decreased intensity or soft S1 (If S1 is softer than S2 at the apex or left sternal border):

- *Lack of leaflet coaptation*: Rheumatic mitral regurgitation
- Long PR interval (mitral valve in semi-closed position at the onset of ventricular contraction)
- Severe aortic regurgitation (AR) (premature closure of mitral valve)[4]
- Aortic stenosis (AS) (partially closed mitral leaflets due to raised LV filling pressures)
- Heart failure with reduced ejection fraction (decreased LV contractility)
- Left bundle branch block
- *Decreased conduction through chest wall*: Hyperinflated lungs in chronic obstructive pulmonary disease (COPD), pleural effusion, and pericardial effusion

Varying intensity of S1:

- *Atrial fibrillation*: Due to changes in cycle length
- *Premature beats*: Again, due to changes in cycle length and position of mitral leaflets prior to LV contraction
- *Atrioventricular dissociation*: As in complete heart block, due to random variation of PR intervals
- *Auscultatory alternans*: S1 becomes soft and loud in alternate beats and is often accompanied by electrical alternans and pulsus paradoxus in severe pericardial tamponade[5]

BOX 2 Splitting of S1.

Wide splitting of S1:

- *Right bundle branch block (RBBB)*: Delay in T1
- *Atrial septal defect (ASD)*: Delay in T1
- Tricuspid stenosis
- *Ebstein anomaly*: Sound produced by closure of the abnormal tricuspid valve is widely split from M1 component and is known as "sail sound".[6]

Reverse splitting of S1:

- *Left bundle branch block (LBBB) and right ventricle (RV) pacing*: Delay in M1
- Mitral stenosis and left atrial (LA) myxoma

BOX 3 Factors affecting intensity of S2.

Increased intensity/loudness of A2:

- Systemic hypertension
- Coarctation of aorta
- Ascending aortic aneurysm
- *Anteriorly positioned aortic root*: Transposition of great arteries and tetralogy of Fallot (ToF)

Decreased intensity/loudness of A2:

- Severe aortic regurgitation or stenosis
- Hypotension

Increased intensity of P2 (If P2 is louder than A2 at left second interspace or if P2 is audible at apex):

- Pulmonary hypertension due to any etiology
- Atrial septal defect (ASD) (P2 may be audible at apex even in absence of pulmonary hypertension)
- Idiopathic pulmonary artery dilation

Decreased intensity of P2:

- Pulmonary regurgitation and stenosis
- ToF (usually inaudible P2)

Physiologic splitting of S2: During inspiration, A2 precedes P2 by 20–60 ms and thus split is considered physiologic and is not appreciated during expiration when A2 and P2 are superimposed.

Wide splitting of S2: If A2 and P2 seem distinct/separated during expiration, wide splitting of S2 is to be suspected for which various causes **(Box 4)**.

Wide and fixed splitting of S2: Fixed splitting is defined as split of A2 and P2 in inspiration as well as expiration with ≤ 20 ms variation in A2–P2 interval between the two.[9] Examples include:

- Large ASD (large left to right shunt prolongs RV ejection and P2; no differential filling between right and left atria)
- Right ventricular failure, pulmonary embolism (RV not able to vary its stroke volume during inspiration)

Paradoxical/reverse splitting of S2: Reverse splitting is defined as splitting of A2 and P2 during expiration while they narrow or fuse during inspiration. During expiration, A2 follows P2 and during inspiration with normal delay of P2, they tend to fuse **(Box 4)**.[10]

BOX 4 Splitting of S2.

Wide variable splitting of S2:

- Electromechanical delay [resulting in delayed activation of right ventricle (RV)]:
  - Right bundle branch block (RBBB)
  - Wolff-Parkinson-White (WPW) syndrome with left ventricular (LV) preexcitation
  - Premature beats arising from LV
- Prolonged RV ejection time:
  - Pulmonary stenosis (valvular, supravalvular, and infundibular)
  - Pulmonary arterial hypertension
  - Biventricular failure
- Reduced LV ejection time:
  - Severe mitral regurgitation (MR)
  - Ventricular septal defect (VSD)
  - Constrictive pericarditis

Wide and fixed splitting of S2:

- Large ASD
- RV failure
- Pulmonary embolism

Paradoxical/Reverse splitting of S2:

- Electromechanical delay (resulting in delayed activation of LV)
  - Left bundle branch block (LBBB)
  - RV pacing
  - WPW with RV preexcitation
  - Premature beats arising from RV
- Prolonged LV ejection time
  - Severe AS and LV outflow tract obstruction
  - Systemic hypertension
  - LV dysfunction and myocardial ischemia
  - Severe AR

Single S2:

- Absence of A2:
  - Severe calcific AS with immobile leaflets
  - Severe AR (due to leaflet destruction as in infective endocarditis)
- Absence of P2:
  - Pulmonary atresia
  - Truncus arteriosus
  - Tetralogy of Fallot (ToF)
  - ToF with absent pulmonic valve
  - Inaudible P2 (obesity and emphysema)
- Fusion of A2 and P2:
  - Aortic stenosis
  - Eisenmenger VSD
  - Single ventricle

Single S2: It results from either absence of A2 or P2 or fusion of A2 and P2. Examples in **Box 4**.

Third Heart Sound

Genesis and timing: S3 is a low frequency sound heard during rapid filling phase of ventricular diastole **(Fig. 1)**. S3 is believed to arise from sudden limitation of longitudinal

expansion of LV wall during the rapid filling phase of diastole.[11] It corresponds to the descent of jugular waveform, usually following S2 by 140–160 ms. S3 is best appreciated with the bell of the stethoscope. LV S3 is heard best at the apex with patient in left lateral decubitus position. RV S3 is heard best at lower left sternal border and like other right-sided heart sounds increase in intensity during inspiration. Addition of S3 and/or S4 to S1/S2 produces tripling or quadrupling of heart sounds which resemble the canter of a horse, referred to as gallop rhythm.

Clinical significance: S3 may be heard in children and healthy young adults. It is usually pathological in people over the age of 40 years and suggests an overloaded ventricle that resists any further filling during early diastole. Certain maneuvers to augment the S3 audibility include exercise (increases filling by increasing venous return) or leg raising. The causes of S3 include the following:

- *Heart failure*: S3 is heard more commonly in systolic heart failure than diastolic failure.[12] S3 also has a prognostic value in HF patients. The presence of S3 was associated with increased risk of development of overt heart failure in patients with asymptomatic LV dysfunction.[13] Another study found an association of S3 in patients of heart failure with increased risk of heart failure hospitalization and mortality.[14] A novel study by Marcus and colleagues evaluated the diagnostic performance of diastolic sounds (S3/S4) in predicting raised left ventricular end-diastolic pressure (LVEDP), reduced left ventricular ejection fraction (LVEF), and raised brain-type natriuretic peptide (BNP). S3 and S4 had low sensitivities (<50%); however, S3 had a good specificity to detect elevated LVEDP, reduced LVEF, or elevated BNP (92%, 87%, and 92% respectively).[15]
- *Mitral regurgitation*: S3 is common in patients with hemodynamically significant MR, but it does not necessarily mean LV systolic dysfunction or elevated filling pressures.[16]
- *Aortic regurgitation*: Presence of S3 in AR suggests LV dysfunction or elevated filling pressure.
- High output states such as thyrotoxicosis and pregnancy
- Athletes[17]
- Right ventricular S3 is heard in various states of right heart overload including right heart failure, significant tricuspid regurgitation (TR), or massive pulmonary embolism.

Differential Diagnoses for S3

- *Opening snap (OS) of mitral stenosis (MS)*: The OS is heard best near left lower sternal border, but radiates all over the precordium, is a higher pitch (louder) sound, and occurs earlier than S3 (80–120 ms after S2). On the other hand, S3 is heard at the apex, has a lower pitch, and occurs 140–160 ms after S2.
- *Splitting of S2*: The two parts of split S2 (A2/P2) have a similar pitch, whereas S3 has a lower pitch and is best heard through the bell of the stethoscope.
- *Pericardial knock*: In constrictive pericarditis, the ventricular diastolic filling is limited to early diastole following which the filling gets limited by the stiff noncompliant pericardium. This sudden cessation of filling produces an early diastolic sound (termed as "pericardial knock") which has higher pitch and frequency than S3 and occurs earlier than S3 (typically 100–120 ms after S2).

Fourth Heart Sound

Genesis and timing: S4 is a low frequency ventricular filling (diastolic) sound that occurs during the atrial filling phase of ventricular diastole **(Fig. 1)**. It occurs when the atria contract and try to push blood in a stiff LV, resulting in vibrations in the cardiohemic system which get transmitted to body surface as fourth heart sound. S4 corresponds to *a*-wave of the atrial pressure tracing.[18] S4 is a low-pitched sound heard best with the bell of the stethoscope. LV S4 is heard best at the cardiac apex with patient in left lateral position while RV S4 is heard best at the lower left sternal border or epigastrium with patient in supine position. RV S4 increases in intensity during inspiration corresponding to the increased RV filling volume. S4 disappears in atrial fibrillation as a result of loss of the atrial kick/filling phase of diastole. Since S3 and S4 are ventricular filling sounds, their presence signifies a relatively

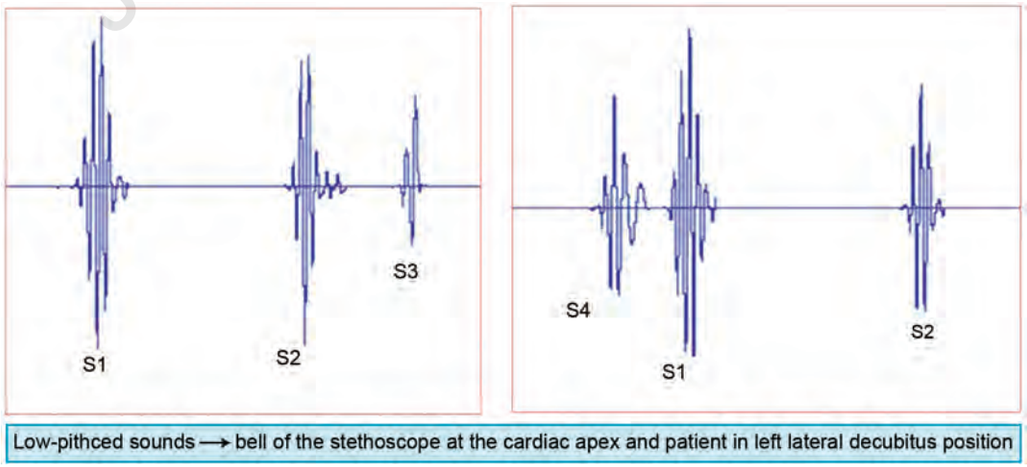

FIG. 1: The third and fourth heart sounds are early and late diastolic filling sounds respectively.

unobstructed AV valve [i.e., absence of significant mitral or tricuspid stenosis (TS)].

Clinical significance of S4: Unlike an S3, an audible S4 is generally abnormal in children and young adults. However, S4 may be heard in otherwise healthy older adults without any cardiac disease due to age-associated decrease in ventricular compliance. When palpable, an S4 is always abnormal, irrespective of patient's age. Examples of conditions that result in S4 include:

- *Myocardial ischemia/infarction*: S4 is present in vast majority of patients during an acute myocardial ischemia/infarction; however, it has poor correlation with the severity of LV dysfunction.[19]
- *Cardiomyopathy*: An S4 is heard in patients with ischemic and nonischemic cardiomyopathy. In patients with chronic coronary artery disease, an audible S4 during an episode of chest pain suggests active myocardial ischemia. S4 is also a frequent finding in patients with chronic LV aneurysm.
- *Diastolic dysfunction*: Conditions that result in a stiff ventricle like LV hypertrophy caused by hypertensive heart disease, aortic stenosis (AS) and hypertrophic cardiomyopathy are often associated with S4.[20,21]
- *Atrioventricular block*: S4 is audible in the setting of prolonged PR interval or first-degree AV block due to separation of S4 from S1. In complete heart block, atria and ventricles contract independent of each other, S4 is heard at a faster rate than S1 and S2. S4 sound occurs randomly irrespective of S1/S2 and may not represent any other hemodynamic abnormality. Detecting S4 in the setting of AV block requires careful auscultation in a quiet room.
- Acute severe MR/AR
- *RV S4*: Pulmonary hypertension and pulmonary stenosis

Ejection Sounds (Clicks)

Ejection sounds or clicks are high frequency early systolic sounds that are produced either by opening of stenotic semilunar valves or opening of normal semilunar valve in a dilated arterial trunk. Ejection clicks occur at the end of isometric contraction phase and beginning of ejection phase of systole and coincide with fully open position of the corresponding semilunar valve. They are more likely to occur in mild than severe stenosis and with mobile rather than immobile leaflets. The mechanism of early systolic sound arising due to dilated arterial trunk in presence of a normal semilunar valve is less clear.

Aortic ejection sound: It occurs approximately 60–80 ms after S1 and about 120–140 ms after the onset of QRS. It is a high frequency and high-pitch sound, heard best with the diaphragm of stethoscope. It is best heard at the apex and is transmitted to all areas of precordium including aortic area or right second interspace. Its intensity does not vary with respiration unlike pulmonary ejection sound.

Clinical significance: Aortic ejection sound occurs in the setting of stenotic but mobile aortic valve and with proximal aortic dilation.

- *Bicuspid aortic valve*: The presence of aortic ejection sound, in absence of other bedside signs of AS, implies a nonstenotic bicuspid aortic valve.[22]
- Aortic stenosis (with mobile leaflets)[23]
- Aortic regurgitation
- Aneurysm of ascending aorta
- Systemic hypertension (due to ascending aorta dilation)

Ejection sound is generally absent in subvalvular or supravalvular AS and hypertrophic obstructive cardiomyopathy (HOCM).

Pulmonary ejection sound: It occurs 90–110 ms after the electrocardiographic Q wave and coincides with maximal opening of the semilunar pulmonic valve. It is a high-frequency sound and is best heard with the diaphragm of the stethoscope. It is best heard at the pulmonic area or the left second interspace, and unlike aortic ejection sound is not transmitted widely. It exhibits a characteristic respiratory variation with its decreased intensity during inspiration (in contrast to other right-sided sounds and murmurs which increase in intensity during inspiration).

Clinical significance: Pulmonary ejection sound occurs in the following settings:

- *Pulmonary valve stenosis*: Pulmonic ejection sound occurs in less severe valvular pulmonic stenosis (PS) as in very severe PS, the degree of leaflet excursion and the RV isovolumetric contraction time decreases and the ejection sound is either absent or gets fused with S1.
- Idiopathic dilation of the pulmonary artery
- Pulmonary hypertension due to any etiology

Nonejection Systolic Sound: Mid-systolic Click

Mitral valve prolapse (MVP) produces a nonejection systolic click which is a high-frequency sound, heard best with the diaphragm of the stethoscope. It occurs at the time of maximal prolapse or billowing of the mitral leaflets into the left atrium (LA) at mid-systole and may or may not be associated with a late systolic murmur.[24,25] The S1-click interval varies with end-diastolic left ventricular volume (LVEDV) and the rate of ejection. The S1-click interval increases with increasing LVEDV (as occurs with supine position, squatting) and shortens with reduced LVEDV (as occurs standing or strain phase of Valsalva maneuver).

Tricuspid valve prolapse also gives rise to a mid-systolic click which is high frequency and best heard with the diaphragm of the stethoscope at lower left sternal border or tricuspid area. It accompanies MVP in most cases; however, it may also occur independently in patients with Ebstein anomaly.

Early Diastolic Sounds

Examples of early diastolic sounds include OS of mitral or TS and tumor plop of atrial myxoma.

Opening snap: The OS is a high-frequency sound produced by opening of diseased AV valves. It corresponds to the moment of maximal opening of AV valves and is absent when the leaflets become calcified and immobile.

Opening snap due to mitral stenosis: It coincides with the maximal opening and doming of the thickened rheumatic mitral valve leaflets and occurs 40–120 ms after S2. It is best heard at the cardiac apex and lower left sternal border using the

diaphragm of the stethoscope. Careful auscultation is needed to differentiate OS from split S2. The interval between OS and S2 (S2-OS interval) is inversely related to the severity of MS.

Functional OS in otherwise nonstenotic mitral valve is also heard in significant MR, thyrotoxicosis, and left to right shunts of ASD or VSD.

Tumor plop: It is heard occasionally in cases of atrial myxoma, when the tumor plops into the ventricle through the AV valve.

Vegetation plop: It is an early diastolic sound which is produced by a large vegetation of mitral valve infective endocarditis prolapsing into the ventricle.[26]

Other Adventitious Sounds

Pericardial friction rub: It refers to a scratching sound generated from rubbing of inflamed pericardial layers (pericarditis). It has systolic as well as diastolic components corresponding to atrial systole, ventricular systole, and rapid-filling phase of ventricle. The rub is best heard through the diaphragm of the stethoscope and its intensity increases with inspiration and patient leaning forward. The rub may be heard throughout the precordium, but best at the left sternal border.

Means–Lerman scratch: In hyperthyroidism, as a result of a hyperdynamic state, a mid-systolic scratching sound is rarely produced due to rubbing of pericardium with the pleura, generating a sound which mimics pericardial friction rub, known as "Means–Lerman scratch".

Mill wheel murmur: This has been described in the setting of air embolism as a crunching or churning sound created due to air bubbles in the right ventricle. It is heard throughout the precordium during systole and diastole.[27]

MURMURS

A murmur on auscultation raises suspicion for valvular heart disease (VHD) and is often followed by echocardiography to confirm the cause of the murmur. The sensitivity and specificity of a murmur on auscultation is variable and depends on the expertise of the examiner, which has generally been on a declining trend given the dominance of imaging in the current era.[28,29] Murmurs arise from the turbulent blood flow across the narrowed or leaking valves and their intensity depends on a number of factors including but not limited to the pressure gradients, size of the orifice, or size of the distal blood vessel into which the blood flows.

Murmur characteristics to be noted during examination include: Location, timing, intensity (loudness/grade), duration, pitch (frequency), configuration, quality, radiation, etc. The intensity or loudness of a murmur is described as grading on a scale of I–VI. Pitch of a murmur refers to its frequency as being either low or high. Various terms are used to describe murmur quality such as harsh, blowing, rumbling, musical, machinery, etc. The configuration of a murmur is described as crescendo or decrescendo or crescendo-decrescendo. Based on timing in cardiac cycle, murmurs can be either systolic or diastolic or continuous (begin in systole and continue to a variable duration in diastole without interruption). The murmurs can be of long or short duration and hence the use of terms like early systolic, holosystolic, early diastolic, or mid-diastolic.

Systolic Murmurs

The causes of a systolic murmur include the following:

- Atrioventricular valve regurgitation, i.e., MR and TR. MR and TR mostly produce a holosystolic murmur; however, it can be early systolic murmur in the setting of acute MR or TR with normal pulmonary artery pressure. MVP produces a late systolic murmur.
- *Aortic stenosis*: Valvular, supravalvular, or subvalvular AS; relative AS due to increased flow across the aortic valve (e.g., aortic regurgitation hyperdynamic states). A mid-systolic murmur also occurs in dilatation of ascending aorta.
- *Pulmonary stenosis*: Valvular, supravalvular, or subvalvular pulmonary stenosis; relative pulmonary stenosis due to increased flow across the valve (e.g., left to right shunt lesions, hyperdynamic states). A mid-systolic murmur also occurs in dilatation of pulmonary artery.
- Ventricular septal defect

Mitral Regurgitation

Mitral regurgitation most commonly produces a holosystolic murmur, but in certain instances it can produce an early systolic (e.g., acute MR) or late systolic murmur (e.g., MVP) or holosystolic murmur with mid-systolic accentuation (e.g., rheumatic MR). The murmur of MR is usually high-pitched and heard best with the diaphragm of the stethoscope at the cardiac apex with patient in left lateral decubitus position **(Fig. 2)**. Generally, the intensity of murmur is grade III or less (so thrill is less common in MR). If the MR jet is directed posteriorly, then the murmur radiates toward the left axilla (most common) and if it is directed more anteriorly, then it radiates toward the base where it may be confused with the murmur of AS or HOCM.[30] Murmur of MR generally has no respiratory variation and may decrease in intensity with standing or Valsalva maneuver. Certain conditions may decrease the intensity of MR murmur including LV dysfunction, low-output states, huge LA size, or associated MS.

In acute MR, the rapid increase of LA pressure and equalization of LV to LA pressure gradient restricts the regurgitation to early systole, i.e., an acute MR produces a decrescendo early systolic murmur.[31] In MVP, the murmur is preceded by a mid-systolic click followed by a late systolic murmur.[32] The murmur of MVP is unique in that it increases in intensity with standing and Valsalva maneuver. Conversely, passive leg raising, isometric handgrip, and squatting reduce the intensity of murmur in MVP (click occurs later and the intensity of murmur decreases).

Tricuspid Regurgitation

Tricuspid regurgitation produces a holosystolic murmur which is best heard with the diaphragm of the stethoscope along the left lower sternal border.[33] A key distinguishing feature of TR murmur is its characteristic increase in intensity with inspiration (Carvallo's sign). This sign, however, is absent in the setting of severe RV failure when the RV volumes do not change significantly with respiratory phases. TR is most

commonly secondary to pulmonary hypertension and hence is accompanied by signs such as loud P2 and left parasternal heave.

The murmur of TR can be early systolic in the setting of primary TR with normal RV pressures as in tricuspid valve IE in intravenous drug abusers. Such a murmur has a lower pitch and a decrescendo configuration just like acute MR. Tricuspid valve prolapse just like MVP produces a late systolic murmur.

Aortic Stenosis

Aortic stenosis produces an ejection systolic crescendo-decrescendo murmur best heard in the right second intercostal area (aortic area) with the diaphragm of the stethoscope **(Fig. 3)**. The murmur is medium pitched, harsh in quality, and radiates into the neck/carotids. A systolic thrill may accompany the murmur over the aortic area or the carotids. The murmur may occasionally radiate to the cardiac apex (where it may be confused with murmur of MR), known as Gallavardin phenomenon. The murmur peaks later (i.e., closer to S2) as the severity of stenosis increases. The longer duration of the murmur and late peaking suggests severe AS, whereas the intensity of murmur may not correlate with the severity of stenosis.

Unlike MR, the murmur of AS varies with cycle length of atrial fibrillation. The A2 component of S2 is diminished

FIG. 2: Holosystolic murmur of chronic severe MR.
(LA: left atrium; LV: left ventricles; MR: mitral regurgitation)

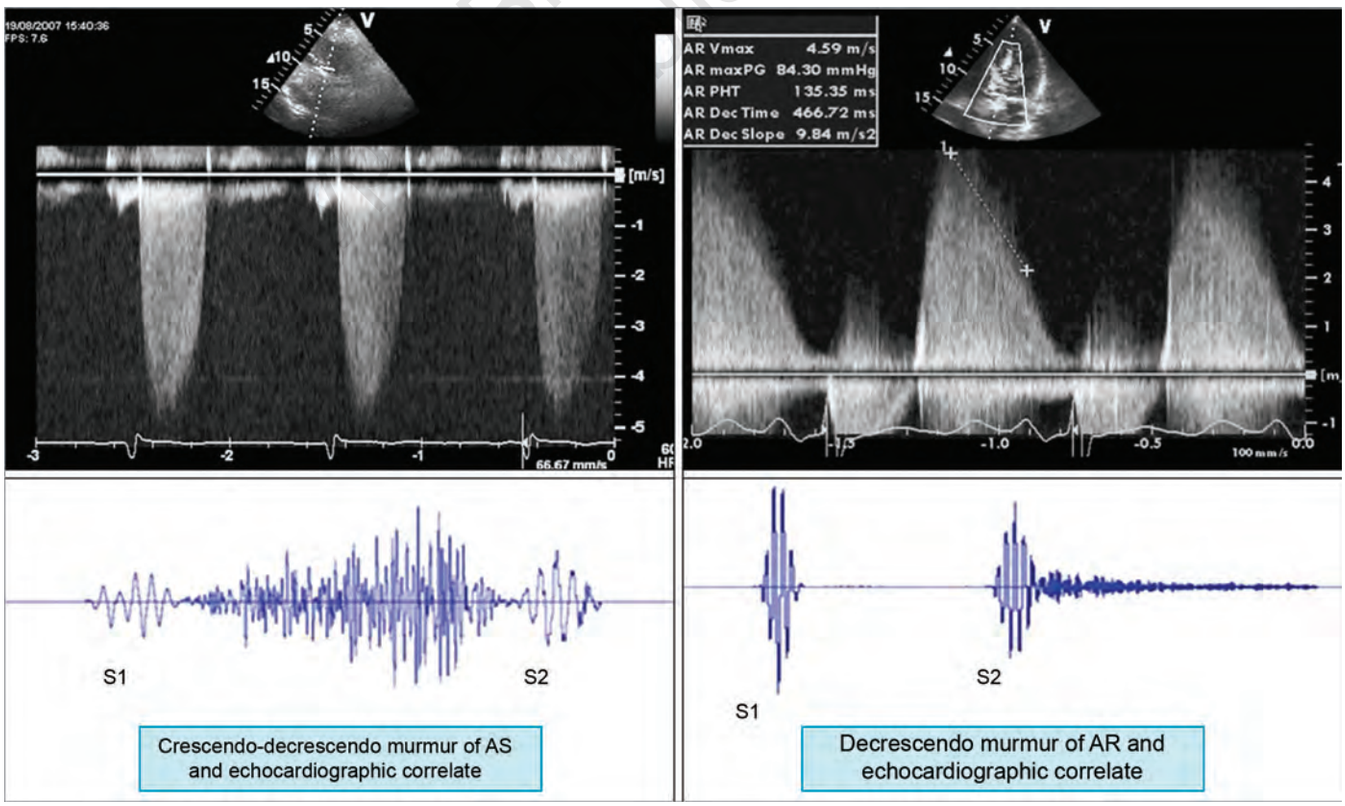

FIG. 3: The configuration of aortic stenosis (AS) and aortic regurgitation (AR) murmurs and their echocardiographic correlates.

in intensity or absent, resulting in single S2 in severe AS. Paradoxical split of S2 may be appreciated in certain cases of severe AS and if present usually indicates a valve gradient of >100 mm Hg.

Aortic ejection sound or click suggests the diagnosis of congenital AS or bicuspid aortic valve. This sound is frequently absent in rheumatic AS.

In supravalvular AS, the murmur is better heard in one interspace higher and radiates more into right than left carotid. The murmur due to subvalvular AS (mostly in HOCM) is best heard along left sternal border and radiates poorly into the neck. The ejection click is also absent in supravalvular or subvalvular AS.

Various points to be considered in differentiation of valvular AS murmur from the murmur due to dynamic LV outflow tract obstruction (LVOTO) in HOCM include:

- Delayed peaking and low amplitude pulse (pulsus parvus et tardus) in severe AS.
- *Standing from squatting position*: This maneuver increases the intensity of murmur in HOCM and decreases the intensity of severe AS murmur.
- *Valsalva maneuver*: During the strain phase, the murmur of HOCM increases while that of severe AS decreases in intensity.

Pulmonic Stenosis

Valvular PS produces an ejection systolic crescendo-decrescendo murmur best heard in the left second intercostal area (pulmonic area) with the diaphragm of the stethoscope, often accompanied by a palpable thrill. In valvular PS, a pulmonic ejection sound or click precedes the murmur. The duration of the murmur correlates with the severity of stenosis, with severe PS leading to a long murmur often submerging A2 component of S2 and ending after it. The murmur of subvalvular or infundibular PS is best heard at a lower location at left parasternal area and is not accompanied by ejection click. S2 is widely split and P2 is reduced in intensity in PS.

Ventricular Septal Defect

The murmur generated due to a VSD varies with the size of the defect and pulmonary pressures which, in turn, determine the magnitude of left to right shunt. Small VSD mostly produces a holosystolic murmur which is loud and often accompanied by a thrill. The murmur is best heard along the left sternal border in the third and fourth intercostal space. Supracristal or outlet VSD murmur may be heard one interspace higher (second intercostal space) where it may be confused with the murmur of PS.

Larger VSD leading to pulmonary hypertension and hence less left to right shunting may produce an early systolic instead of holosystolic murmur. This is accompanied by signs of pulmonary artery hypertension (PAH) like loud P2 and left parasternal heave. In Eisenmenger patients, there may be no murmur across the VSD, instead a mid-systolic murmur due to dilated pulmonary artery is heard. Therefore, in a patient of VSD, a holosystolic murmur suggests favorable hemodynamics or relatively normal pulmonary pressures.

Increased Flow States

Increased blood flow through normal semilunar valves produces relative aortic or pulmonic stenosis and hence ejection systolic murmurs (ESMs) in the aortic and pulmonic areas respectively. This occurs in hyperkinetic states such as anemia, thyrotoxicosis and pregnancy. Similarly, increased forward flow across the aortic valve in patients with AR produces an ESM even in absence of AS. In a patient with ASD and left to right shunting of blood and hence increased flow across the pulmonic valve, an ESM at the pulmonic area may be audible.

Innocent Murmurs

The presence of a systolic murmur on auscultation but a normal echocardiogram is not an uncommon situation. Such murmurs are mid-systolic (ejection systolic) and are not accompanied by any other abnormal findings on auscultation. These so-called innocent or flow murmurs are soft and short ESM with normal S1 and S2 and no evidence of any hemodynamic abnormality. Examples include a young adult with an ESM at the pulmonic area caused by flow across the normal pulmonic valve creating vibrations in the pulmonary trunk. The flow or innocent murmurs are quite common in infants and children.[34]

Diastolic Murmurs

Like systolic murmurs, diastolic murmurs may also be classified into early, mid, and late diastolic murmurs. Early diastolic murmurs begin with the A2 or P2 component of S2 and occur in setting of AR or pulmonic regurgitation (PR). Mid-diastolic murmurs occur at a clear interval after S2 in the setting of stenosis of AV valves (mitral or TS). Late diastolic murmur occurs just before S1 and examples include MS and Austin–Flint murmur. There are no physiologic/innocent diastolic murmurs and all diastolic murmurs need cardiac evaluation for the cause.

Early Diastolic Murmurs

Aortic regurgitation: The murmur of AR is early diastolic, high-pitched, decrescendo, and blowing quality heard best with the diaphragm of the stethoscope (pressed firmly) with the patients leaning forward and breath held in full expiration **(Fig. 3)**. The murmur is best heard in left third or fourth intercostal space in parasternal area if it is due to a primary valve problem and right second intercostal space if it is due to aortic root dilation.[35] The configuration of the murmur is decrescendo because of the similar configuration of the regurgitant jet which progressively declines. The quality of the murmur is occasionally musical (instead of blowing) in a setting of regurgitation due to flail everted aortic cusp.[36]

The duration of murmur is quite variable. Mild chronic AR has a short diastolic murmur and the duration may increase with increasing severity of AR. The severity of AR correlates better with the duration of murmur than the intensity of murmur. However, acute severe AR has a short diastolic murmur due to rapid equalization of pressures between aorta and LV.

Maneuvers such as hand grip and squatting increase peripheral vascular resistance and increase the intensity of AR murmur.

Pulmonary regurgitation: PR occurs most commonly in the setting of pulmonary hypertension, referred to as Graham Steell murmur. The murmur is an early diastolic, high-pitched, decrescendo, and blowing murmur which follows the loud P2 and is of variable duration. It is best heard in the left second interspace with the diaphragm of the stethoscope. It increases in intensity with inspiration and is decreased during the strain phase of Valsalva maneuver.

The PR in a patient with tetralogy of Fallot (ToF) repair generally produces a soft low-pitched murmur given the absence of pulmonary hypertension. A similar low-pitch murmur is also heard in conditions such as idiopathic dilation of pulmonary artery, postpulmonary valve balloon dilation, and congenital absence of pulmonary valve.

The differentiation of murmurs of aortic and pulmonary regurgitation is made of the basis of company they keep: a loud P2, systolic murmur of TR, and absence of peripheral signs of AR favor PR. Also, AR begins with A2, while there is a gap between A2 and murmur in PR (A2–P2 gap).

Dock's murmur: Rarely a significant stenosis of left anterior descending coronary artery produces a diastolic murmur which resembles AR. It is heard in the left second and third interspace typically a little lateral to the left sternal border.[37] The murmur is abolished after revascularization of the lesion.

Mid-diastolic Murmurs

Mitral stenosis: The murmur of MS is a mid-diastolic low-pitched rumbling murmur best heard with the bell of the stethoscope at the cardiac apex with the patient in left lateral decubitus position. It characteristically starts with a mitral OS **(Fig. 4)**. The duration of the murmur varies with the severity of MS. In mild stenosis, there is a brief mid-diastolic rumble followed by presystolic accentuation (in patients with sinus rhythm) while in severe stenosis, murmur can be holodiastolic with presystolic accentuation. Thus, in severe MS, the OS occurs earlier and murmur is longer in duration.

The intensity of the murmur correlates poorly with the severity of stenosis, e.g., low flow across a critically narrowed valve may produce a soft murmur or even be silent. Factors that decrease the intensity of MS murmur include: Decreased cardiac output (low-flow states), marked RV enlargement, COPD, obesity, marked LA enlargement (lowers LA pressures even with severe MS), and concomitant TS or AS.

Increased flow across a normal mitral valve also produces a mid-diastolic murmur (MDM). Such examples include MR, VSD, PDA, etc.

Tricuspid stenosis: The murmur of TS is a mid-diastolic rumbling murmur best heard along the left lower sternal border. The murmur characteristically increases in intensity during inspiration.[38] Isolated TS is uncommon and most patients have concomitant MS. Most patients with TS have atrial fibrillation, those in sinus rhythm have a late diastolic murmur.

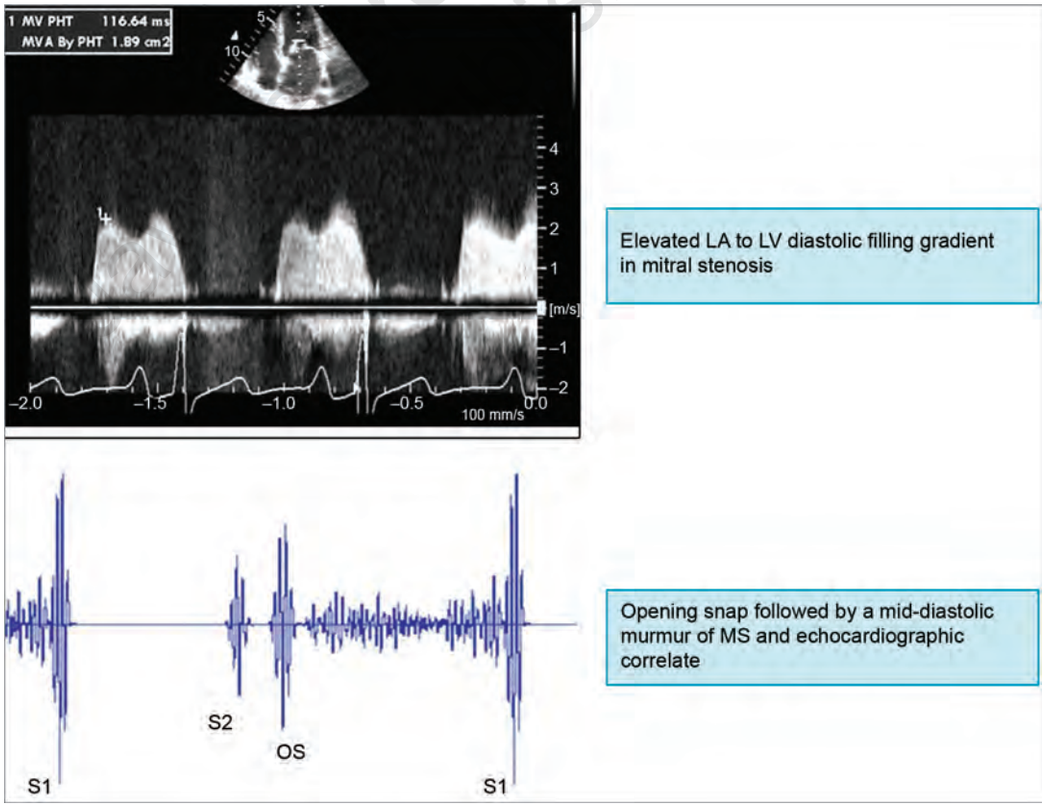

FIG. 4: The mid-diastolic murmur of MS and its echocardiographic correlate.
(LA: left atrium; LV: left ventricle; MS: mitral stenosis)

Atrial myxoma: Atrial myxoma can cause obstruction of the AV valves and produce an MDM mimicking MS. The characteristics of the murmur may however change with change in body posture and may be accompanied by a tumor plop.[39]

Carey Coombs murmur: This refers to a mid-diastolic rumble that occurs in the setting of acute rheumatic fever and is believed to occur due to acute mitral valvulitis instead of MS. Like MS, it is best heard with the bell of the stethoscope at the cardiac apex with the patient in left lateral decubitus position.

Rytand murmur: It refers to an MDM that can occasionally be heard in complete heart block (CHB) when the atrial contraction coincides with rapid filling phase of ventricular diastole.

Late Diastolic Murmurs

Mitral stenosis: In a patient of rheumatic MS in sinus rhythm, there is an increase in flow across the valve with atrial contraction toward the end of ventricular diastole. This produces the characteristic presystolic accentuation of the MDM. However, this presystolic accentuation may also be occasional present in patients in AF as a result of reduction in effective mitral valve orifice with continued antegrade flow during isovolumetric contraction phase.[40]

Austin Flint murmur: This refers to a mid-late diastolic rumbling murmur in patients of severe AR with a structurally normal mitral valve. Several theories have been put forth to explain the genesis of the murmur including mitral valve leaflet fluttering caused by the impinging jet of AR, premature closure of mitral valve resulting in relative MS and regurgitant jet striking the LV endocardium.[41-43] The presence of Austin Flint murmur indicates a regurgitant fraction of >50% and is typically heard best at the cardiac apex with the bell of the stethoscope. Austin Flint murmur is accompanied by other peripheral signs of severe AR unlike MS.

Continuous Murmurs

Continuous murmurs begin in systole and continue without interruption into diastole submerging S2. These murmurs do not have to occupy whole of systole or diastole, they simply start in systole and extend into some part of diastole. These murmurs occur in following settings:

- *Aortopulmonary communications*: Patent ductus arteriosus, aortopulmonary window, shunts such as Blalock Taussig, Waterson and Potts shunt, collaterals between systemic and pulmonary arteries (e.g., in ToF with pulmonary atresia).
- *Arteriovenous communication*: Arteriovenous fistulas and ruptured sinus of Valsalva aneurysm (RSOV) into right atrium or ventricle
- *Narrowing of an artery*: Coarctation of aorta, Takayasu arteritis, renal artery stenosis, and peripheral pulmonary stenosis
- *Turbulent flow through a vein*: Total anomalous pulmonary venous connection, (TAPVC), and venous hum

Patent ductus arteriosus: The murmur of PDA is also known as Gibson's murmur or machinery murmur. It is best heard in the first or second left intercostal space just beneath the left clavicle. Aortic pressures always exceed the pulmonary artery pressures, so any communication between the two leads to a shunt throughout systole and diastole and hence a continuous murmur. The intensity of the murmur usually peaks at S2 **(Fig. 5)**. In pulmonary hypertension, the diastolic flow and the

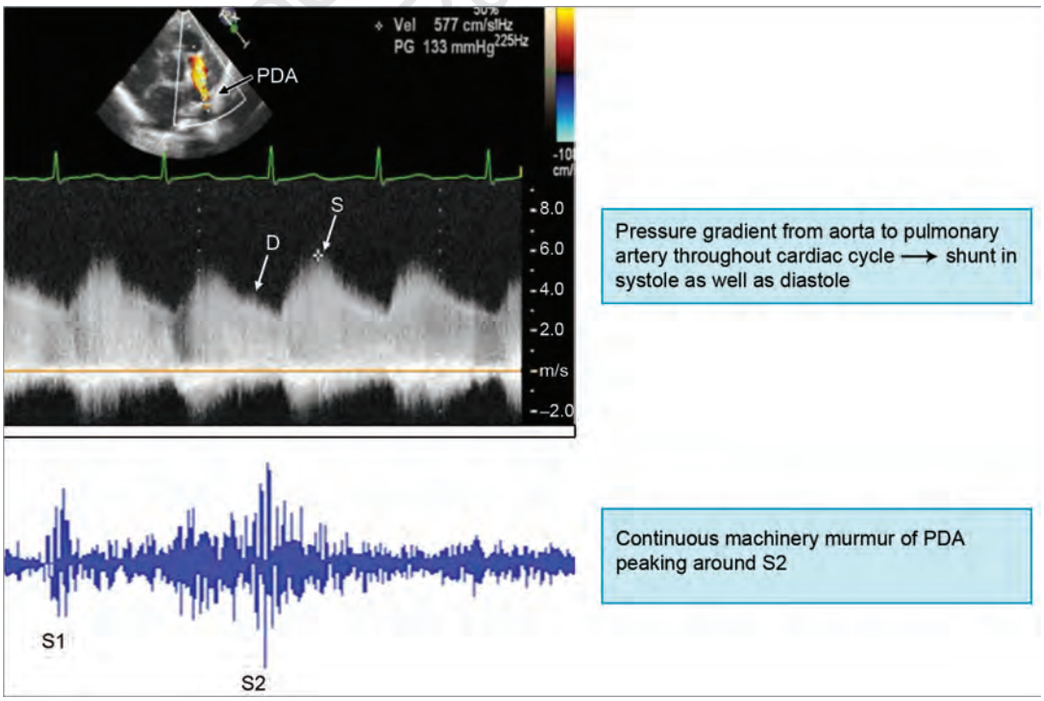

FIG. 5: The machinery or Gibson's murmur of patent ductus arteriosus (PDA) and its echocardiographic correlate.

diastolic part of the murmur are diminished or even absent. When pulmonary artery pressures reach systemic levels so that there is no gradient, murmur may be absent (silent ductus).

Ruptured sinus of Valsalva aneurysm (RSOV): Most commonly the RSOV involves rupture into either RA or RV and therefore there exists a pressure gradient in both systole and diastole, resulting in a continuous murmur. The murmur is loud with a sawing quality and is accentuated by handgrip maneuver. The murmur may be heard throughout the precordium, but is best heard at right or left lower parasternal area (in case of RSOV into RA), mid-to-lower left sternal border (in case of RSOV into RV), or upper left parasternal area (in case of RSOV to RVOT).

Congenital coronary artery fistula: The continuous murmur of a coronary artery fistula varies in location, duration, and character depending on the exact site of fistula. About 50% fistulae involve the right coronary artery (RCA) and 45% involve the left coronary artery. About 90% of fistulae drain into the right-side cardiac chambers. The murmur of a fistula involving RCA into RA or coronary sinus is usually heard along the parasternal area, while a fistula involving left circumflex and coronary sinus is heard in the left axilla. The intensity and configuration of the murmur varies between fistulae. When a coronary fistula drains into right or LA or coronary sinus, the pressure gradients across the fistula, the flow and hence the murmur intensity is higher during systole. If a coronary fistula drains into RV, then the pattern of murmur depends on a number of factors including compression by RV musculature during systole which decreases the intensity of systolic component of the murmur.

Lutembacher syndrome: Lutembacher syndrome is the combination of ASD and rheumatic MS. In a patient with tight MS and restrictive ASD, left to right shunt across the ASD occurs throughout the cardiac cycle, which may produce a continuous murmur.[44] The murmur is best appreciated at the right lower sternal edge.

CONCLUSION

Cardiac auscultation remains a key skill for all doctors, to corroborate the working diagnosis considered in the wider context of the patient's presentation. It is an oft-examined part of clinical examination, requiring not only a structured approach but also the use of manoeuvres to exploit differences in murmur characteristics. Comprehension of anatomy, physiology, and underlying physics, with mastery of physical examination, can uncover many potential pathologies and prevent serious complications. Since early detection of cardiac murmurs can be essential to reducing morbidity and mortality, healthcare providers should master these murmurs and their common etiologies.

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CHAPTER 8

Artificial Intelligence in General Cardiology

Saurabh Deshpande, Deepak Padmanabhan

ABSTRACT

Artificial intelligence (AI) is a branch of computer science concerned with building smart machines performing human-like tasks. Although this sounds very simple, it is really not. As Eliezer Yudkowsky has quoted—"by far, the greatest danger of AI is that people conclude too early that they understand it". In the vast world of AI, we are still trying to navigate ourselves in something known as narrow AI (domain-specific AI). In the medical field, AI attempts to come to our rescue by enabling us to understand data with a variance that seemingly has no meaning, identify patterns that are slowly undulating and providing a comprehensive "zoomed out" view that may not be evident to human interpretation and experience. Any AI technology goes through—intentionality, intelligence, and finally, adaptability.

In this review, we deal with what AI is, how exactly did it evolve, how it has been applied in real-world practice and the necessary safeguards against the same. We conclude it by discussing various challenges that exist in its current forms and how regulatory authorities and administration reactions will determine its future progress.

INTRODUCTION

Artificial intelligence (AI) is ubiquitous in our daily lives through "autocomplete" on our statements, population of Google searches on our social media platforms and "personalized" news and advertisements on the internet.[1] AI systems can be categorized into narrow (domain-specific), general (strong), and super AI. The narrow AI is where the current AI research in medicine lies.[2] It has been instrumental in identifying a pathological specimen on histology, detecting malignant mammographic lesions in radiology and detecting cardiac status on retinal evaluation.[3-5] Use of AI in cardiology is fast developing built as it is, on the hitherto unprecedented availability of data from electronic health records, wearable sensors, and imaging modalities.[6]

Artificial intelligence is a set of technologies that allow for—intentionality, intelligence, and adaptability. Intentionality refers to the process of sensing the environment and reacting to the same. Intelligence in the form of processing various inputs to arrive at a decision. Adaptability means the ability to change the future based on the experience from the past.

HISTORY OF ARTIFICIAL INTELLIGENCE

It is difficult to pinpoint the exact start of AI since the earliest steps were the culmination of efforts over centuries. The short story "Runaround" by Isaac Asimov published in the 1942 issue of "Astounding Science Fiction" is considered an important landmark in AI history as is the work of Alan Turing and its application on the code-breaking machine called "Bombe".[7-13] The history of AI has many a "false dawn" but the development of advanced computing technology capable of handling large volumes of data has been the difference between the times in the past and current iterations.[8,14-18] The development of AI-equipped machines like "Deep Blue" and the massive growth of machine-based data lead to the use of convolutional neural network (CNN) in various technological advances over the last two decades.[8]

The modern AI developments rest on machine learning (ML) and deep learning (DL) algorithms. ML uses techniques that enable computers to improve tasks without being explicitly programmed. DL deals with the development of algorithms that learn from the vast amount of data that has been fed as input and CNN forms an integral part of it.[6]

GENERAL PRINCIPLES OF ARTIFICIAL INTELLIGENCE FOR THE CLINICIANS

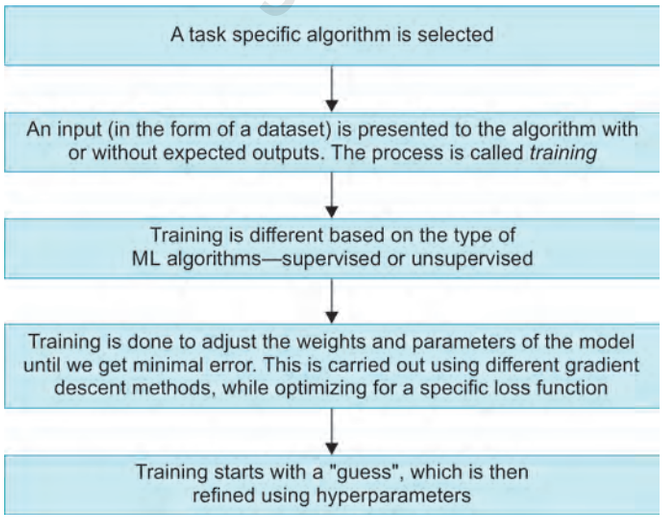
Machine Learning

The development of any algorithm uses a set of rules which then are hardcoded into the system to create a relationship between input and output. This is called an expert system, wherein the scope of scenarios is limited.[1] ML is a step ahead of expert systems in which there is an input which is processed using one of these general algorithms, which then can provide interesting insight into the input data, its relationship with output, or output data. This may or not be something that humans may have gleaned **(Flowchart 1)**.

The input presented is in the form of data which decides all the rules related to the algorithm to be used. So, data becomes the most important part of any model. The data has to be clean, easily available, and versatile to be applicable to real-life practice.[19] The rules created should fit the data well, which is done by a process called bias-variance tradeoff (bias—how well the model fits the data; variance—how well the model performs when presented to the new and subtly different data).[1] Training of this data starts with an initial "guess" at the solution, then data is tested on this guess and refined as required. The input data needs to be divided into smaller batches to ensure that the computational resources are available to process the data. ML algorithms learn and adjust the parameters called "model parameters" during the learning process. But, there are also some preconfigured parameters, which are not adjusted automatically, which are called "hyperparameters", e.g., batch size (how many samples in each batch), learning rate (adjustment of weight at every step), repetition of training (how many times the model has been shown to the whole data).[1,20] The adjustment of these hyperparameters is a key to the success of the training.

Machine learning has two types of training—supervised and unsupervised:[1,6]

1. *Unsupervised*: Only inputs are provided to the algorithm without outputs and the algorithm is used to find the internal associations/groups in the data.



FLOWCHART 1: Development of a typical machine learning (ML) model.

2. *Supervised*: Both input and output data are presented and a generalized algorithm (e.g., neural network) is used to approximate a complex mathematical relationship between input and output. The output data needs to be verified and should be consistent with the inclusion–exclusion criteria. The older models prepared in the past used conventional statistics and were limited. The newer model that uses multiple neural layers (so-called "deep model") learns the representation of input by itself. The subfield of these neural networks is called "deep learning" and the most common model for this is CNN.[21]

Convolutional neural network has been traditionally used in computer vision, image recognition, and language processing.[22] The algorithm has filters which start with random weights and parameters for the inputs, which are optimized during self-training.[21] Convolutional filters are the windows used in CNNs which are capable of recognizing precisely one feature.[23] The data is run through various filters and then the data is pooled again. The pooled data from various parts of the batches are run through a set of convolutional filters as a complete set to get a model output. This has been explained in **Figures 1A to C** with an example of an electrocardiographic (ECG) recording.

Neural Language Processing

Neural language processing (NLP) integrates linguistics, computer science, and AI.[21] Electronic records data is mostly in the form of free text. NLP can help to convert this data into a structured format.[24] This has been found useful in the extraction of lung cancer stage from pathology reports, breast cancer diagnosis/staging from mammography reports, diagnose critical limb ischemia from clinical notes, etc.[25-27] In cardiology, it has been found useful in the cardiac imaging where etiology of heart failure (HF) could be accurately diagnosed with NLP based reading of the cardiac magnetic resonance (CMR) imaging reports.[28]

APPLICATIONS OF ARTIFICIAL INTELLIGENCE (SUCCESS STORIES) IN CARDIOLOGY

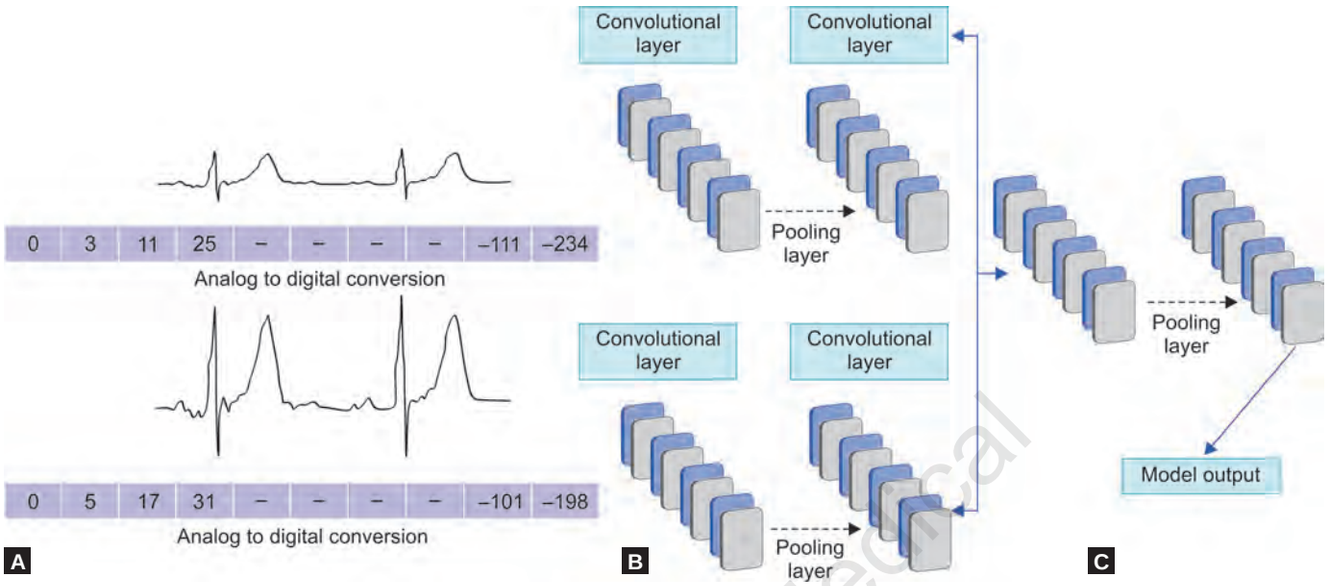
This section provides an overview of the applications of AI in the cardiology field.[29]

Artificial Intelligence-enhanced ECG

ECG is a commonly used and inexpensive tool used by clinicians and is an ideal substrate for AI—widely available and easy to store and transfer in digital format.[21] AI-enhanced ECG (AI-ECG) has been found to be useful for the diagnosis of various cardiac diseases.

Automated ECG Interpretation

This has been one of the most important parts of the AI-ECG research and various groups all around the world have been successful in recognizing massive ECG data with the help of AI algorithms.[30,31] Clinical outcomes in "Digital Electrocardiography" study used single-lead ECG traced to identify six types of abnormalities on 12-lead ECG but



FIGS. 1A TO C: Convolutional neural network (CNN) with an example of electrocardiographic (ECG) tracing. (A) Conversion of analog to digital signals (numbers are representational only) across different ECG leads (only two leads are shown here). (B) The data is assigned random weights and parameters and run through convolutional filters. Then the data is pooled and those two factors are readjusted (training). This process is repeated separately for different leads. (C) the data across the leads again goes through a separate set of convolutional filters and finally the model output is created. This output is then subjected to a bias-variance tradeoff and the adjustment of hyperparameters until the model with the required fit and variance is prepared.

TABLE 1: AI-ECG studies.

Application of AI-ECG	Dataset (s) used	ECG type
Automated ECG interpretation	Telehealth Network of Minas Gerais[31] (Brazil; 2010–2018 with 1,676,384 patients); Mayo Clinic[33] (USA, 1994–2017 with 449,380 patients); Huazhong University[32] (Wuhan, China; 2012–2019 with 71,520 patients)	12-lead
Classification of heart rhythms	iRhythm technologies/Stanford university[30] (USA, 2013–2017 with 53,549 patients); China Physiological Signal Challenge-2018[79] (2018 with 6,877 patients)	Single lead 12-lead
LV dysfunction estimation	Mayo Clinic[36] (USA, 1994–2017 with 449,380 patients)	12-lead
AF care	Mayo Clinic[37] (USA, 1994–2017 with 449,380 patients); Heart eHealth Study[45] (Multinational, 2016–2017 with 9,750 patients)	12-lead Single lead
HCM diagnosis, serum potassium level assessment	Mayo Clinic[41,43] (USA, 1994–2017 with 449,380 patients)	12-lead
Cardiac structural parameters[#] and diseases[$]	University of California, San Francisco[42] (USA, 2010–2017 with 36,186 patients)	12-lead
Overall survival	Geisinger[80] (USA, 1984–2019 with 253,397 patients)	12-lead

[#]Left ventricular mass, left atrial volume, early diastolic mitral annular velocity.
[$]Hypertrophic cardiomyopathy, amyloidosis, pulmonary artery hypertension, and mitral valve prolapse.

(AF: atrial fibrillation; AI-ECG: artificial intelligence-based electrocardiography; HCM: hypertrophic cardiomyopathy; LV: left ventricular; USA: United States of America)

external validation is forthcoming;[31] another group showed that application of CNN to a single-lead ECG can outperform cardiologists;[30] a study done with a 12-lead ECG dataset (training and validation) of >180,000 ECGs of >70,000 patients, which showed that 21 types of rhythm abnormalities were more accurately diagnosed by the model than the physicians working in the cardiology department **(Table 1)**.[32-80] A group working at the Mayo Clinic have demonstrated that CNN can identify 66 different diagnostic codes while working on an internal dataset of >8 million ECGs and they have also developed a method to translate these ECG features into ECG codes and text strings.[33] The evident downsides to all this is—low accuracy without human oversight, computer-driven ECG interpretation influencing human ECG interpretation introducing bias.[21,34]

Detection of Left Ventricular Systolic Dysfunction

A study from Mayo clinic used linked ECG and echocardiographic data from >40,000 patients to identify patients with left ventricular (LV) systolic dysfunction [LV ejection fraction (LVEF) ≤ 35% by echocardiography] based on ECG alone.[35] In

the external prospective validation cohort, the model's area under the curve (AUC) was 0.92 with sensitivity, specificity, and accuracy of 82.5%, 86.8%, and 86.5%, respectively, to detect LVEF of ≤35%.[36]

Use of Artificial Intelligence–ECG in Atrial Fibrillation Care

Identifying the probability of atrial fibrillation (AF) from a sinus rhythm ECG in the period of a month before or after the recorded ECG was obtained from an algorithm developed using half a million ECGs from >120,000 patients. The model performed well in the validation cohort with an AUC of 0.87, a sensitivity of 79%, specificity of 79.5%, and accuracy of 79.4%.[37] Its potential applications in the detection of AF as a cause for stroke, personalized anticoagulation for patients deemed to be at risk of CVA in patients with AF at the input cost of recording an ECG make for fascinating applications. It also outperformed the CHA_2DS_2Vasc score in the prediction of CVA in these patients and complimented the score when used in combination with it.[38]

Detection of Incident Cardiomyopathy

A model trained with 2,500 HCM patients and >50,000 age/sex-matched controls was successfully able to diagnose HCM with an AUC of 0.96, a sensitivity of 87%, and specificity of 90% with similar model performance independent of the presence of LVH on the 12-lead sinus rhythm ECG. These values were also translated when a single-lead ECG was used making it scalable and widely dispersible.[39-41]

Similar model performances have been noted for LV mass, left atrial volume, early diastolic mitral annulus velocity, and pulmonary arterial hypertension (PAH). AUC of 0.94 for PAH, 0.86 for amyloidosis, and 0.77 for mitral valve prolapse detection was present.[42]

Detection of Electrolyte Abnormalities and Drug Levels in the Blood

An AI-ECG CNN model trained with >1.5 million ECGs from 450,000 patients with a serum potassium level of ≥5.5 mmol/L showed a sensitivity of 90% and specificity of 89% in an external validation cohort making it a valuable screening tool in patients.[43] Similarly, a model outperformed the traditional corrected QT (QTc) interval for monitoring of serum levels of dofetilide providing proof of concept that drug levels monitored using ECG changes lend themselves better to AI interpretation than the human evaluation for the same ($r = 0.85$ vs. 0.64).[44]

Wearable and Mobile Technologies

Data collection tools have now progressed a long way since the first ECG was recorded. Adjustment of the algorithms to handle input from various ECG recording modalities ranging from a watch to a stethoscope with the relevant differences in the sampling frequency and bit rates will determine the way forward.[36,41,45-47] The ECG will therefore be akin to a drop of blood which gives us insight into the health of the individual.

Artificial Intelligence: Echocardiogram

Echocardiography is a specialized investigation imaging tool which in the hands of trained operators has revolutionized cardiology. However, the quality of the operator is a significant limiting factor in the output obtained from the use of the echocardiogram. This coupled with the rapid changes in technology makes the optimal use of a given echo machine in the service of the patient challenging. The application of AI in echocardiography **(Table 2)** can help with—classification (section recognition), optimization (automatic segmentation of cardiac cavity), volume and LVEF calculation, disease diagnosis, and prognostication.[48-88] This remains a work in progress but when carried to its possible conclusion can provide solutions beyond the limitations of the individual operator allowing them to provide better care to their patients subject to differences in a population cohort.[54-56]

Neural Language Processing in Cardiology

Neural language processing has been found useful in the diagnosis and prognostication of certain cardiovascular disorders.[57] The manual extraction of this data can be time-consuming and prone to human error.[58] A study done at Mayo clinic used data from 12,372 HCM patients (with 2,257 CMR reports + images) (1994–2019) with an NLP model that showed an accuracy of 85–87% for the classification of HCM into "yes/possible/no".[59] A similar NLP based model from Cleveland Clinic based on 923 CMR reports of the patients with HF could accurately extract the diagnoses—cardiac amyloidosis, cardiac sarcoidosis, and myocarditis.[28]

The study done by Solomon et al. on 927,884 physician-adjudicated echocardiographic reports (519,967 patients) with NLP algorithm and coding for aortic stenosis (AS) revealed that NLP classified 11.2% of echocardiographic reports (104,090 reports) as any AS out of which only 64.6% (67,297) had been coded as AS.[60]

Neural language processing has been found useful in the diagnosis of peripheral arterial disease (PAD) from clinical notes. The NLP based model from 6,861 patient reports, preprocessed with the least absolute shrinkage and selection operator (LASSO)-based model, showed an AUC of 0.91 (as against 0.82 based on the notes alone).[61]

Digitization of clinical notes and applications of the NLP algorithms to the same can provide unique insights into patient management, especially in the absence of trained manpower to perform the data mining.

Nuclear Cardiology

Artificial intelligence has been incorporated into nuclear cardiology for image processing, the performance of single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) motion correction, reconstruction, tomographic oblique reorientation, quantification, and high-level analysis results.[62]

The study incorporating ML algorithm on imaging variables showed higher accuracy than manual reporting (86% vs. 81%, $p < 0.01$)[63] as did a study predicting revascularization with an AUC of 0.81 (similar to that of an experienced angiography reader).[64,65]

TABLE 2: AI-echo studies.

Author, year	AI model	Aim	Cohort	Exclusions	Results
Sengupta et al.,[81] 2016	Associate memory classifier (S)	Constriction vs. restriction with speckled tracking and structural data	*n* = 94 (44 restrictive; 50 constrictive)	Incomplete data	• AUC: 0.96 • Accuracy: 93.7%
Narula et al.,[82] 2016	Support vector machine, random forest, artificial neural network (S)	HCM vs. athletes heart by speckled tracking and structural data	*n* = 139 (77 athletes; 62 HCM)	Non-sinus rhythm, CAD, DM; LVEF< 50%	• Sensitivity: 87% • Specificity: 82%
Madani et al.,[48] 2018	CNN (S)	Classification of 15 echo windows using 2D echo and still image data	*n* = 267 (random from database)	NA	Accuracy: • Images: 91.7% • Videos: 97.8%
Omar et al.,[83] 2018	CNN (S)	Normal vs. abnormal wall motion from strain analysis of 3D echo data	*n* = 61 (dobutamine stress echo)	Suboptimal echo windows	• Sensitivity: 81% • Accuracy: 75% • Specificity: 65%
Zhang et al.,[84] 2018	CNN (S)	Identification of 23 views, quantification of chamber size, LVEF, distinguish HCM, amyloidosis, PAH	277 echos; 8,666 echos for mass/volume; 6,417 echos for segmentation-derived LVEF; 5,993 echos for disease detection (1,258 disease, 4,735 control)	HCM undergoing septal myectomy/ alcohol ablation/ pacemaker implant/ICD implant	• Accuracy for view classification: 84% • Mean deviation in chamber volume 15–26% • LVEF absolute difference 6% • C stat: HCM—0.93, amyloidosis—0.87, and PAH—0.85
Kwon et al.,[52] 2019	CNN (S)	Predict in-hospital mortality for patients with heart disease	*n* = 25,776	Missing data	AUC: • Overall: 0.9; CAD: 0.96; HF: 0.91
Samad et al.,[53] 2019	Nonlinear random forest classifier (S)	Predict survival following routine echo	*n* = 171,519 patients (331,317 echo studies) with 90 clinical variables, LVEF and 57 echo measurements	Missing data (>90%); ambiguous measurements	AUC for: • 1-year mortality: 0.85 • 5-year mortality: 0.89
Behnami et al.,[85] 2019	3D CNN with uncertainty modeling	Estimation of LVEF and categorization into four groups based on it	*n* = 2,181 (with apical two chamber and four chamber views)	Without biplane LVEF estimation	• Mean absolute error: 4.5% • Accuracy for categorization: 91%
Kusunose et al.,[86] 2020	3D CNN	Estimate and differentiate reduced and preserved LVEF	*n* = 340 (with HF) (185 LVEF <50%, 155 LVEF ≥50%) Validation with 189 patients (68 LVEF <50%, 121 LVEF ≥50%)	NA	AUC: 0.92
Salte et al.,[87] 2021	CNN–PWC-net	Automated global longitudinal strain (GLS) measurements vs. software-based method	*n* = 200	Poor echo window	Correctly classify three apical views and perfect timing of cardiac events in 89%. GLS bias of (−1.4 ± 0.3%)
Asch et al.,[88] 2021	Neural network	Test accuracy of automated measurements determines whether they can be used for classification of LVEF	*n* = 166	NA	Agreement with reference LVEF values—*r* = 0.86–0.95 with <2% bias

(AUC: area under the curve; CAD: coronary artery disease; CNN: convolutional neural network, DM: diabetes mellitus; HCM: hypertrophic cardiomyopathy; HF: heart failure; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; PAH: pulmonary arterial hypertension; PWC-net: pyramidal processing, warping, and the use of cost volume; RWMA: regional wall motion abnormality; S: supervised; US: unsupervised)

Coronary Angiography and Interventional Cardiology

Coronary angiography (CAG) image reconstruction and analysis have been successfully carried out with the use of DL algorithms.[66] A trained CNN-based model showed the high precision to detect diameter stenosis (88.2%), thrombus (82.6%), and dissection (85.5%), and a high recall rate (85.8%).[67] Another DL-based study was able to detect the cardiac phase with 92.6% accuracy, sensitivity of 92.4%, and specificity of 92.9%.[68] A multinational noninferiority using 1,008 instantaneous wave-free ratio (iFR) traces (691 unique and 317 duplicate) comparing an ML algorithm and heart team opinion with regard to the appropriateness of coronary angioplasty and the angioplasty strategy found that ML was noninferior to the expert opinion [appropriateness for angioplasty—89.3% (expert) vs. 89.4% (ML), $p = 0.0073$; angioplasty strategy—88.8% (expert) vs. 89.7% (ML), $p < 0.0001$].[68]

Sudden Cardiac Arrest Recognition

An ML algorithm was able to recognize out-of-hospital cardiac arrest (OHCA) distress calls better than a medical dispatcher working in the emergency call center (85% vs. 77.5%, $p < 0.001$) while another algorithm can detect terminal breathing sounds using a mobile smartphone on the person to activate emergency response automatically.[69] Personalized assessment of the risk of sudden cardiac arrest (SCA) using in patients with low EF using data derived from creating electroanatomical maps of the heart represents a very exciting new advance in prognosticating patients.[70]

CURRENT STATE OF ARTIFICIAL INTELLIGENCE IN INDIA

Artificial intelligence research in India is still far behind the developed nations (H index of 100 vs. 138 for Japan and 413 for the United States of America). The only company which has dedicated research toward AI is Tata Consultancy Services (TCS). Indian Institute of Science (IISc) contributes the most toward AI research in India (7.5% of total research). The industry contribution toward AI research is minuscule (14%). The proposed centers for AI research in India are—Indian Institute of Technology (IIT) Bombay and IIT Patna Joint contribution, IISc reinforcement learning, National Association of Software and Services Companies (NASSCOM) collaborated with state governments (e.g., Karnataka, Andhra Pradesh, etc.), IIT Bombay and Wadhwani Foundation Centers Collaboration, etc.

With more and more literature getting available in the field of AI, we need to know how to evaluate that using a few basic steps:

- Examination of the data:
  - Is it high quality?
  - How was it collected?
  - Are there similarities with the target population dataset?
- Examination of the model performance:
  - Is it robust? (sensitivity/specificity/negative-positive predictive value)
  - Is there subgroup analysis and external validation?
- Understanding the proposed model application:
  - Is the application dataset similar to the training dataset?
  - Can the model be periodically tested against a standard criterion?
  - Any unintended consequences of the model and how to monitor/measure them?
- Examination of the model findings compared with the existing knowledge:
  - Comparison with clinical intuitions and guidance
  - Does the model substitute human involvement or improve it?

Recently, a guideline document has been published which helps with the clinical trial protocols involving AI research [SPIRIT-AI (Standard Protocol Items: Recommendations for Interventional Trials—Artificial Intelligence)].[71]

CHALLENGES OF ARTIFICIAL INTELLIGENCE

Several challenges must be addressed before the universal use of AI for healthcare improvement.[72] They can be classified as **(Box 1)**—role of researchers, administration, regulatory bodies as well as insurance providers become key in ensuring that adequate validation in the population at risk accounting for variances in race, ancestry, and ethnicity are allowed for before allowing for use of these algorithms to aid physicians. Additionally, the ethical questions that may arise from the outputs of the algorithms on seemingly healthy individuals and the ramifications of the same need to be assessed and a roadmap created to aid the clinician in the management of the patient.

A detailed analysis of challenges faced and ethical concerns regarding AI implementation and their probable solution has been discussed in the World Health Organization (WHO) document.[72]

As humans, we are social and hence are faced with situations where we are faced with social dilemmas where no right decision exists clearly.[73] This has been explained with a simple example where an autonomous vehicle is made to choose between running over a pedestrian or sacrificing itself with the passengers inside.[74,75]

The human component of trust in the outputs of AI algorithms is also key since the final decision-making has to be from the clinician whereas AI remains a tool in the guidance of the same. Social similarity, peer review, and peer utilization are all important aspects in this regard.

FUTURE OF ARTIFICIAL INTELLIGENCE

- Future applications of AI-ECG:[21]
  - Sudden cardiac arrest prediction
    - Going beyond LVEF for ischemic and nonischemic cardiomyopathies
    - Risk stratification in HCM and channelopathies
  - Predict exacerbation of HF and severity and staging of HF
  - Angina and stress ECG analysis to identify patients who will benefit from invasive coronary evaluation
  - Coronavirus disease-2019—Faster and cheaper diagnosis (based on ECG)

BOX 1 Challenges in wider application of artificial intelligence (AI) in healthcare.

1. Overestimation of the use of AI
   - Overly optimistic assumptions of infrastructre and institutional context
   - Ethical conundrums with use of AI, e.g., finding out human immunodeficiency virus or psychiatric disease in population may lead to unnecessary stigmatization
   - Appropriateness and adaptation in diverse country like India where there are many languages and scripts
2. Digital divide
   - In a country like India, there is a great digital divide in rural and urban population
   - The infrastructure development for the same may be difficult
3. Data collection and use
   - Since there are multiple sources for the data collection and robustness of the data
   - Training data will have one or more systemic biases
   - Data colonization: It may foster a divide between those who accumulate, acquire, analyze, and control such a data and those who provide it without any control over it
4. Accountability and responsibility for decision making
   - Developers and designers of AI cannot be held responsible as AI-guided systems can function independently of their developer. This problem will be worse with automated AI
   - Many hands problem, since there will be many people responsible for making a particular AI model
5. Autonomous decision-making
   - Delegation of clinical judgment on AI may not be legal
   - Such kind of autonomy may disrupt clinician–patient and healthcare system to technology provider relationship
6. Bias and discrimination associated with AI
   - AI models may perpetuate the biases in the datasets, e.g., age/sex/race related, etc.
   - Biases related to the developer
7. Risk to safety and cybersecurity
   - Patient safety could be at risk if there are errors in the system, code errors due to human programming, and flaws in computer codes
   - An algorithm running without human oversight can be hacked to generate revenue for a certain recepient, which brings in the question of cybersecurity
8. Impact on labor and employment in heath sector
   - Most jobs in healthcare will require trained digital skills
   - New jobs may be required like—trainers (who evaluate AI technologies), explainers (who explain how and why the algorithm should be trusted), and sustainers (who monitor and identify unintended consequences of AI
   - With AI systems working to reduce their work burden, the doctors and nurses may be able to provide more time to their patients
   - AI may make the doctors too much reliant on technology
9. Commercialization of AI
   - Lack of transparency
   - Overall business model of the firms who can use the surplus data for commercial purpose
   - Growing power of certain companies may exert over the development, deployment, and use of AI in health

- Voice signal analysis from chronic heart disease patients may predict rehospitalization for HF, based on a study in 10,583 patients. This may be helped with AI algorithms.[76]
- Systolic time interval (STI) measured on ballistocardiogram (BCG) (manual and automated) correlated well with transthoracic echo-derived STI in a variety of LVEF subgroups. A model based on this may automate the prediction of LVEF with the help of AI algorithm-based BCG measurements.[77]
- Noninvasive fetal electrocardiography can be done with the help of AI, after which the need for intrapartum cardiotocography will not be there. Currently, the fetal heart rhythm detection is done via invasive (scalp electrodes) or noninvasive (Doppler—inaccurate and artifactual) means which may be replaced by AI-based fetal electrocardiography.[78]

CONCLUSION

Artificial intelligence has a role in cardiology. Its development is critical to allow to aid physicians in better managing their patients. It carries with it the promise of democratizing medical care allowing for uniform management of patients irrespective of the limitations of the treating physician. Robust validation of the algorithms in the patient population where it is proposed to be used remains key as is the regulatory oversight of the same. Physicians and students need to be taught how to use and interpret AI-derived outputs to ensure that AI is only an

aiding tool and not a decision-maker. Finally, there is a need of the hour for individual physicians, healthcare institutions and professional societies to participate in the effort of developing, validating and application of AI-based algorithms via national and international collaboration to aid in better management of the local populace needing specialized healthcare.

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CHAPTER 9

Clinical and Noninvasive Assessment of Aortic Stenosis

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ABSTRACT

Aortic stenosis (AS) is the most common valvular heart disease and a source of considerable morbidity and mortality. The recent advent of transcatheter aortic valve replacement (AVR) has greatly expanded the therapeutic horizon for AS and has placed a lot of emphasis on accurate diagnostic assessment of AS. As a result, our understanding of AS has evolved significantly over the past few years. Several hemodynamic subsets of AS are now recognized, including the classical high-gradient AS, normal-flow low-gradient AS, classical low-flow low-gradient severe AS, and paradoxical low-flow low-gradient severe AS. Thorough clinical assessment and transthoracic echocardiography (TTE) remain the cornerstone of AS assessment, supplemented by other diagnostic modalities such as transesophageal echocardiography (TEE), dobutamine echocardiography (DbE), computed tomography (CT), and cardiac magnetic resonance (CMR) imaging as needed.

INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart disease and, hence, a significant cause of cardiovascular morbidity and mortality. Approximately 5% of adults >65 years have AS and about 2–9% of those aged >75 years have severe AS.[1,2] Degenerative, rheumatic, or congenital (unicuspid/bicuspid) AS are the most common varieties encountered in clinical practice with other less common etiologies being connective tissue disease, previous radiotherapy and metabolic disorders such as Fabry's disease and alkaptonuria. While degenerative AS has been the most common cause of AS in the developed nations, rheumatic heart disease (RHD) and congenital bicuspid aortic valve (BAV) have been the most dominant etiologies in developing countries such as India.[3] However, over the years, degenerative AS has become increasingly common in India too.

Degenerative AS is pathophysiologically a very distinct disease as compared to rheumatic AS or BAV disease. Pathologically, degenerative AS shares some similarities with atherosclerosis and, therefore, these patients often have other manifestations of atherosclerosis, such as increased arterial stiffness or coronary artery disease. These abnormalities contribute to the hemodynamics and clinical presentation of AS by causing an increase in left ventricular (LV) afterload and/or a decrease in LV function. Hence, the clinical presentation of degenerative AS is often much more complex and brings up several diagnostic and therapeutic challenges.[3,4]

A thorough clinical examination followed by transthoracic echocardiography (TTE) remains the cornerstone of AS assessment. However, several other diagnostic modalities such as transesophageal echocardiography (TEE), dobutamine echocardiography (DbE), computed tomography (CT), and cardiac magnetic resonance (CMR) imaging are often needed for a comprehensive assessment required for accurate clinical decision-making and for guiding management **(Table 1)**. This is especially important in patients with discordant measures of AS severity [i.e., an aortic valve area (AVA) ≤ 1 cm^2 with mean gradient < 40 mm Hg] which is encountered in almost up to 40% of patients with severe AS.[5]

HEMODYNAMIC CLASSIFICATION OF AORTIC STENOSIS

Aortic stenosis is considered severe when AVA is <1.0 cm^2 (or indexed AVA < 0.6 cm^2/m^2). However, the valve gradient may vary depending on the flow conditions, resulting in several hemodynamic subsets of severe AS **(Flowchart 1)**.[6] When mean aortic valve gradient is ≥40 mm Hg or peak transvalvular velocity is ≥4 m/s, it represents the conventional high-gradient severe AS, the most common form of severe AS. However, as mentioned above, nearly 40% of all patients with severe AS (AVA < 1 cm^2) have mean aortic valve gradient < 40 mm Hg. This is known as low-gradient severe AS. This may occur in

TABLE 1: Advanced imaging techniques for multimodality assessment of aortic stenosis.

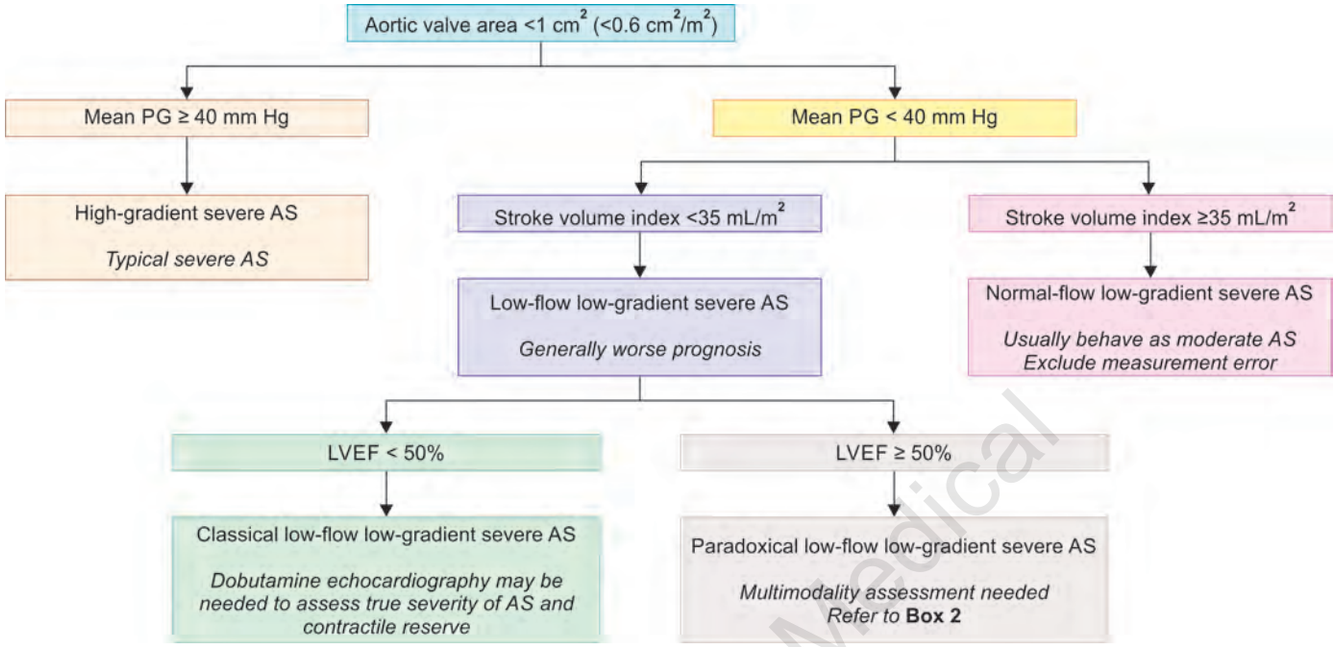
Imaging technique	Useful indications	Interpretation	Comments
GLS (strain imaging)	• Detection of subclinical LV systolic dysfunction • Explaining low-flow situation despite preserved LVEF • Prognostic assessment • Guiding intervention in asymptomatic severe AS with normal LVEF	• GLS less negative than approximately—15% indicates significantly increased risk of adverse events • Low GLS predicts adverse outcomes even after intervention	• A decreased GLS may justify earlier intervention in asymptomatic AS to prevent further irreversible LV myocardial injury. However, there is currently no randomized trial data to support such approach • In asymptomatic severe AS, reduced GLS implies a need for closer follow-up, if intervention is not immediately contemplated
TEE (with or without three-dimensional echocardiography)	• Aortic valve planimetry during transthoracic echocardiography is often unreliable and poorly reproducible, especially when extensive calcification is present • An alternative to CT for preprocedural evaluation for TAVR, if CT is not possible due to some reason	• TEE often permits better assessment of aortic valve opening and is more reliable for aortic valve planimetry • More reliable for distinguishing bicuspid from tricuspid aortic valve	• In patients with LFLGAS, TEE cannot distinguish between pseudo-severe AS and true-severe AS • Semi-invasive procedure
Dobutamine echocardiography	To differentiate between pseudo-severe and true-severe AS in patients with LFLGAS, usually with decreased LVEF	• Severe stenosis is suggested if maximum velocity > 4.0 m/s or a mean gradient > 40 mm Hg is achieved during dobutamine infusion provided that valve area does not exceed 1.0 cm^2 at any flow rate • >20% increase in stroke volume from baseline suggests presence of contractile reserve	• Guideline mandated test for classical LFLGAS to decide further course of management • Absence of contractile reserve is a predictor of a high-surgical mortality and poor long-term outcome even after valve replacement
CT for aortic valve calcium score (noncontrast)	Confirmation of true severity of AS in LFLGAS (classical as well as paradoxical)	• AS is likely to be severe if aortic valve calcium score is >2,000 (Agatston method) in men and >1,200 in women • AS is highly likely to be severe if corresponding values are >3,000 and >1,600, respectively	• Good correlation with hemodynamic measures, noninvasive nature, easy availability, and being completely flow independent makes it an excellent choice in discordant AS • May underestimate AS severity in the absence of extensive calcification (e.g., young patients with bicuspid aortic valve, women)
Contrast CT	Comprehensive evaluation of aortic valve, aortic root, rest of the aorta and vascular access site in patients undergoing TAVR	Comprehensive assessment of anatomy is performed, and various measurements obtained as per TAVR protocol	A detailed CT assessment is almost indispensable prior to TAVR
CMR	To characterize myocardial damage due to severe AS, especially in asymptomatic patients with normal LVEF	T1 values, extracellular volume quantity, and late gadolinium enhancement are evaluated to quantify the extent of myocardial fibrosis	CMR features of myocardial fibrosis are strong predictors of mortality; thus, CMR can have a potential role in timing of intervention in asymptomatic severe AS

(AS: aortic stenosis; CMR: cardiac magnetic resonance; CT: computed tomography: GLS: global longitudinal strain; LFLGAS: low-flow low-gradient aortic stenosis; LV: left ventricular; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; TAVR: transcatheter aortic valve replacement; TEE: transesophageal echocardiography; VTI: velocity time integral)

conjunction with either normal transvalvular flow (stroke volume index or SVi ≥ 35 mL/m^2) or reduced flow [SVi < 35 mL/m^2, which is known as low-flow low-gradient severe AS (LFLGAS)]. The reduced flow in LFLGAS may either be due to reduced left ventricular ejection fraction [(LVEF) < 50%, "classical" LFLGAS] or may occur even in the presence of preserved LVEF ("paradoxical" LFLGAS).[7]

ASSESSMENT OF AORTIC STENOSIS

The natural history of AS is characterized by a prolonged "latent period" of few decades during which the LV is exposed to sustained increase in afterload resulting in several adaptive changes in the LV myocardium. Although initially beneficial, these changes eventually become maladaptive leading to LV



FLOWCHART 1: Hemodynamic subsets of severe aortic stenosis.
(AS: aortic stenosis; LVEF: left ventricular ejection fraction; PG: pressure gradient)

myocardial dysfunction and the development of symptoms. Angina, syncope, and exertional dyspnea are the classical symptoms of severe AS. The onset of symptoms marks a major transition in the natural history of AS because the subsequent clinical course is rapid downhill. Approximately 30% of the asymptomatic subjects with severe AS develop symptoms within 2 years and once symptoms appear, the average mortality is 25% per year. The median survival varies according to the presentation and is reported to be 2, 3, and 5 years, for heart failure, syncope, and angina, respectively.[8,9] This underscores the importance of timely diagnosis of severe symptomatic AS which, if missed in the narrow window period, may prove to be disastrous for the patient. At the same time, it is equally important to distinguish that the symptoms and/or LV systolic dysfunction are partly or completely secondary to true severe AS and not due to the associated comorbidities such as coronary artery disease.

Clinical Assessment

Clinical cardiac examination has become increasingly neglected in the era of sophisticated technology due to relatively low sensitivity and specificity of the former. However, it provides the first clue to the presence of AS and can be corroborative for decision-making in doubtful cases. Once significant AS is suspected, following clinical signs point to a severe disease:

- Systolic decapitation of blood pressure (BP) causing narrow pulse pressure
- Weak carotid/peripheral pulse with delayed systolic peak (pulsus parvus et tardus)
- Heaving type LV apex due to pressure overload
- Left-side fourth heart sound may be palpable as a presystolic gallop due to forceful atrial contraction into a hypertrophic noncompliant LV.
- Absent/diminished A2 component of the second heart sound as the aortic cusps are almost immobile.
- Paradoxical splitting of the second heart sound—LV ejection time is so prolonged that aortic valve closes later than the pulmonary valve.
- Mid- or late-peaking ejection systolic murmur in the aortic area as it takes longer for the blood to be ejected through a narrowed orifice [the same phenomenon is also evident in the continuous-wave (CW) Doppler trace across the aortic valve].
- Although not accurate, a loud systolic murmur (grade > 4) also indicates more severe AS as severe obstruction causes more turbulence and increase in the velocity.

It should be remembered that these clinical findings vary quite widely with prevailing hemodynamic conditions such as atrial fibrillation, hyperdynamic state, uncontrolled hypertension or development of LV systolic dysfunction, and pulmonary hypertension.[10]

Echocardiographic Evaluation

Echocardiography is the cornerstone in the evaluation of AS. TTE is the first modality used and is supplemented by TEE and DSE, as required. AVA and transvalvular velocity and gradient are the main measurements for determining severity of AS, whereas aortic valve morphology, LV thickness, LV mass, LV systolic and diastolic function, left atrial size, and pulmonary artery systolic pressure provide corroborative evidence. The advent of new echocardiographic technologies such as

strain imaging and three-dimensional (3D) echocardiography has made it possible to obtain more information about the LV myocardial dynamics and valve morphology.

Morphological Assessment of the Valve

A thorough evaluation of the aortic valve morphology in different short-axis and long-axis views is essential to understand the etiology and mechanism of AS. It also provides an idea about the AS severity, which is very helpful in corroborating Doppler findings and minimizing diagnostic errors. Significant valvular AS is unlikely in the absence of calcification or restricted motion of leaflets. If the valve appears normal, supravalvular or subvalvular obstruction, depending on site of turbulence, should be suspected as the cause of increased LV outflow gradients. On the contrary, markedly thickened and restricted aortic valve leaflets should always raise a suspicion of significant AS, even if the valve gradient is not increased (possibly LFLGAS).

Parasternal short axis (PSAX) view at the great artery level is the best for anatomical assessment of the aortic valve. Degenerative aortic valve disease has characteristic thickening and calcification of aortic valve leaflets without commissural fusion. There is marked restriction of aortic leaflet movement and opening but the leaflet tips are relatively free. In contrast, RHD is characterized by commissural fusion which results in a fixed triangular systolic orifice. The thickening and calcification are most prominent along the edges. Moreover, rheumatic AS is usually accompanied by mitral valve involvement; isolated aortic valve involvement is very uncommon (<5%) and isolated rheumatic AS is even rarer.[11]

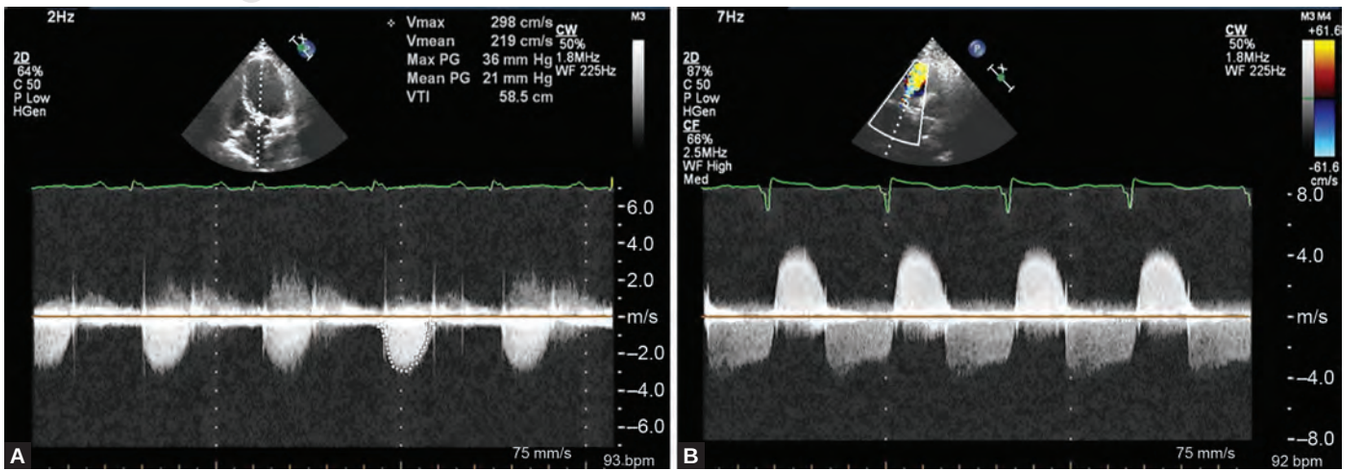
Congenital BAV with superimposed calcification is another very common cause of AS. BAV has a prevalence of 0.5–2% in the general population.[12,13] Parasternal long axis (PLAX) view provides the first clue to the presence of bicuspid valve where an asymmetric diastolic line of closure is seen instead of central closure of a tri-leaflet valve. In PSAX view, two leaflets can be seen with or without a raphe. A bicuspid valve most often results from fusion of the right and left coronary cusps, resulting in a larger anterior and smaller posterior cusp with two commissures forming an elliptical opening in systole. All patients with BAV should undergo a comprehensive assessment of the aorta also, to assess for dilatation and/or coarctation.[14,15] Congenital AS, if unicuspid, presents early in life (first or second decade) and can be recognized by a single cusp with central opening where no true commissure is present or may be unicommissural when leaflet is attached to a single commissure and folds on itself forming an eccentric orifice.

Mean/Peak Gradient and Peak Velocity

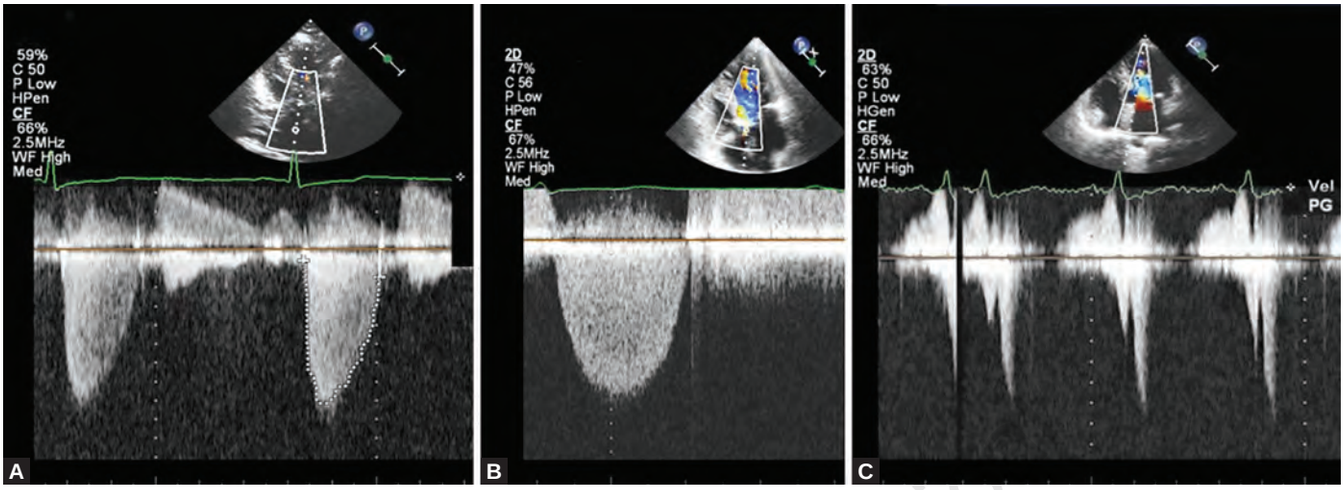
Transvalvular velocity and gradient are the easiest measurements to obtain but are flow-dependent and require caution in interpretation.[6] CW Doppler in apical five-chamber view is used for obtaining these measurements. Proper alignment of the ultrasound beam with the blood flow direction is essential to avoid underestimation. Every effort should be made to interrogate the aortic valve flow in multiple echocardiographic windows, especially if there is discrepancy between the aortic valve opening and the gradient. In almost up to 50% of cases, right parasternal or suprasternal window allows the best alignment and yields the highest velocity measurements **(Figs. 1A and B)**.[16,17]

Once a uniform velocity curve with a dense outer edge and clear maximum velocity is recorded, the outer edge of the spectral Doppler curve is traced to obtain peak velocity, mean and peak gradients, and velocity time integral (VTI). Only the dense part of the signal should be traced, without including the fringes. In case of irregular rhythm, average value of 3–5 beats should be taken. The shape of the Doppler curve can itself provide a hint about the severity and site of obstruction. A severe obstruction will have a rounded curve whereas milder obstruction will produce a triangular early peaking Doppler curve. Dynamic obstruction in hypertrophic cardiomyopathy typically results in a "dagger-shaped" curve with an early concave and late-peaking signal **(Figs. 2A to C)**.

The estimation of gradient from the velocity is based on the simplified Bernoulli equation as gradient = 4 V^2, where V is the velocity across the aortic valve. This equation assumes that there is almost complete dissipation of the kinetic energy as the blood passes through the narrowed orifice. However, this may



FIGS. 1A AND B: Utility of right parasternal view in assessing aortic stenosis severity. (A) The peak jet velocity hardly reaching 3 m/s in apical five-chamber view; (B) In right parasternal view, the peak jet velocity is reaching almost 4 m/s.



FIGS. 2A TO C: The shape of continuous-wave spectral Doppler envelope as an indicator of the site and severity of left ventricular outflow obstruction. (A) Early peaking jet of moderate aortic stenosis; (B) Parabolic jet of severe aortic stenosis; (C) Late peaking jet in a patient with hypertrophic cardiomyopathy.

not be true in patients with small aortic root in whom some of the kinetic energy carried by the high velocity jet is recovered in the proximal aorta resulting in some recovery of the pressure. In such cases, the Doppler method overestimates the actual pressure gradient obtained by cardiac catheterization. Therefore, a correction of this "pressure recovery phenomenon" needs to be incorporated when estimating aortic valve gradient in patients with small (diameter < 3 cm) aortic root/ascending aorta.[6,18] The following equation can be used for this purpose:

$$\text{Pressure recovery (mm Hg)} = 4\,V^2 \times 2\,\text{EOA/AoA} \times (1 - \text{EOA/AoA})$$

Where, V is the peak transvalvular velocity, EOA is effective orifice area of the aortic valve, and AoA is the cross-sectional area of the proximal ascending aorta.

Aortic Valve Area

As already discussed, AVA is the most important measurement of AS severity. Unlike transvalvular velocity and gradient, AVA is less sensitive to alterations in transvalvular flow and, thus, provides a more accurate and stable measure of AS severity over a range of hemodynamic states.

There are two methods for estimating AVA during echocardiography—planimetry and the continuity equation.[6] Planimetry involves direct tracing of the aortic valve orifice in a gray-scale image **(Fig. 3)**. When feasible, it can permit an accurate assessment of AS severity. However, thickening and calcification of the aortic valve leaflets commonly present in severe AS often preclude accurate planimetry. TEE may help in such cases by providing a better visualization of the aortic valve orifice. The measurement should be performed exactly at the tips of the aortic valve leaflets. If available, 3D echocardiography can be used for properly aligning the imaging plane with the aortic valve orifice **(Fig. 4)**.

Given the challenges inherent to planimetry, continuity equation is the most used method for estimation of AVA. It is feasible in almost every patient with AS, unless there is a significant subvalvular obstruction. However, it is also highly

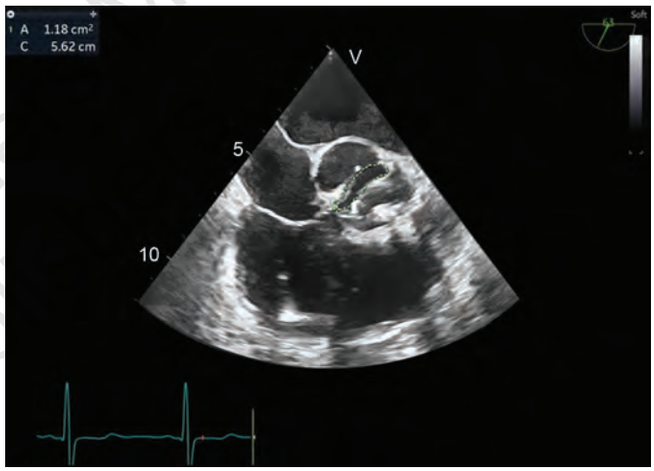


FIG. 3: Measurement of aortic valve area by planimetry during transesophageal echocardiography.

error-prone and proper care must be taken while obtaining all the required measurements **(Box 1)**.

Continuity equation is based on the conservation of mass principle which implies that the volume of blood ejected through the LV outflow tract (LVOT) will all pass through the stenosed aortic valve. The volume of blood passing through any tubular structure can be calculated by multiplying cross-sectional area of that structure with the VTI of the spectral Doppler flow signal across the same structure. Using these principles, the continuity equation can be presented as below **(Figs. 5A to C)**:

$$\begin{aligned} \text{Flow across LVOT} &= \text{Flow across aortic valve, or} \\ \text{LVOT area} \times \text{LVOT VTI} &= \text{AVA} \times \text{aortic valve VTI, or} \\ \text{AVA} &= (\text{LVOT area} \times \text{LVOT VTI})/\text{aortic valve VTI, or} \\ \text{AVA} &= (0.785 \times \text{LVOT diameter}^2 \times \text{LVOT VTI})/\text{aortic valve VTI} \end{aligned}$$

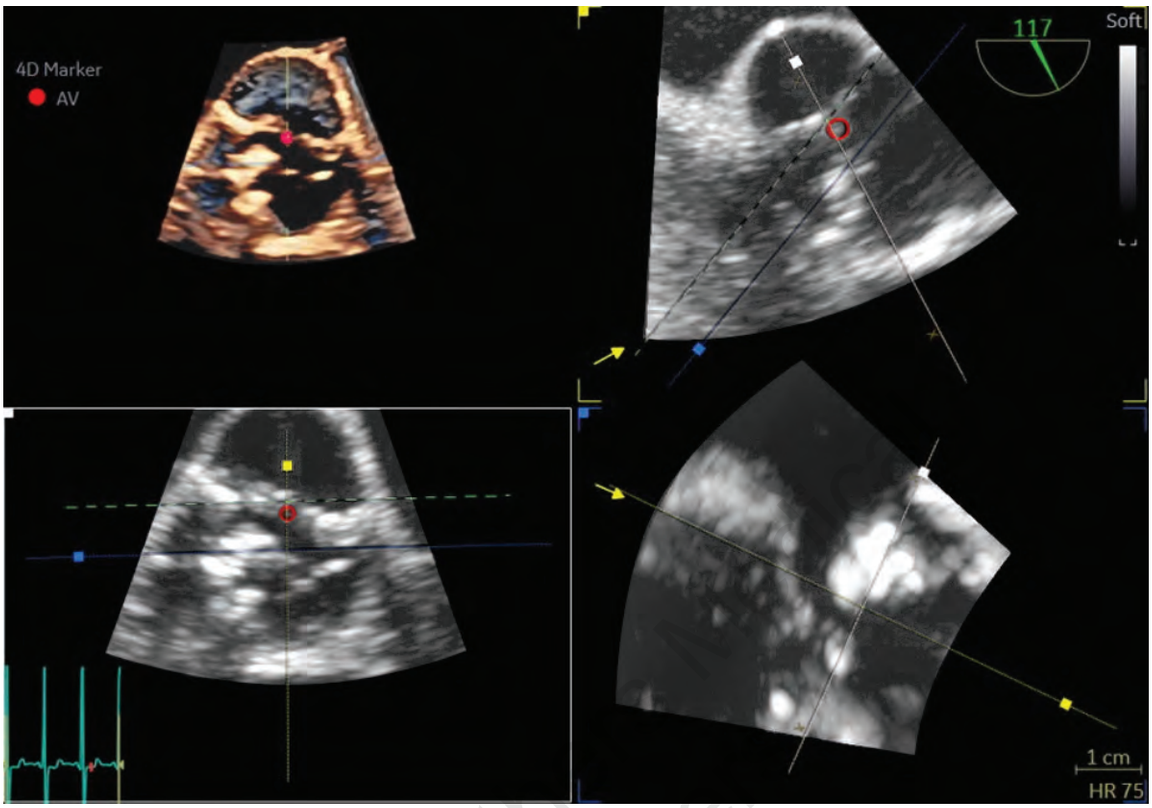


FIG. 4: The role of three-dimensional echocardiography for proper alignment of the imaging plane at the leaflet tips for accurate measurement of aortic valve area by planimetry.

BOX 1 Key points to avoid measurement errors during echocardiographic assessment of aortic stenosis.

- Multiple echocardiographic windows to obtain maximal values for aortic valve velocity and gradient. Right parasternal window should always be checked whenever the valve gradient is unexpectedly low
- The dense outer edge of the continuous-wave spectral waveform at aortic valve should be traced, without including the fringes
- For measuring LVOT-VTI, the pulsed-wave sample volume is first placed at the valve and then slowly withdrawn apically until a suitable trace with clean edges and no aliasing is obtained
- The LVOT diameter should be measured at the insertion point of the aortic cusps (and not 1 cm below this level) in the parasternal long-axis window

  The measurement should be performed from inner-edge to inner-edge, during mid-systole or at the time of maximum valve opening

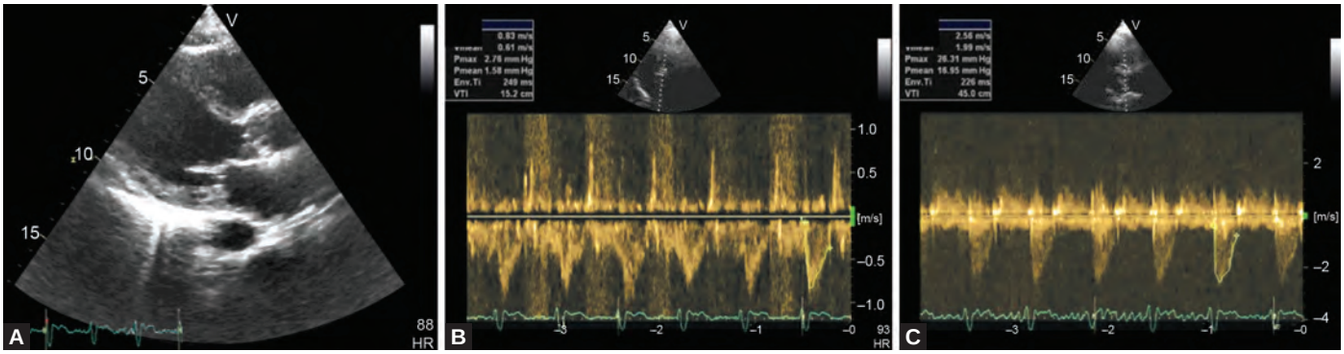
  Proper imaging plane allowing diameter measurement perpendicular to the long-axis of the LVOT should be chosen. If calcium is present at the site of measurement, it is usually included in the measurement
- Associated lesions should be taken into account before deciding about the severity of AS. For example, mitral stenosis may underestimate AS severity; associated aortic regurgitation can cause high gradients
- Sometimes, in patients with anteriorly directed severe MR, the MR jet may get erroneously picked during aortic valve gradient measurement in the apical five-chamber view. The MR jet can be distinguished from the AS jet by its much earlier onset (even before the onset of LVOT flow). Careful evaluation of the valve morphology will also help in avoiding this error
- Uncontrolled hypertension, any high flow state, etc. should be treated first and then the study should be repeated before making a final decision. Controlling blood pressure adequately is particularly important in the presence of low-flow and low-gradient scenario

(AS: aortic stenosis; LVOT: left ventricular outflow tract; MR: mitral regurgitation; VTI: velocity time integral)

Accurate measurement of LVOT VTI, LVOT area, and aortic valve VTI is essential to ensure accurate estimation of AVA.[6,7,19] The following section describes how to obtain these measurements accurately.

Aortic valve VTI is derived using CW Doppler, as described above. The potential sources of error and the technique to avoid them are already discussed.

The LVOT VTI is measured using pulsed-wave (PW) Doppler in apical five-chamber view. Proper placement of the sample volume is extremely crucial. Measuring too close to the aortic valve or too far from the valve will result in overestimation or underestimation of the LVOT flow, respectively. It is suggested that the sample volume should first be placed at the level of the aortic valve and then gradually moved toward the LV apex.



FIGS. 5A TO C: Continuity equation for estimation of aortic valve area by planimetry. (A) Measurement of left ventricular outflow tract diameter in parasternal long-axis view; (B) Pulsed-wave Doppler for measurement of left ventricular outflow tract velocity time integral in apical five-chamber view; (C) Measurement of aortic valve velocity time integral using continuous-wave Doppler in apical five-chamber view.

The earliest point where a clear velocity envelope is obtained without aliasing or spectral broadening is the site for measuring LVOT VTI. Once again, aligning Doppler beam with the blood flow direction and tracing only the dense part of the signal are essential.

The LVOT diameter is measured in the parasternal long-axis view, as the distance between the insertion points of the aortic cusps. The measurement is performed from inner-edge to inner-edge and is obtained during mid-systole or at the time of maximum aortic valve opening. Utmost care should be taken to obtain an accurate measurement because even a small error gets amplified as the diameter is squared to derive the LVOT area. Proper alignment of the imaging plane showing LVOT in the long-axis is essential. If there is significant calcification at the site of measurement, the imaging plane showing calcium should preferably be avoided and if not possible, then the measurement should be performed including the calcium in it.[7,20]

It should be noted that the above method actually describes the measurement of aortic annulus, and not really the LVOT. However, it has been shown that the LVOT has a tubular shape without any appreciable change in its diameter for a few mm below the aortic valve. The measurement at the level of aortic annulus is preferable because it has much greater reproducibility. Moreover, it also provides the best correlation with CMR-measured LV SV, as compared to measurements performed below the level of the aortic annulus.[21]

Finally, it should also be remembered that the continuity equation described above assumes LVOT to be circular with a fixed diameter throughout the systole. Both of these assumptions are incorrect and add another source of error.

Dimensionless Velocity Index

Considering the potential for error in the measurement of LVOT diameter, it can be removed from the continuity equation to provide an alternate measure of AS severity (i.e., LVOT VTI/aortic valve VTI). This dimensionless VTI ratio expresses AVA as a proportion of the LVOT area with a value of <0.25 indicating severe AS.

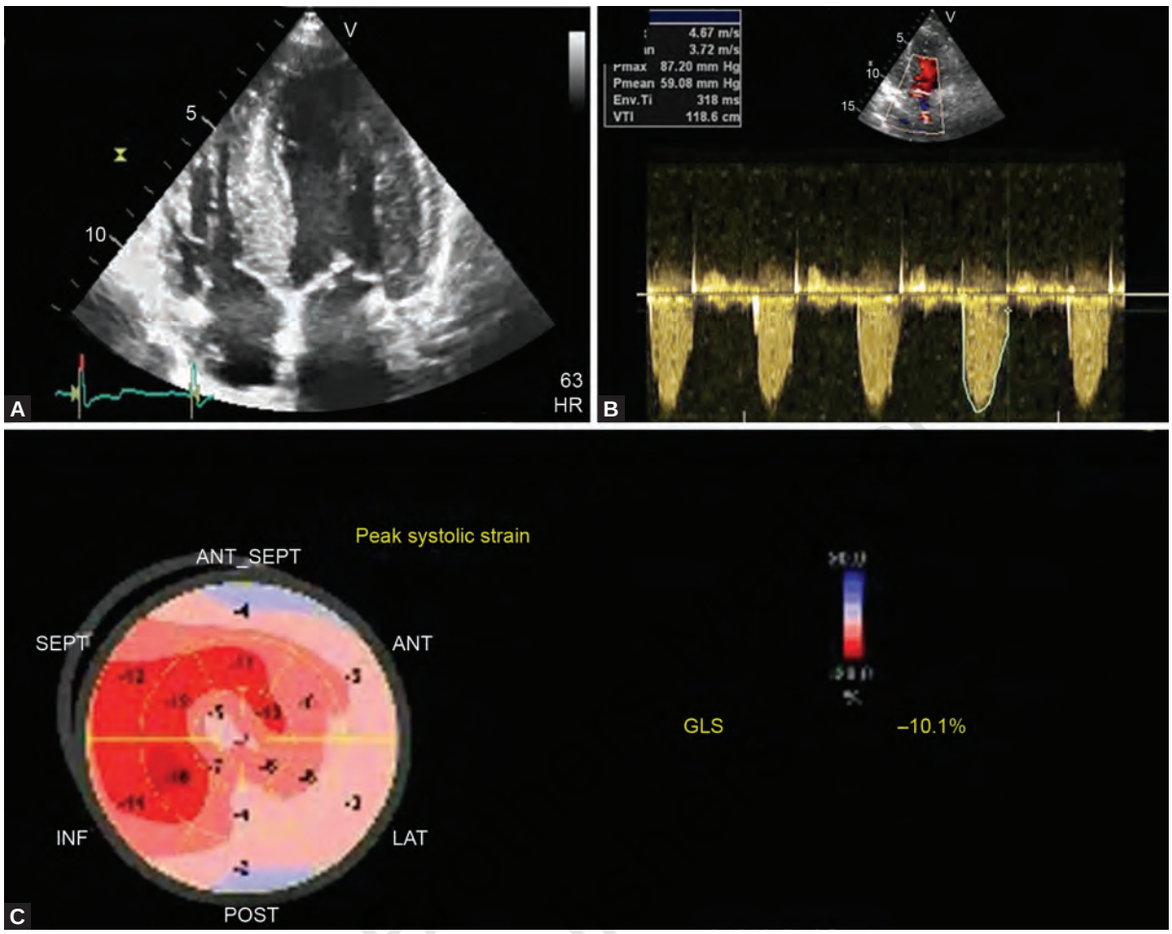
Left Ventricular Ejection Fraction and Global Longitudinal Strain

Impairment of LV systolic function with LVEF < 50% is a class I indication for aortic valve replacement (AVR) in severe AS.[22,23] Hence, accurate measurement of LVEF is essential in every patient with AS. Biplane Simpson's method is the recommended echocardiographic method for this purpose.[24] When available, 3D echocardiography allows a more accurate estimation of LV volumes and EF.[24,25]

Despite the enormous data supporting the clinically utility of LVEF, it is now well recognized that LVEF is not a sensitive measure of LV systolic dysfunction. This is particularly true for conditions associated with LV hypertrophy, such as AS.[26] The chronically elevated LV afterload in AS results in compensatory LV hypertrophy which eventually leads to progressive myocyte injury, myocyte apoptosis, and replacement fibrosis. A fall in LVEF occurs only when significant myocardial injury has already occurred. Thus, the impairment of LVEF, especially reduction below 50%, which is the currently recommended threshold for surgical intervention, is actually a late event in the course of the disease. A study from the Mayo Clinic followed up 2,017 patients with severe AS who had undergone AVR. It was found that the patients with baseline LVEF 50–60% had significantly elevated risk of adverse events during follow-up as compared to those with LVEF > 60%.[27]

Over the last two decades, global longitudinal strain (GLS) has emerged as a useful measure of LV systolic function which is more sensitive than LVEF to detect early myocardial dysfunction.[28-30] Strain refers to the percentage change in the length of a myocardial segment during a specific phase of cardiac cycle. Negative strain denotes shortening whereas positive strain denotes lengthening. GLS is the average longitudinal strain of all LV myocardial segments during systole. Longitudinal shortening of the LV is determined predominantly by the subendocardial muscle fibers. Since most of the cardiac diseases, especially valvular heart disease, first affect the subendocardial layer, GLS is one of the earliest measures of LV systolic function to get impaired. In most of the cardiac conditions, impairment of GLS occurs much before there is any apparent fall in LVEF. Consequently, hundreds of studies in a variety of cardiac conditions have shown that GLS is a more sensitive measure of LV systolic dysfunction than LVEF and has strong and incremental prognostic value over LVEF.[28-30]

Impairment of GLS is common in patients with severe AS with preserved LVEF and is associated with high risk of adverse events **(Figs. 6A to C)**.[31] Recently, a meta-analysis was published which included 10 studies with 1,067 patients with significant



FIGS. 6A TO C: Subclinical left ventricular systolic dysfunction in a patient with severe aortic stenosis with concentric left ventricular hypertrophy. (A) Markedly hypertrophied left ventricle; the left ventricular ejection fraction was supernormal; (B) High aortic valve gradient consistent with severe aortic stenosis; (C) Global longitudinal strain (GLS) was markedly impaired (–10.1%).

AS who were asymptomatic and had preserved LVEF (LVEF > 50%).[32] The patients were followed up for a median of 1.8 years. GLS had incremental value over LVEF for prediction of all-cause mortality. Inflection point seemed to occur at a cut-off value of –14.7% below which there was a sharp increase in the mortality risk. Other studies have suggested that early AVR in patients with subclinical LV systolic dysfunction detected using strain imaging might help to prevent irreversible LV deterioration.[33-35] Based on such evidences, several investigators have proposed using GLS for timing surgical intervention in asymptomatic severe AS.[31] However, the guidelines are yet to endorse this since there is currently no randomized study to prove that strain-guided management does indeed improve patient outcomes. Nevertheless, the finding of reduced GLS in an asymptomatic patient with severe AS and preserved LVEF (>50%) should at least prompt a closer follow-up than what is recommended by the current guidelines. Besides this, impaired GLS is also useful for explaining reduced SV in patients with paradoxical LFLGAS.

Global longitudinal strain is estimated using speckle tracking echocardiography. Good quality gray-scale images in apical two-, three-, and four-chamber views with a frame rate of 50–80 frames per second are required for optimum analysis.[36,37] Most of the current generation echocardiography equipment has inbuilt software that allows rapid and online estimation of GLS in less than a minute, once appropriate images have been acquired.

Impact on Other Cardiac Chambers

Progressive LV myocardial damage secondary to long-standing severe AS results in LV systolic and diastolic dysfunction which subsequently leads to a deleterious impact on the structure and function of the upstream cardiac chambers. The extent of such cardiac damage can be assessed using echocardiography and provides prognostic information. Genereux et al. have proposed a staging classification of AS based on the extent of such cardiac damage:[38]

- *Stage 0*: No cardiac damage
- *Stage 1*: LV damage (LV hypertrophy, diastolic dysfunction, and systolic dysfunction)
- *Stage 2*: Left atrial or mitral damage (increased left atrial size, moderate or severe mitral regurgitation, and atrial fibrillation)
- *Stage 3*: Pulmonary vascular or tricuspid damage (elevated pulmonary artery systolic pressure and moderate or severe tricuspid regurgitation)
- *Stage 4*: Right ventricular damage (moderate or severe right ventricular dysfunction)

Dobutamine Echocardiography

In patients with LFLGAS, both classical and paradoxical, an important question to address is whether reduced AVA is truly due to severe AS or is due to inadequate valve opening secondary to inadequate LV ejection force (the so-called "pseudo-severe" AS). A severely calcific noncompliant valve is unlikely to be affected by the flow conditions but a moderately stenotic partially compliant valve may open less in the presence of low SV. DbE can be useful in recognizing this phenomenon and distinguishing true-severe AS from pseudo-severe AS.

The use of DbE has been common in patients with classical LFLGAS for assessing contractile reserve and the impact of inotropic stimulation on valve gradients and AVA[6,7] **(Flowchart 2)**. The dobutamine infusion is started at a low dose (5 μg/kg/min) and increased every 3–5 minutes to a maximum dose of 20 μg/kg/min. Care is taken to avoid a significant increase in heart rate (>10 bpm increase or exceeding 100 bpm). LV SV, LVOT VTI, aortic valve VTI, and aortic valve gradients are measured at each stage. An increase in LV SV ≥ 20% is considered to indicate the presence of contractile reserve. If AS is truly severe, increased LV SV results in increase in the mean aortic valve gradient to ≥40 mm Hg while the AVA remains <1 cm^2. However, if the AS is not severe, then the AVA increases to >1 cm^2 but the transvalvular gradient does not increase much. In patients in whom LV SV fails to increase sufficiently, the severity of AS can still be determined by calculating projected AVA.[7] Projected AVA refers to the calculated AVA at an assumed transvalvular flow rate of 250 mL/s. The flow rate is the rate at which the blood is ejected through the aortic valve orifice and can be calculated by dividing SV in milliliter with the ejection duration in seconds.

To calculate projected AVA, first the valve compliance is calculated using the following equation:

Valve compliance = (AVA at peak dose – AVA at baseline)/ (peak flow rate – flow rate at baseline)

Once the valve compliance is calculated, the projected AVA can then be calculated as follows:

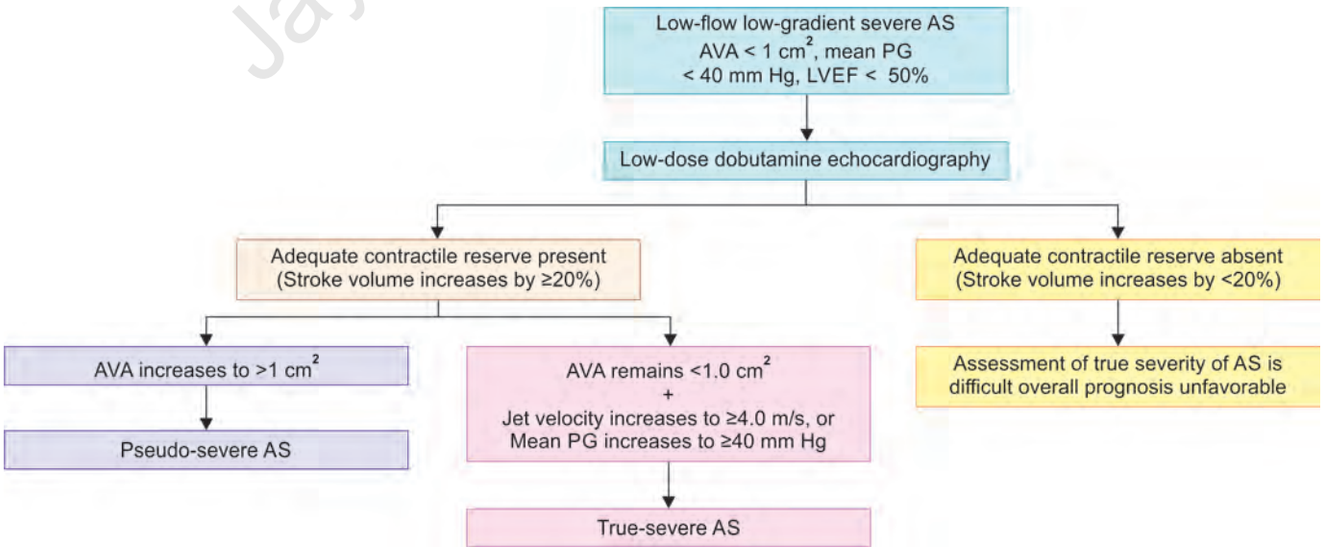
Projected AVA = AVA at baseline + valve compliance × (250 – flow rate at baseline)

Dobutamine echocardiography has also been used for assessing true severity of AS in patients with paradoxical LFLGAS. However, its use in this subset is challenging because of the presence of small LV cavity size and significant LV systolic dysfunction which may result in the development of dynamic LVOT obstruction, hypotension, or atrial fibrillation during the test.[39]

The presence of true-severe AS helps in identifying patients who are likely to benefit from intervention. In addition, the contractile reserve itself is a good prognostic marker. The lack of adequate contractile reserve is associated with high surgical risk and poor clinical outcomes. However, compared with medical management, AVR [especially transcatheter AVR (TAVR)] is still beneficial in these patients.[40-43] The advent of TAVR has, in fact, created an uncertainty about the utility of DbE in the evaluation of AS. The recent studies have shown that TAVR may benefit majority of the patients with apparent LFLGAS, regardless of the presence of contractile reserve or the true severity of AS.[44]

Global Left Hemodynamic Load

Degenerative AS is a disease of elderly. There are also some suggestions that it shares pathogenic similarities with atherosclerosis and is, in fact, a part of the generalized atherosclerotic disease process.[45,46] For these reasons, degenerative AS is often accompanied by other manifestations of systemic vascular disease.[47,48] Thus, reduced arterial compliance with increased systemic arterial stiffness is a common finding in these patients. The increased arterial stiffness adds another reason for increased LV afterload (arterial load) to already existing valvular load. This double afterload compromises LV ejection performance and reduces



FLOWCHART 2: Interpretation of dobutamine echocardiography in low-flow low-gradient aortic stenosis.
(AS: aortic stenosis; AVA: aortic valve area; PG: pressure gradient)

LV SV and transaortic gradient leading to the development of LFLGAS. The increased vascular load has also been shown to be a poor prognostic marker, independent of other measures of AS severity.[49-53]

Several different parameters have been used to quantify total LV afterload in patients with severe AS. The most commonly used among these is valvuloarterial impedance or ZVa. ZVa is calculated using the following equation:[50]

$$ZVa = (\text{systolic BP} + \text{mean transaortic pressure gradient})/\text{LV SVi}$$

A value > 4.5 mm Hg/mL/m^2 indicates increased LV afterload.

Several studies have shown that increased ZVa is an important mechanism responsible for LFLGAS and has prognostic implications.[49-53]

Although ZVa is considered a measure of global hemodynamic load, it is not really a direct measure of systemic arterial compliance. Furthermore, as the equation for ZVa includes mean valve gradient and LV SVi, ZVa may not be an ideal parameter to determine the impact of systemic arterial stiffness on LV ejection performance. Arterial pulse wave velocity (PWV) is currently the most validated method to noninvasively quantify arterial stiffness. Liu and colleagues reported significant association between AS severity and high PWV measured invasively.[54] More recently, a study evaluated the relationship between noninvasively measured arterial PWV, transvalvular flow, and gradient. Contrary to the prevailing understanding, the study showed that arterial PWV was not a determinant of low-flow state. Instead, an increasing PWV was associated with increasing transvalvular flow and gradient.[55]

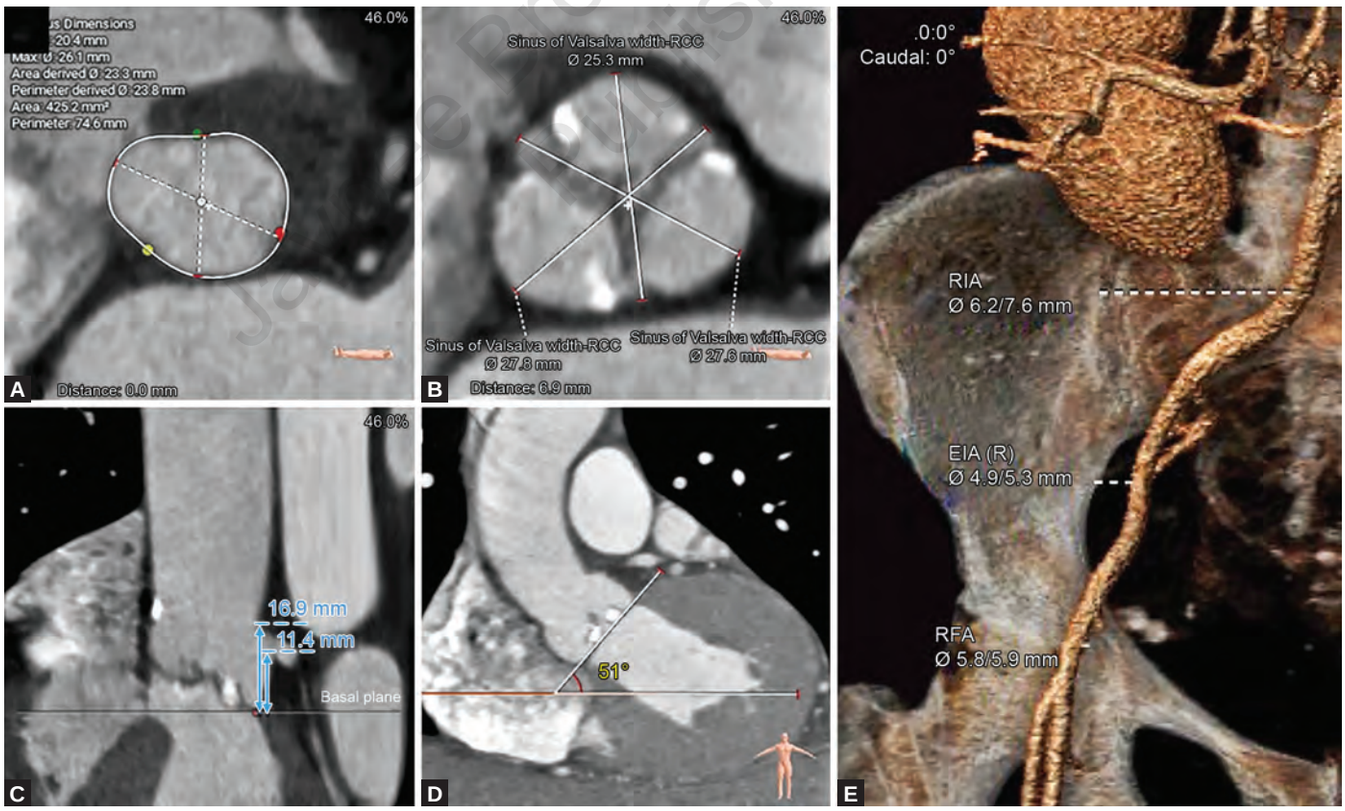
Nevertheless, it is safe to assume that in discrepant cases, if the ZVa and/or PWV is high, it is likely that the AS is true-severe and should be managed accordingly.

Computed Tomography

Discordant low-gradient AS has become a diagnostic challenge and many times advanced echocardiography techniques are not enough to reach a conclusion. In such cases, CT and CMR can provide valuable information about both AS severity and the extent of myocardial damage.[56,57]

Contrast-enhanced CT permits excellent visualization of the aortic valve, can distinguish between bicuspid and tricuspid aortic valves, and also provides a good idea about the AS severity. In patients with degenerative AS, the extent of aortic valve calcification is a reliable surrogate for AS severity. Accordingly, CT-aortic valve calcium score is used as one of the parameters to confirm AS severity in the presence of LFLGAS. An aortic valve calcium score >1,200 (Agatston method) in women and >2,000 in men supports a diagnosis of severe AS whereas scores >1,600 and >3,000 respectively indicate that severe AS is highly likely.[58]

In patients undergoing TAVR, CT of the aortic valve and entire aorta is an integral part of the preprocedural work-up[59] **(Figs. 7A to E)**. CT is used for providing accurate estimation of the aortic annulus and aortic root size, for delineating coronary



FIGS. 7A TO E: Computed tomography for comprehensive assessment of a patient undergoing transcatheter aortic valve replacement. (A and B) Measurement of aortic annulus and root dimensions; (C) Measurement of coronary height from the annulus; (D) Assessment of aortic root angulation; and (E) Evaluation of the vascular access site.

anatomy in relation to the aortic valve leaflets, for excluding any significant aortic root pathology and for assessing the suitability of the vascular access route for the procedure. Only when there is significant preexisting renal dysfunction with high risk of renal worsening with contrast administration that CT is excluded from the pre-TAVR work-up.

Cardiac Magnetic Resonance Imaging

As discussed earlier, the natural history of severe AS is characterized by a long latent period during which progressive myocardial injury and fibrosis take place. Recognition and quantification of this myocardial damage can be useful in predicting outcomes and may even help in timing intervention. CMR is currently the most useful noninvasive imaging modality for myocardial tissue characterization. T1 maps, extracellular volume quantification, and late gadolinium enhancement are the key CMR parameters that help in assessment of myocardial fibrosis. Recent studies have validated diagnostic accuracy of these measurements by providing histological confirmation.[60] At the same time, correlation of CMR abnormalities with clinical outcomes has also been demonstrated.[61-64] Given these findings, it has been suggested that CMR could be used for deciding about intervention in patients with asymptomatic severe AS, especially in those with echocardiographic evidence of subclinical LV systolic dysfunction.[31] However, widespread use of CMR for this purpose is precluded by logistic issues and the lack of randomized trial data.

Integrated Assessment

The diagnosis of severe AS is relatively straightforward when the mean valve gradient is ≥40 mm Hg and AVA is ≤1 cm^2. However, in discordant cases, a stepwise assessment, incorporating information from different diagnostic modalities, is required **(Flowchart 1 and Table 1)**:

- Ensure that there is no measurement error.
- Evaluate the aortic valve morphologically. A densely calcified valve with markedly reduced opening is likely to be severely stenotic. A TEE may be performed for better assessment of aortic valve morphology; planimetry of the aortic valve can also be performed.
- Estimate LV SVi. If it is <35 mL/m^2, it indicates low-flow situation. Transvalvular flow rate is another useful metric, with <200 mL/s indicating low-flow.[65,66]
- If the aortic valve flow is normal and mean valve gradient low, then it is likely that AS is not severe. Such patients generally have better prognosis.
- A low transaortic flow is associated with worse prognosis regardless of the underlying mechanism of low flow. Further evaluation is needed to determine true severity of AS.
- In such patients, if LVEF is <50% (i.e., classical LFLGAS) and there is no other identifiable cause for LV systolic dysfunction, AS is likely to be severe. A careful evaluation of the aortic valve morphology will further confirm that. However, concomitant coronary artery disease presents a major diagnostic challenge. DbE may be performed to rule out pseudo-severe AS and to assess LV contractile reserve.
- If LVEF is >50% (i.e., paradoxical LFLGAS), further assessment of true severity of AS is often challenging. The features that support a diagnosis of severe AS are summarized in **Box 2**.
- In all patients with LFLGAS, especially those with paradoxical LFLGAS, a careful evaluation should be done to rule out cardiac amyloidosis. It has been shown that transthyretin amyloidosis may be present in almost up to 15% patients with severe AS and almost up to 30% of those with LFLGAS.[67]
- In patients diagnosed with severe AS, a comprehensive cardiac assessment should be performed to determine the impact of severe AS on other cardiac chambers. Formal staging for cardiac damage may also be performed.
- Once the diagnosis of severe AS is confirmed and intervention is contemplated, additional assessment would be needed to collect information required for guiding the intervention (surgical AVR or TAVR).

BOX 2 **Findings that support a diagnosis of severe aortic stenosis in paradoxical low-flow low-gradient aortic stenosis.**

- Elderly patient (especially women) with significant LV hypertrophy and small LV cavity size
- Clinical examination (symptoms physical findings) consistent with severe aortic stenosis
- Aortic valve mean pressure gradient 30–40 mm Hg
- Elevated natriuretic peptide levels
- Low flow confirmed by other techniques than standard Doppler technique
- Reduced LV GLS
- High ZVa
- Elevated aortic valve calcium score

(GLS: global longitudinal strain; LV: left ventricular; ZVa: valvulo-arterial impedance)

CONCLUSION

Aortic stenosis is the most common valvular heart disease and a source of considerable morbidity and mortality. The recent advent of TAVR has greatly expanded the therapeutic horizon for AS and has placed a lot of emphasis on accurate diagnostic assessment of AS. As a result, our understanding of AS has evolved significantly over the past few years. However, this area remains a "work in progress" and staying abreast with the latest updates in this field is essential for proper management of the patients with AS.

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CHAPTER 10

Clinical Approach to Mitral Regurgitation

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ABSTRACT

Mitral regurgitation (MR) is a common valvular disorder that can arise from abnormalities of any part of the mitral valve apparatus. These include the valve leaflets, annulus, chordae tendineae, and papillary muscles. The left atrium (LA) and ventricle are also integrally involved with mitral valve function.

The most common etiologies of MR include mitral valve prolapse (MVP), rheumatic heart disease, infective endocarditis, annular calcification, cardiomyopathy, and ischemic heart disease. The pathophysiology, clinical manifestations, and management of MR differ with the chronicity of the disease and the etiology.

The etiology, pathophysiology, and clinical approach of MR will be reviewed in this chapter.

INTRODUCTION

Evaluation of the patient with mitral regurgitation (MR) begins with a directed history and physical examination. The clinician should recognize that symptoms may be subtle, owing to insidious progression and self-limitation of physical activity. Exercise testing can be useful for assessment of functional status and elicitation of symptoms; and exercise echocardiography may reveal elevated pulmonary artery pressures, worsening of MR, or blunted left ventricular (LV) or right ventricular contractile reserve. Key steps in the management of such patients with MR include identification of MR, definition of the etiology of MR (including whether MR is primary or secondary) assessment of MR severity, followed by treatment decisions.

ETIOLOGY AND PATHOPHYSIOLOGY

Mitral regurgitation can be caused by organic disease (e.g., rheumatic fever, ruptured chordae tendineae, myxomatous degeneration, and leaflet perforation) or a functional abnormality, congenital MR is rare but is commonly associated with myxomatous mitral valve disease. Alternatively, it can be associated with cleft of the mitral valve, as occurs in persons with Down syndrome, or an ostium primum atrial septal defect.

Acute Mitral Regurgitation

Acute MR is characterized by an increase in preload and a decrease in afterload causing an increase in end-diastolic volume (EDV) and a decrease in end-systolic volume (ESV). This leads to an increase in total stroke volume (TSV) to supranormal levels. However, forward stroke volume (FSV) is diminished because much of the stroke volume regurgitates as the regurgitant stroke volume (RSV). This, in turn, results in an increase in left atrial pressure (LAP). According to the Laplace principle, which states that ventricular wall stress is proportional to both ventricular pressure and radius, LV wall stress in the acute phase is markedly decreased since both of these parameters are reduced.

Chronic Compensated Mitral Regurgitation

In chronic compensated MR, the left atrium (LA) and ventricle have sufficient time to dilate and accommodate the regurgitant volume. Thus, LA pressure is often normal or only minimally elevated. Because of the LV dilatation via the process of eccentric hypertrophy, TSV and FSV are maintained. Wall stress may be normal to slightly increased as the radius of the LV cavity increases but the end-diastolic LV pressure remains normal. As the LV progressively enlarges, the mitral annulus may stretch

and prevent the mitral valve leaflets from coapting properly during systole, thus worsening the MR and LV dilatation.

Chronic Decompensated Mitral Regurgitation

In the chronic decompensated phase, cardiac dysfunction has developed, impairing both TSV and FSV (although ejection fraction still may be normal). This results in a higher ESV and EDV, which in turn causes an elevation of LV and LA pressure, ultimately leading to pulmonary edema and, if left untreated, cardiogenic shock.

ETIOLOGY

Acute Mitral Regurgitation

Causes of acute MR include coronary artery disease, infectious endocarditis, chordae tendineae rupture (as with myxomatous valve disease), valvular surgery, and other conditions.

- Coronary artery disease [ischemia or acute myocardial infarction (MI)] may result in papillary muscle dysfunction or rupture; it does not cause chordae tendineae dysfunction or rupture as they are not vascularized. The posteromedial papillary muscle is supplied by the terminal branch of the posterior descending artery and is more vulnerable to ischemic insult than the anterolateral papillary muscle, which is usually supplied by both the left anterior descending and circumflex arteries. Transient ischemia may result in transient MR associated with angina. MI or severe prolonged ischemia produces irreversible papillary muscle dysfunction and scarring.
- Infectious endocarditis features include the following: Abscess formation, vegetations, rupture of chordae tendineae, and leaflet perforation
- Following valvular surgery, acute MR may occur as a result of trauma, percutaneous valvuloplasty, or suture interruption.
- Tumors (most commonly atrial myxoma)
- Myxomatous degeneration [mitral valve prolapse (MVP), Ehlers–Danlos syndrome, and Marfan syndrome]
- Ruptured chordae tendineae (trauma, MVP, endocarditis, and spontaneous)
- Systemic lupus erythematosus (Libman–Sacks lesion)
- Acute rheumatic fever (Carey Coombs murmur)
- Acute global LV dysfunction
- Prosthetic mitral valve dysfunction

Chronic Mitral Regurgitation

Causes of chronic MR include the following:

- Rheumatic heart disease
- Systemic lupus erythematosus
- Scleroderma
- Myxomatous degeneration (MVP, Ehlers–Danlos syndrome, and Marfan syndrome)
- Calcification of mitral valve annulus
- Infective endocarditis (can affect normal, abnormal, or prosthetic mitral valves)
- Functional MR[1] [dilation of mitral valve annulus, anormal tethering of leaflets due to enlargement of LV cavity and stretch of papillary muscles and chordae (dilated cardiomyopathies and aneurysmal dilation of the LV)]
- *Hypertrophic cardiomyopathy*: Systolic anterior motion of the mitral valve
- Paravalvular prosthetic leak
- Congenital (mitral valve clefts, mitral valve fenestrations, and parachute mitral valve abnormality)
- Drug-related[2-4] (ergotamine, methysergide, pergolide, anorexiant medications) MR may be due to a primary abnormality (sometimes referred to organic MR) of one or more components of the valve apparatus (leaflets, chordae tendineae, papillary muscles, and/or annulus) or may be secondary (previously referred to as functional MR) to another cardiac disease (such as coronary heart disease or a cardiomyopathy)

Primary Mitral Regurgitation Etiology

- Degenerative mitral valve disease (including MVP) is the most common cause of primary MR in developed countries. It includes a spectrum of disease ranging from myxomatous mitral valve disease (also known as myxomatous degeneration with redundancy of anterior and posterior mitral leaflets and the chordae), seen primarily in younger populations, and fibroelastic deficiency disease, seen primarily in older populations. It is not clear if these are two distinct disease processes or manifestations of a single disease.
- Rheumatic heart disease is uncommon in developed countries but continues to constitute a significant burden in the rest of the world. Rheumatic valve disease often results in MR in the first 2 decades of life, while mitral stenosis and mixed mitral stenosis plus MR are more often seen in adults.
- Infective endocarditis
- Trauma, which can cause ruptured chordae and acute MR.
- Use of certain drugs, such as ergotamine, bromocriptine, pergolide, and cabergoline, as well as anorectic drugs that are no longer available such as fenfluramine and benfluorex have been reported to induce MR, although the evidence for cause-effect relationship between exposure to these drugs and mitral valve disease remains weak.[2-4]
- Congenital malformations including valve cleft
- Mitral annular calcification is a common finding in older adults that is often associated with mild to moderate MR and is less commonly associated with severe MR.
- Causes of flail or partial flail mitral leaflet include MVP, infective endocarditis, trauma, and rupture of a papillary muscle in the setting of an acute MI.

Secondary Mitral Regurgitation Etiology

- *Coronary heart disease*: MR in patients with coronary disease most often is due to a regional wall motion abnormality distorting the mitral valve apparatus resulting in inadequate leaflet, closure. In patients with previous MI, chronic MR is seen due to adverse ventricular remodeling. However, MR also can occur with transient myocardial dysfunction

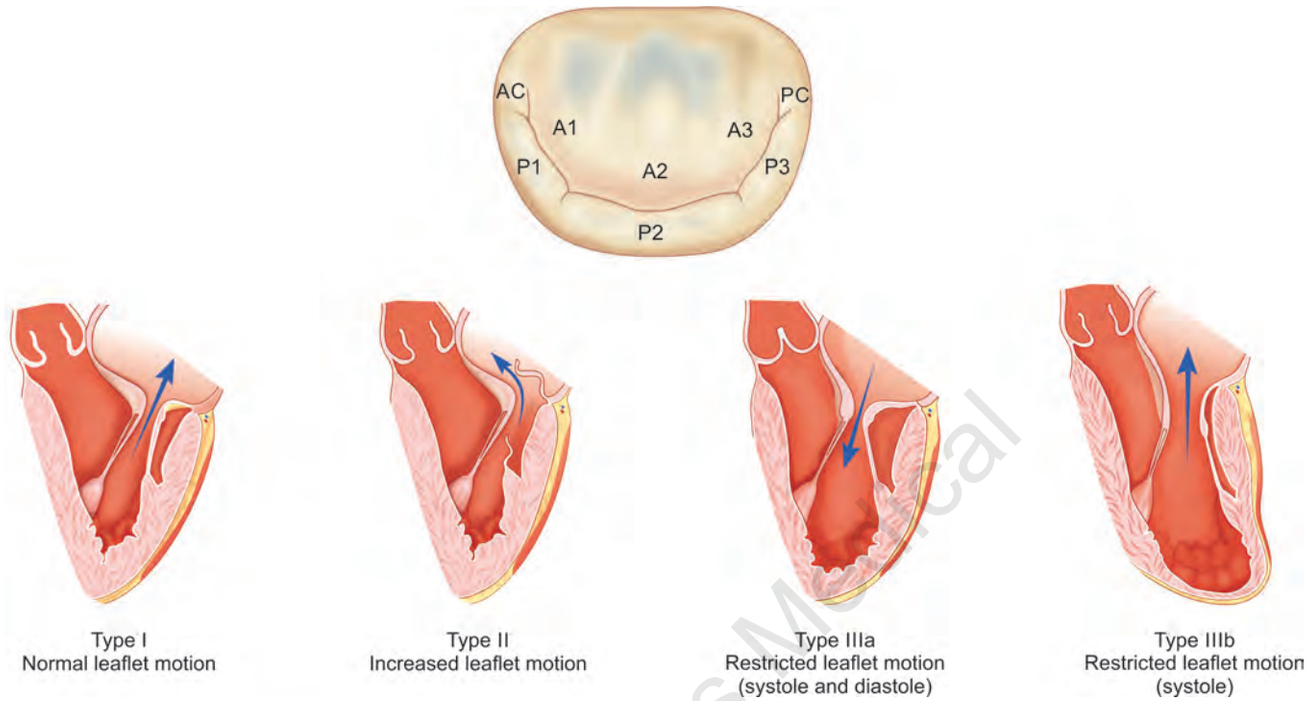


FIG. 1: Carpentier classification system of mitral regurgitation (MR).

so that MR severity (and symptoms) may acutely worsen with ischemia, exercise, or other changes in hemodynamic conditions.
- Dilated cardiomyopathy, with MR due to myocardial dyssynchrony, papillary muscle displacement, and annular dilation.[5]
- Hypertrophic cardiomyopathy with MR due to abnormal systolic anterior motion of the mitral leaflets.
- Right ventricular (RV) pacing can cause worsened or de novo secondary MR.
- Atrial functional MR occurs in the setting of heart failure with preserved ejection fraction and/or atrial fibrillation and is characterized by annular dilation and inadequate leaflet coaptation despite normal LV size and systolic function.

Carpentier classification system ***(Fig. 1)***: Type I (normal leaflet motion); type II (excessive leaflet motion); and type III (restricted leaflet motion), subcategorized as type IIIA (restricted during both systole and diastole) and type IIIB (restricted only during systole).

EPIDEMIOLOGY

Acute and chronic MR affect approximately 5 in 10,000 people. Myxomatous degeneration has replaced rheumatic heart disease as the leading cause of mitral valvular abnormalities. MVP has been estimated to be present in 4% of the normal population. With the aid of color Doppler echocardiography, mild MR can be detected in as many as 20% of middle-aged and older adults. MR is independently associated with female sex, lower body mass index, advanced age, renal dysfunction, prior MI, prior mitral stenosis, and prior MVP.

International data: In areas other than the Western world, rheumatic heart disease is the leading cause of MR.

CLINICAL MANIFESTATIONS

Symptoms: The nature and severity of the symptoms associated with chronic MR are related to the severity of MR, its rate of progression, the pulmonary artery pressure, arrhythmias (e.g., atrial fibrillation), and associated cardiac disease. Because of the importance of identifying the transition from asymptomatic to symptomatic MR in determining the timing of mitral valve surgery, a careful history is important to establish a good estimate of baseline exercise tolerance. Since symptoms occur late in patients with primary MR, serial monitoring of asymptomatic patients is required.

Patients with isolated mild-to-moderate primary MR are asymptomatic, since there is little volume overload of the ventricle and cardiac hemodynamics, and forward cardiac output remains normal. Most remain asymptomatic until there is LV cavity enlargement with systolic dysfunction, pulmonary hypertension, or the onset of atrial fibrillation. The most common symptoms are exertional dyspnea and fatigue due to the combination of a decreased forward (i.e., effective) cardiac output, an increase in LAP due to backflow across the mitral valve, and pulmonary artery hypertension. Another common clinical presentation is paroxysmal or persistent atrial fibrillation. Patients with severe MR and LV enlargement eventually progress to symptomatic heart failure with pulmonary congestion and edema. At this stage of LV dilatation, the myocardial dysfunction is often irreversible due to the long-standing MR. In some cases, irreversible LV systolic dysfunction occurs in the absence of symptoms.

Most patients with chronic secondary MR (ischemic or nonischemic) have mild MR, and the clinical presentation (including symptoms and signs of heart failure) generally reflects the state of ventricular dysfunction more than the state of the mitral valve. However, patients with only mild secondary

MR at rest may develop severe MR with exercise, leading to acute pulmonary edema. Among patients with chronic secondary MR who develop symptoms, the most common complaints reflect decreased forward or effective cardiac output and include weakness, fatigue, and exercise intolerance. Patients with more severe disease or with exercise-induced worsening of MR may present with symptomatic heart failure or pulmonary edema. However, it may be difficult to separate symptoms due to primary LV systolic dysfunction from those due to the added burden of secondary MR.

Other symptoms such as thromboembolism, hemoptysis, and right-sided heart failure do occur, but are less common than with mitral stenosis. However, there is an increased risk of infective endocarditis in patients with an abnormal mitral valve and moderate to severe MR.

Physical examination: In chronic primary MR, the arterial pulse is normal until very late in disease progression because LV ejection time and FSV remain normal. With acute MR or with end-stage chronic severe MR, there is a rapid reduction in the volume of forward flow late in systole along with a decrease in ejection time, so that the arterial pulse falls off rapidly, which may give the impression of a bounding pulse, similar to that seen with aortic regurgitation. However, the pulse pressure is normal with MR. A brisk carotid upstroke and hyperdynamic cardiac impulse may be noted, and a prominent LV filling wave may be present.

Enlargement of the LV results in a leftward displacement of the apical impulse; it is usually brisk or hyperdynamic. When the MR is severe or when there has been an acute exacerbation of the regurgitation as a result of chordal rupture, an S3 and a palpable thrill may be present. Crackles (rales) may be detected but are absent in many patients with symptomatic disease. Signs of right-sided congestive heart failure are typically absent unless there is associated mitral stenosis or the MR is of long standing and is very severe.

Physical examination cannot reliably distinguish chronic severe MR due to primary valve disease from secondary MR due to ischemic heart disease or dilated cardiomyopathy.

Palpation of the arterial pulse is helpful in differentiating aortic stenosis (AS) from MR, both of which may produce a prominent systolic murmur at the base of the heart and apex. The carotid arterial upstroke is sharp in severe MR and delayed in AS; the volume of the pulse may be normal or reduced in the presence of HF. The cardiac impulse, as with the arterial pulse, is brisk and hyperdynamic. It is displaced to the left, and a prominent LV filling wave is frequently palpable in thin patients.

AUSCULTATION

- When chronic severe MR is caused by defective valve leaflets, S1, produced by mitral valve closure, is usually diminished.
- Wide splitting of S2 is common and results from the shortening of LV ejection and an earlier A2 because of reduced resistance to LV ejection.
- In patients with severe pulmonary hypertension, P2 is louder than A2.
- The abnormal increase in the flow rate across the mitral orifice during the rapid filling phase is often associated with a third heart sound (S3), which should not be interpreted as a feature of HF in these patients, and this may be accompanied by a brief diastolic rumble.
- The systolic murmur is the most prominent physical finding; it must be differentiated from the systolic murmur of AS, tricuspid regurgitation (TR), and ventricular septal defect (VSD). In most patients with severe MR, the systolic murmur commences immediately after the soft S1 and continues beyond and may obscure the A2 because of the persisting LV-LA pressure difference after aortic valve closure.
- The holosystolic murmur of chronic MR is usually constant in intensity, blowing, high-pitched, and loudest at the apex, with frequent radiation to the left axilla and left infrascapular area, particularly with posteriorly directed jets. Radiation toward the sternum or aortic area, however, may occur with abnormalities of the posterior leaflet and is particularly common in patients with MVP and flail involving this leaflet.
- The murmur shows little change, even in the presence of large beat-to-beat variations of LV stroke volume, as in AF. This finding contrasts with that in most midsystolic (ejection) murmurs, such as in AS, which vary greatly in intensity with stroke volume and therefore with the duration of diastole.
- Little correlation has been found between the intensity of the systolic murmur and severity of MR. In patients with severe MR caused by LV dilation, acute MI, or paraprosthetic valvular regurgitation, or in those who have marked emphysema, obesity, chest deformity, or a prosthetic heart valve, the systolic murmur may be barely audible or even absent, a condition referred to as "silent" MR.
- The murmur of MR may be holosystolic, late systolic, or early systolic. When the murmur is confined to late systole, the regurgitation usually is secondary to MVP and may follow one or more mid-systolic clicks and typically is not severe. Such late systolic MR is often associated with a normal S1 because initial closure of the mitral valve cusps may be unimpaired.
- Occasionally, a late systolic murmur of papillary muscle dysfunction may be noted, becoming louder or holosystolic during acute myocardial ischemia, and may disappear when ischemia is relieved.
- A midsystolic click preceding a mid- to late-systolic murmur, and the response of that murmur to a number of maneuvers, helps to establish the diagnosis of MVP.
- Early systolic murmurs are typical of acute MR. When the LA v-wave is greatly elevated in acute MR, the murmur may diminish or disappear in late systole as the reverse pressure gradient declines. As noted, a short and low-pitched diastolic murmur following S3 may be audible in patients with severe MR, even without accompanying MS.

Dynamic Auscultation

Auscultation during positional changes or the Valsalva maneuver can be quite helpful in characterizing the MR murmur.

- When MR is holosystolic, it typically varies little during respiration. However, sudden standing usually diminishes the murmur, whereas squatting augments it.
- The late systolic murmur of MVP behaves in the opposite direction, decreasing in duration with squatting and increasing in duration with standing. Similarly, with the Valsalva maneuver, MVP clicks may occur earlier in systole with lengthening of the murmur.
- Holosystolic MR murmur is often softer during the strain of the Valsalva maneuver and shows a left-sided response (i.e., a transient overshoot that occurs six to eight beats after release of the strain).
- The murmur of MR usually is intensified by isometric exercise, differentiating it from the systolic murmurs of valvular AS and obstructive HCM, both of which are reduced by this intervention.
- The murmur of MR caused by LV dilation decreases in intensity and duration after effective therapy with cardiac glycosides, diuretics, rest, and particularly vasodilators.

In addition to the classic holosystolic murmur, other types of murmurs can be heard in chronic MR:

- When the posterior leaflet is predominantly involved (due to prolapse or chordal rupture), the murmur may radiate anteriorly toward the sternum and is heard well at the base. This type of murmur is often confused with AS but does not radiate to the carotid arteries.
- When the anterior leaflet is predominantly involved (due to prolapse or chordal rupture), the murmur is often loud, radiates to the back, and may be heard on the top of the head as a result of the excellent sound transmission along the vertebral column.
- A mid- to late-systolic murmur, harsh in quality, is often heard when the MR is due to prolapse or papillary muscle displacement (previously known as papillary muscle dysfunction). When the murmur is confined to late systole, the volumetric severity of MR is usually only mild to moderate, even if the murmur is loud. S1 is intact in this setting, since the initial closure of the mitral leaflets is normal. The murmur of papillary muscle displacement is variable and becomes louder and longer when there is an acute ischemic episode.
- Infrequently, the large diastolic volume across the mitral valve with severe MR produces an early diastolic murmur.
- When the cause is MVP, a mid-systolic click (correlating with the maximal prolapse and tension on the chordae) may be heard and the murmur may start in mid to late systole.
- Heart failure and the volume and geometry of the LV can affect the timing, intensity, and quality of the MR murmur. In patients with MR due to dilation of the valvular annulus, the murmur often diminishes in intensity or disappears as the heart failure is treated and LV function improves.

DIAGNOSIS AND EVALUATION

Differential Diagnosis

- The holosystolic murmur of MR resembles that produced by a VSD, but the latter is usually loudest at the sternal border and is often accompanied by a thrill in the parasternal area.
- The murmur of MR may also be confused with that of TR, but the latter is usually lower in pitch and is heard best along the left sternal border, with augmentation during inspiration and a prominent v-wave and y-descent in the jugular venous pressure (JVP).
- When the chordae tendineae to the posterior leaflet of the mitral valve rupture, the regurgitant jet is often directed anteriorly, so that it impinges on the atrial septum adjacent to the aortic root and causes a prominent systolic murmur at the base of the heart.
- On the other hand, when the chordae tendineae to the anterior leaflet rupture, the jet usually is directed to the posterior wall of the LA, and the murmur radiates to the axilla and may be transmitted to the spine or even the top of the head.
- Patients with rheumatic disease of the mitral valve exhibit a spectrum of abnormalities, ranging from pure MS to pure MR. The presence of a S3, a rapid LV-filling wave and prominent LV impulse on palpation, and a soft S1 all favor predominant MR.
- By contrast, an accentuated S1, a prominent OS with a short A2-OS interval, and a soft, short systolic murmur all indicate predominant MS.
- Elucidation of the predominant valvular lesion may be complicated by the presence of a holosystolic murmur of TR in patients with pure MS and pulmonary hypertension; this murmur may sometimes be heard at the apex when the right ventricle is greatly enlarged.

Chest radiograph: A chest radiograph is not indicated to diagnose MR but it may be obtained in patients with dyspnea of uncertain cause. The most common finding on the chest radiograph is cardiomegaly, resulting from enlargement of the LV and the LA. However, LV size does not correlate with the severity of MR, nor does LA size correlate with the elevation of LAP. LA enlargement may also be observed in the anteroposterior (AP) view as a double shadow in the right cardiac silhouette and/or straightening of the left cardiac border due to the large LA appendage.

Left ventricular enlargement causes the cardiac silhouette to be displaced toward the left chest wall and the chamber becomes globular. Evidence of LV enlargement due to volume overload may be observed (particularly in chronic MR), although pulmonary congestion (e.g., increased pulmonary markings) may not be observed until heart failure has developed.

The right ventricle is usually normal in size unless there is pulmonary hypertension. Similarly, the lung fields are usually clear unless congestive heart failure is present. Calcification of the mitral valve annulus may be seen.

Electrocardiogram: An electrocardiogram is not required for the diagnosis of MR but is routinely obtained to assess for concurrent conditions and to serve as a baseline for future comparison. The electrocardiogram in chronic MR most often reflects the hemodynamic burden placed on the LA, which can lead to LA enlargement, similar to that seen in mitral stenosis. The P wave broadens (>0.12 second in lead II), becomes

increased in amplitude, has notching, and has a significant negative component in V1 (called "P-mitrale"). Other changes are less specific. Chronic MR is often complicated by the development of atrial fibrillation. Ischemia or infarction in the inferior or posterior leads is present when acute MR is due to papillary muscle rupture. In chronic mitral valve regurgitation, LV dilatation and hypertrophy are observed with increased QRS voltage and ST-T wave changes in the lateral precordial leads.

Exercise testing: It can be useful for assessment of functional status and symptomatic elicitation; and exercise echocardiography may reveal elevated pulmonary artery pressures, MR worsening, or blunted LV or RV contractile reserve.

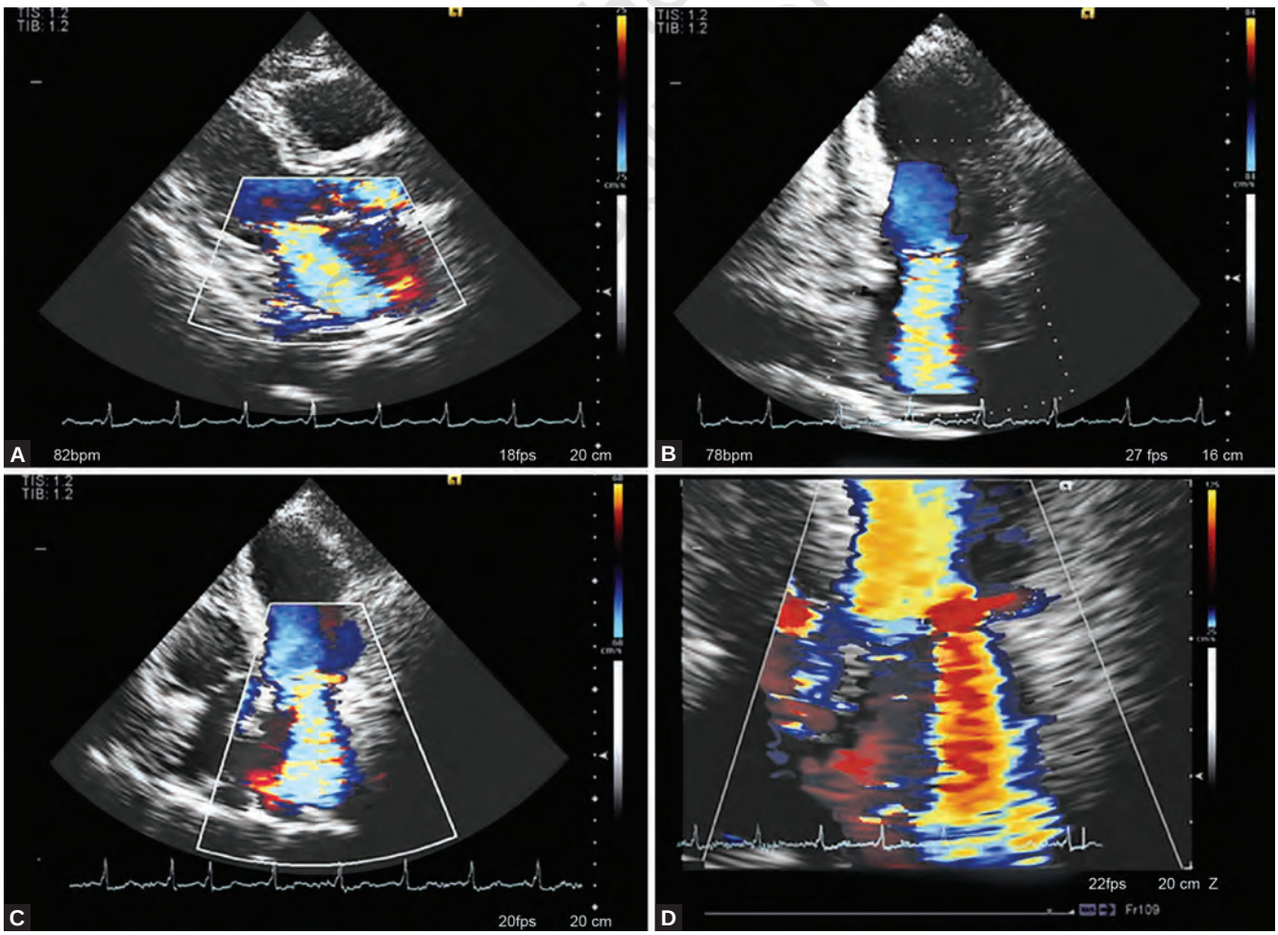
Echocardiography: Determine the mechanism and etiology of MR, usually with transthoracic echocardiography (TTE), or, if the image quality is poor, with transesophageal echocardiography (TEE). Perform assessment of the mitral apparatus, careful measurement of LA volume, and LV diameter and volume.[6,7]

Distinguish between primary MR (due to abnormalities of the mitral leaflets or subvalvular apparatus) and secondary MR (due to LA or LV geometric changes with a functionally normal mitral valve). In addition to LV dilatation or regional or global abnormalities of LV systolic function, secondary MR also can be caused by pure LA and mitral annular dilatation (i.e., "atrial functional MR").

The initial assessment of the MR severity should be with color-flow Doppler ultrasonography, and it should include quantitative parameters such as the effective regurgitant orifice area, regurgitant volume, and regurgitant fraction. A comprehensive approach is recommended, in which multiple parameters are evaluated and integrated to form a final determination of MR severity. Additional testing including TEE and cardiac magnetic resonance imaging (CMRI) should be used when the assessment of MR on TTE is not definitive. Severe MR criteria based on two-dimensional (2D) echocardiography **(Fig. 2 and Table 1)**.

Brain Natriuretic Peptide assessment

Pizarro et al. found that in patients with severe asymptomatic MR and normal LV function, levels of brain natriuretic peptide (BNP)[8] have an independent and additive prognostic value. In a prospective study of 269 consecutive patients with severe asymptomatic organic MR and LV ejection fraction above 60%, the receiver-operating characteristics curve yielded an optimal cut-off point of 105 pg/mL of BNP that was able to discriminate patients at higher risk. Pizarro et al. recommend considering BNP assessment in the routine clinical workup for



FIGS. 2A TO D: Transthoracic echocardiography showing severe mitral regurgitation.

TABLE 1: Executive summary from the European Association of Cardiovascular Imaging.[9]

	Primary mitral regurgitation	Secondary mitral regurgitation
Qualitative		
Mitral valve morphology	Flail leaflet, ruptured papillary muscle, severe retraction, and large perforation	Normal leaflets but with severe tenting, poor leaflet coaptation
Color flow jet area	Large central jet (>50% of LA) or eccentric wall impinging jet of variable size	Large central jet (>50% of LA) or eccentric wall impinging jet of variable size
Flow convergence	Large throughout systole	Large throughout systole
Continuous wave Doppler jet	Holosystolic/Dense/Triangular	Holosystolic/Dense/Triangular
Semiquantitative		
Vena contracta width (mm)	≥7 (≥8 mm for biplane)	≥7 (≥8 mm for biplane)
Pulmonary vein flow	Systolic flow reversal	Systolic flow reversal
Mitral inflow	E-wave dominant (>1.2 m/s)	E-wave dominant (>1.2 m/s)
TVI mitral/TVI aortic	>1.4	>1.4
Quantitative		
EROA (2D PISA, mm^2)	≥40 mm^2	≥40 mm^2 (may be ≥30 mm^2 if elliptical regurgitant orifice area)
Regurgitant volume (mL/beat)	≥60 mL	≥60 mL (may be ≥45 mL if low flow conditions)
Regurgitant fraction (%)	≥50%	≥50%
Structural		
Left ventricle	Dilated (ESD ≥40 mm)	Dilated
Left atrium	Dilated (diameter ≥55 mm or volume ≥60 mL/m^2)	Dilated

(2D: two-dimensional; EROA: effective regurgitant orifice area; ESD: end-systolic diameter; LA: left atrium; PISA: proximal isovelocity surface area; PMR: primary mitral regurgitation; SMR: secondary mitral regurgitation; TVI: time-velocity integral)

risk stratification, which may aid in the selection of patients for early surgery.

Medical Care

Prehospital care: For the patient with acute MR, the electrocardiogram should be examined closely for evidence of acute MI. If present, treatment with supplemental oxygen, analgesics for anginal chest pain, and sublingual nitrates for acute MI are the components of prehospital care. In the absence of acute MI, endocarditis should be excluded with blood cultures.

Transthoracic echocardiography should be performed.

Emergency department care: Any patient with acute or chronic mitral valve regurgitation with hemodynamic compromise should be evaluated for acute MI. Consultations with specialists in cardiology and cardiothoracic surgery should be obtained early during patient stabilization.

Diuretic therapy is administered to individuals with pulmonary congestion, and an echocardiogram must be performed immediately. Patients with hemodynamic compromise should be expeditiously transferred to a cardiac critical care unit for central and pulmonary arterial pressure monitoring.

Medical Therapy

Afterload-reducing agents (such as nitrates and antihypertensive drugs) and diuretics are helpful for maintaining the forward cardiac output in persons with MR with symptoms and/or LV dysfunction. Beta-blockers and biventricular pacing are used for primary treatment of LV dysfunction in functional MR **(Flowchart 1)**.

Intra-aortic balloon counterpulsation should be considered in the patient with acute MR and hemodynamic compromise.

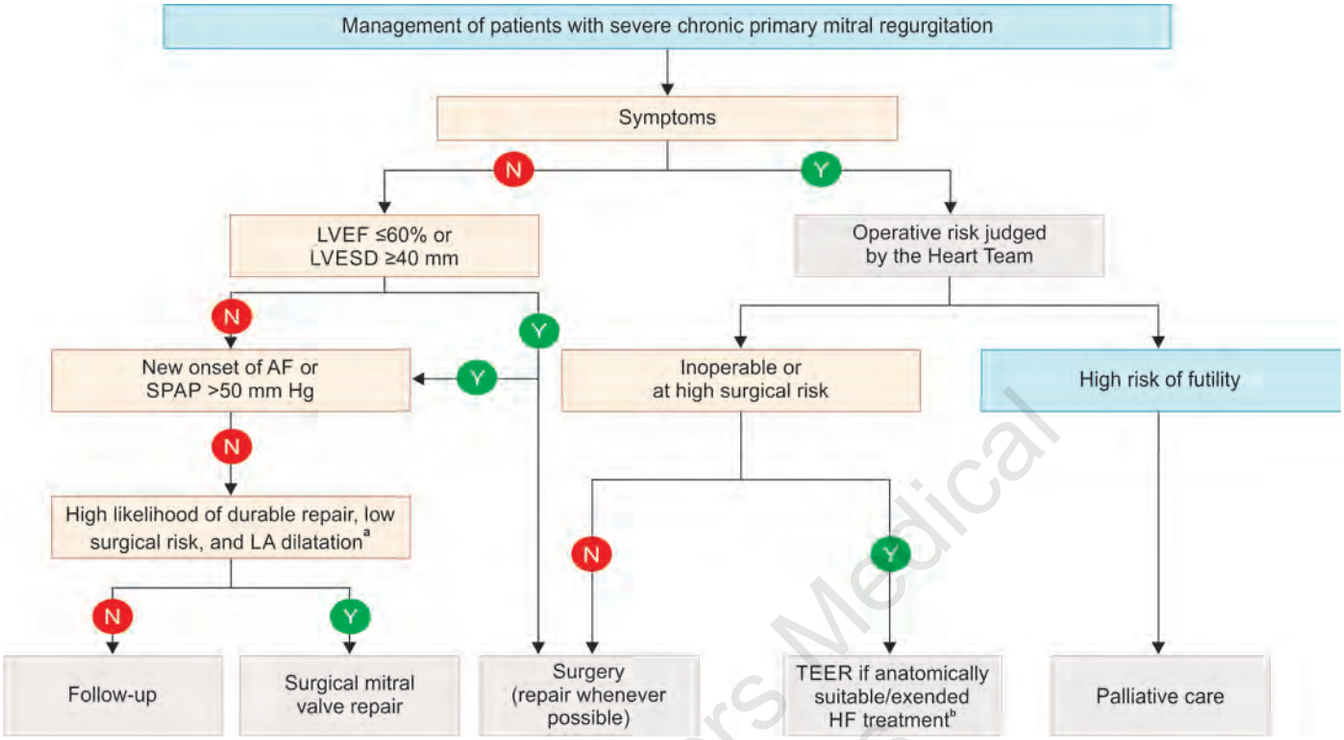
If atrial fibrillation is encountered, maintenance of a normal ventricular response with β-blockers, calcium-channel blockers, and/or digitalis therapy is considered.

Anticoagulation is considered for patients who develop atrial fibrillation or have had mitral valve replacement.

Procedures

The American College of Cardiology/the American Heart Association (ACC/AHA) class I indications for performing cardiac catheterization are as follows:

- Left ventriculography and hemodynamic measurements are indicated when noninvasive tests are inconclusive regarding severity of MR, LV function, or the need for surgery.
- Hemodynamic measurements are indicated when pulmonary artery pressure is out of proportion to the severity of MR as assessed by noninvasive testing.
- Left ventriculography and hemodynamic measurements are indicated when the clinical and noninvasive findings are conflicting regarding severity of MR.
- Coronary angiography is indicated before mitral valve repair or mitral valve replacement in patients at risk for coronary artery disease or when the MR is suspected to be ischemic in origin.



[a] LA dilatation: Volume index ≥60 mL/m^2 or diameter ≥55 mm at sinus rhythm.

[b] Extended heart failure treatment includes the following: CRT; ventricular assist devices; heart transplantation.[10]

FLOWCHART 1: Management of patients with severe chronic primary mitral regurgitation.

(AF: atrial fibrillation; HF: heart failure; LA: left atrium/left atrial; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MR: mitral regurgitation; SPAP: systolic pulmonary arterial pressure; TEER: transcatheter edge-to-edge repair)

Key considerations regarding treatment from the 2017 American College of Cardiology (ACC) expert consensus decision pathway on the management of MR include the following:

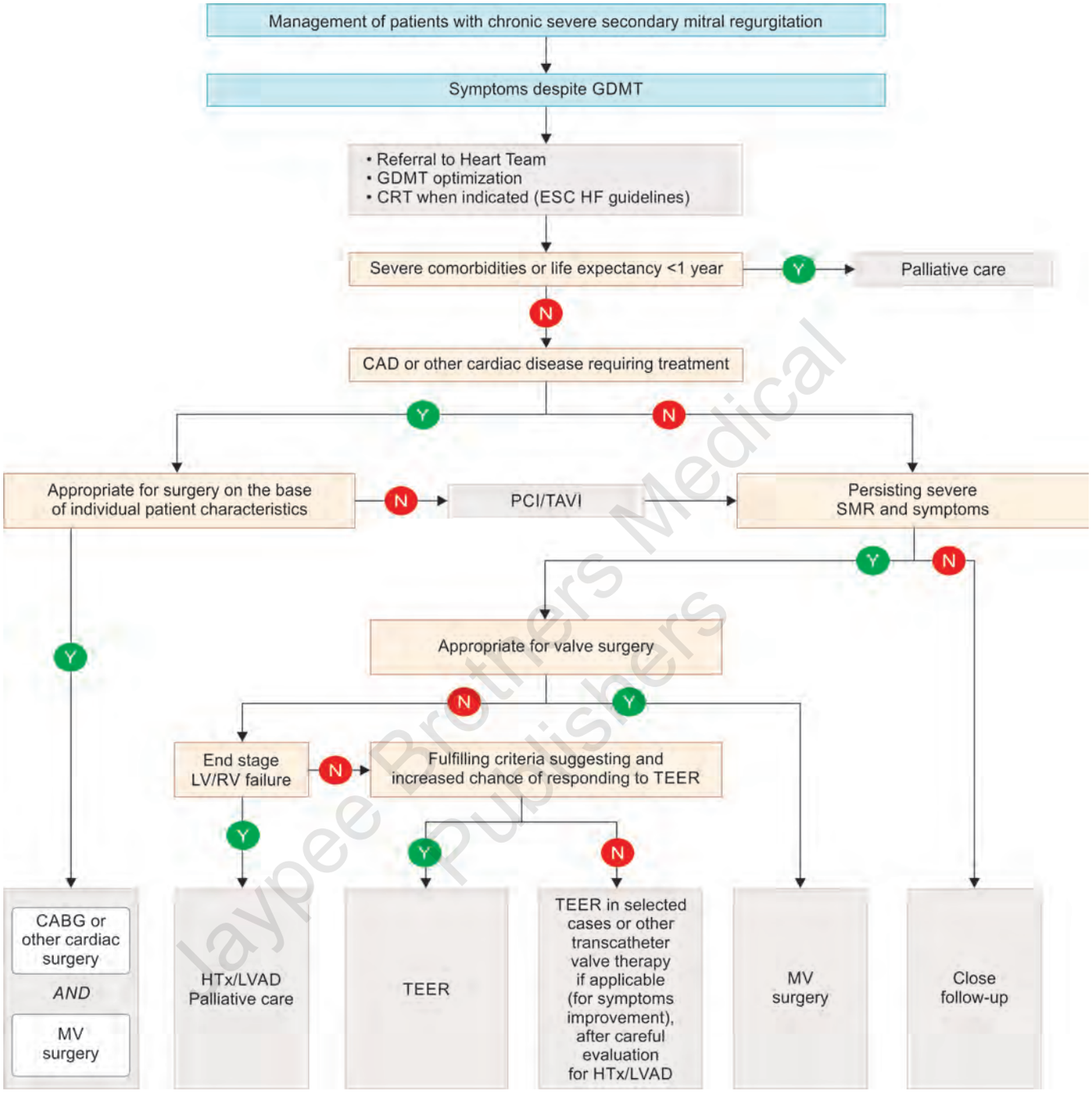
- Decisions regarding the optimal treatment of chronic MR are based on multiple variables, including MR type, MR severity, hemodynamic consequences, disease stage, patient comorbidities, and the experience of the heart valve team and its members.
- The principal intervention for primary MR is surgery; however, transcatheter mitral valve repair using an edge-to-edge clip plays a very limited role. Whenever feasible, mitral valve repair is strongly preferred over mitral valve replacement for primary MR.
- Surgical treatment for secondary MR should be considered only after appropriate medical and device therapies have been instituted **(Flowchart 2)**.
- Common techniques for mitral valve repair for primary MR include nonresection techniques using artificial chords or ipsilateral chordal transfer, triangular resection with annuloplasty ring, and sliding leaflet valvuloplasty with annuloplasty ring.
- Common techniques for mitral valve repair for secondary MR include restrictive remodeling with a rigid annuloplasty ring, and chordal-sparing mitral valve replacement.
- A primary determinant of successful repair is the surgeon's experience. For asymptomatic (stage C1) patients, patients with complex mitral pathoanatomy, and patients who desire a minimally invasive or robotic approach to mitral valve repair, consider referral to an experienced mitral surgeon at a comprehensive valve center.
- Long-term follow-up of patients after surgical or transcatheter mitral intervention is essential for the assessment of durability, functional outcomes, and survival.

Surgical Care

- Surgery is recommended for moderate to severe (grade >3) MR in symptomatic patients or those with LV dysfunction.
- The risks and benefits of surgery should be assessed based on the age and comorbidity of each individual patient with the decision to proceed or not to proceed being grounded in uniformly accepted guidelines.

Consider the following:

- Operative mortality is higher in patients older than 75 years.
- Coronary artery disease and other valvular diseases are prevalent in older patients who often require concomitant coronary artery bypass surgery, further increasing operative risk.
- Outcomes are worse in patients with severe MR and marked LV dysfunction.
- As outcomes are worse in patients with severe MR and pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg), surgical referral is advised prior to development of pulmonary hypertension.



FLOWCHART 2: Management of patients with chronic severe secondary mitral regurgitation.

(CABG: coronary artery bypass grafting; CAD: coronary artery disease; CRT: cardiac resynchronization therapy; ESC-HF: the European Society of Cardiology-heart failure; GDMT: guideline-directed medical therapy; HT: heart transplantation; LV: left ventricle; LVAD: left ventricular assist device; MV: mitral valve; PCI: percutaneous coronary intervention; RV: right ventricle/right ventricular; SMR: secondary mitral regurgitation; TAVI: transcatheter aortic valve implantation; TEER: transcatheter edge-to-edge repair)

- Right ventricular dysfunction is associated with worse survival of functional MR and LV dysfunction.

PERCUTANEOUS TREATMENT OF MITRAL REGURGITATION

In October 2013, the United States Food and Drug Administration (FDA) approved the MitraClip valve repair system for patients with symptomatic degenerative MR with a prohibitive risk for mitral-valve surgery. Approval was based on registry data and the Endovascular Valve Edge-to-Edge Repair Study (EVEREST II), in which percutaneous repair of the mitral valve was less effective in reducing MR but was associated with similar improvement in clinical outcomes and with superior safety.

Various percutaneous strategies for treatment of MR are also under investigation.

Double-orifice mitral valve repair using an implanted device that grasps and approximates the edges of the mitral valve leaflets at the origin of the regurgitant jet has been compared with mitral valve surgery for patients with 3+ to 4+ MR in a randomized trial.

Percutaneous double-orifice mitral valve repair appears safer than surgery, primarily due to reduced risk of transfusion. Although surgery results in more favorable reduction of MR, quality of life at 1 year is similar for both approaches. Surgical mitral valve repair remains the criterion standard intervention for severe MR; however, percutaneous double-orifice repair is a viable alternative for patients at high risk for surgery.

The 5-year results from the EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) that compared percutaneous mitral valve repair with the MitraClip device with conventional mitral valve surgery revealed increased rates of grade 3+ and 4+ MR (12.3%) and surgery (27.9%) with percutaneous repair than with conventional repair (1.8% and 8.9%, respectively). The majority of surgery following percutaneous repair (78%) occurred within the first 6 months. The 5-year mortality was similar between the two groups: 20.8% for percutaneous repair and 26.8% for conventional surgery.

Complications

Medical complications of MR may include the following:

- Pulmonary edema
- Congestive heart failure
- Irreversible LV systolic dysfunction
- Thromboembolism resulting from atrial fibrillation

Surgical complications may include the following:

- Operative risks include infection, bleeding, intraoperative MI, and stroke.
- In young patients, bioprosthetic valves (i.e., porcine valves) have a propensity for early degeneration due to calcification.
- Mechanical valve complications include prosthetic valve dysfunction and valve thrombosis with or without embolism, particularly in the patient who is not adequately anticoagulated.
- Hemolysis may occur in the patient with a ball and cage mechanical valve because of mechanical valve destruction of circulating red blood cells. Hemolysis in the patient with a tilting disk valve usually indicates the presence of a perivalvular leak.
- Thromboembolism in patients with mechanical valves who are on anticoagulation therapy occurs at a rate of 1–3% per year.
- In the absence of anticoagulation, thromboembolism occurs at a rate of approximately 1.5% per year with a porcine valve.
- Prosthetic valve infection may occur in bioprosthetic or mechanical valves.

CONCLUSION

- Mitral regurgitation is caused by either a primary abnormality of one or more components of the valve apparatus (leaflets, chordae tendineae, papillary muscles, and/or annulus) or is secondary (often referred to as functional MR) to LV dysfunction. In the developed world, the most common etiologies of MR are degenerative mitral valve disease (a primary cause) and coronary heart disease (a secondary cause).
- After corrective surgery or other intervention, increased afterload may contribute to a decline in ejection fraction in patients with decompensated MR, especially if chordal preservation techniques are not employed. In compensated ventricles, however, afterload does not increase postoperatively with valve repair or replacement with chordal preservation.
- The major change that occurs during the evolution from acute to chronic MR is an enlargement of the LV. In chronic compensated MR, LV contractility, loading conditions, and ejection fraction remain within the normal range with the large EDV being responsible for the enhanced TSV. An enlarged compliant LA contributes to the prevention of severe pulmonary venous hypertension. During this compensated phase of chronic MR, most patients remain asymptomatic.
- Since patients may or may not experience symptoms during the transition from compensated to decompensated chronic MR, monitoring for evidence of decompensation, including periodic measurement of LV size and systolic function by echocardiography, is required.
- Patients who exhibit one or more markers of a decompensated ventricle are at high risk of persistent postoperative LV enlargement, depressed postoperative ventricular function, and a poor or suboptimal clinical result.

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CHAPTER 11

Interpretation of Cardiac Symptoms

Chandan Kumar Das

ABSTRACT

Despite mega advancements in diagnostic tools of medical science the symptom analysis by a critical approach to all ailing patients still stands first. Interrogation and clinical examination should never be done in a hurry or in an open and crowded place. The patient's mothertongue is the most preferred language for communication. Cardiac symptoms vary from case to case and it depends on which part of the heart is affected. It is highly modified by comorbidities. Cardiac symptoms vary from congenital heart disease through rhythm disturbances, valvular disease, coronary artery disease (CAD), myocardial disease, pericardial disease, and sometimes noncardiac disease like thyrotoxicosis. The major symptoms associated with cardiac disease include chest discomfort (angina), dyspnea, fatigue, edema, palpitations, and syncope. Cough, hemoptysis, and cyanosis are additional examples. Claudication, limb pain, edema, and skin discoloration usually indicate a vascular disorder. Cardiac symptoms should be analyzed based on the "cooking of hypothesis".

INTRODUCTION

The great saying by Sir William Osler "Always Listen to The Patients, They Might Be Telling You the Diagnosis" needs to be incorporated into the mind of all practicing clinicians. Many of us still remember the clinical tips and tricks of our beloved doyen of medicine and cardiology, Dr BC Roy who used to teach us that symptoms say the diagnosis; you have to pick it carefully.

Despite the super advancement in the technical aspect of medical science, the symptom analysis by a critical approach to all ailing patients still stands as the gold standard. But, this critical approach is critical in the true sense. Few practical points need to be well understood before one goes for symptom analysis or its interpretations.[1]

- Who is the history giver?
- Medium (language) of communication
- Whether the patient has a bias?
- For ignorant patients, it may be necessary to go for leading questions.
- It should not be done in a hurried way or amidst the crowd.

A history giver in the case of an adult should be preferably the patient himself/herself, provided he/she is in sound mental status. It is often seen that the husband or wife exaggerates the symptoms of their spouse. While assessing a child the ideal history giver is the mother. In the case of a very old patient who has some element of dementia, it is always better to ask or verify the symptoms from a close family member or the attendant.

Patient's mothertongue is the most preferred language for communication. It is therefore always meritorious for a clinician to become a multilinguistic as far as possible. The interpreter plays a vital role in many such cases.

Nowadays many patients do come to clinics after surfing the internet. These patients rearrange their symptoms as per the description seen on the internet. Here, sometimes the clinician has to go through nightmares to diffuse the preoccupied bias and extract the exact symptoms.

Some ignorant patients may tell the unimportant issues repeatedly without going to the depth of the main sufferings. Here, the clinician has to tactfully induce some leading questions. For example, an acute coronary syndrome (ACS) (acute inferior wall myocardial infarction) patient may only say about his dizziness ignoring the initial chest discomfort, sweating, and dyspnea.

Interrogation and clinical examination should never be done in a hurry or in open and crowded places. The patient does not feel easy to communicate in such a way of approach. The clinician has to make all efforts to get the patient's confidence. Of course, it is needless to mention here that one should not

forget to keep one female attendant before attending a female patient even during history taking.

In case of emergency, it is not possible to go for detailed history taking. A few important points need to be hinted at here. In such cases the patient should get immediate life-saving care like keeping the patient in a comfortable posture, starting oxygen, and intravenous access. If the patient is alert and capable of communicating, one should be brief to ask about the chief discomfort for which the patient has sought medical attention, any drug allergy and if possible what drugs the patient is on.

Cardiac symptoms vary from case to case and it depends on the part of the heart affected. It is highly modified by comorbidities. Cardiac symptoms vary from congenital heart disease through rhythm disturbances, valvular disease, coronary artery disease (CAD), myocardial disease, pericardial disease and sometimes noncardiac disease like thyrotoxicosis.

HISTORY TAKING

The ailments of the heart can be divided into the following categories for better understanding: (1) Congenital heart disease, (2) Valvular heart disease, (3) Coronary heart disease, (4) Myocardial heart disease, (5) Pericardial heart disease, and (6) Miscellaneous diseases affecting the heart.

The history of illness of a patient is a sealed treasury for the physicians. One has to open it systematically, carefully, and methodically to derive its full benefit to arrive at a close diagnosis.[2] It has to be ascertained that in a cardiovascular evaluation you should be able to draw a maximum of three close diagnoses after completion of history taking. After you complete the physical examination, you should be able to come down to two close diagnoses. And the relevant cardiac investigation(s) should pick up one of these two diagnoses. So, the questions you are going to ask the patient with the available time should be relevant and specific.[3]

Before you start the history taking it is mandatory to know the symptomatology of the cardiovascular system. Because eyes cannot see what the mind does not know. The major symptoms associated with cardiac disease include angina (chest discomfort), dyspnea, fatigue, edema, palpitations, and syncope. Cough, hemoptysis, and cyanosis are additional examples which are uncommon but clinically significant. Claudication, limb pain, edema, and skin discoloration usually indicate a vascular disorder. Many cardiovascular diseases may present with noncardiovascular symptoms like weakness of one side or a part of the body (stroke due to cerebral embolism), jaundice (chronic heart failure leading to hepatic congestion), and oliguria (heart failure) and cough with hemoptysis [mitral stenosis (MS)]. If the patient complains of shortness of breath, one should be able to understand what might have caused shortness of breath or dyspnea in this patient. This is called "cooking of hypothesis". For example, here the patient with a history of shortness of breath might have had heart disease, a lung disease, upper or lower respiratory tract obstruction disease or anemia or a patient with morbid obesity. As a discipline of history, one has to start asking some relevant questions or leading questions. This is because the patient does not know how to subdivide or break up his or her symptoms. You can ask the patient whether this shortness of breath comes at rest or it comes during physical exertion only. Has he/she been told by a doctor as an asthmatic in the past? If it comes with exertion, then to what extent of exertion? Is it on heavy exertions like climbing stairs beyond the third floor or simply walking a few steps even inside the room? After you decide the exact type of shortness of breath, you should ask the duration of this illness. Whether it is progressive in nature, i.e., it was coming after climbing up three stairs 6 months back and now for the last 15 days, it comes even after one stair. This tells you that the pathology of your hypothesized disease is progressive. Here, it could be a valve lesion (MS) or an atherosclerotic CAD with progressive myocardial ischemia manifesting as angina equivalent or even a failing heart. Similarly, when a patient complains of chest discomfort or angina, its duration, mode of appearance, and relief are to be asked. The approach to the patient with known or suspected cardiovascular disease begins with a directed history and targeted physical examination, the scope of which depends on the clinical context at the time of presentation.

The history of a patient needs to be evaluated in a stepped manner like history of present illness, history of past illness, family history, occupational history, sleep history and sometimes treatment history. It should be informative, relevant, and precise.

Considering the objective assessment of major symptoms of a patient with cardiac disease New York Heart Association (NYHA) has classified the functional capacity **(Table 1)**. Among many such group classifications, the NYHA classification is being used most frequently. The functional status of a cardiac patient speaks about the progressive behavior of the disease.

ANGINA

Angina is the most common symptom of myocardial ischemia that is come across in cardiology practice. It is described as heavy chest pressure or squeezing, a burning feeling or

TABLE 1: The New York Heart Association Classification.

Functional capacity	Objective assessment
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present, even at rest. If any physical activity is undertaken, discomfort is increased

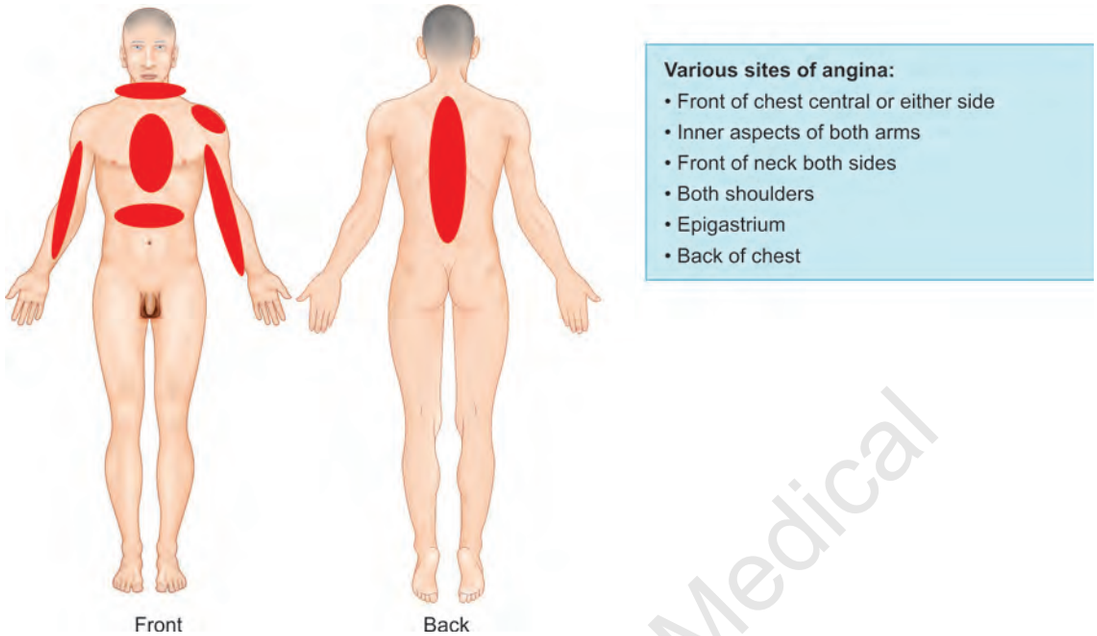

FIG. 1: Various sites of angina.

difficult breathing that typically builds over several minutes (2–10 minutes) and radiates toward the left shoulder and arm, epigastrium, back, and neck (see **Fig. 1**).

Mechanism of angina: The mechanisms of cardiac pain and the neural pathways involved are poorly understood. It is presumed that angina pectoris results from ischemic episodes that excite chemosensitive and mechanoreceptive receptors in the heart. Stimulation of these receptors results in the release of adenosine, bradykinin, and other substances that excite the sensory ends of the sympathetic and vagal afferent fibers. The afferent fibers traverse the nerves that connect to the upper five thoracic sympathetic ganglia and upper five distal thoracic roots of the spinal cord. Impulses are transmitted by the spinal cord to the thalamus and neocortex.[4]

Clinically, chest pain may be difficult to diagnose most of the time because of its diverse etiologies and individual variation in expressions. Hence, one brief chart of differential diagnosis at the fingertips is necessary to be kept ready. A short analysis of differential diagnosis of chest pain or angina has been shown in **Table 2**.

Atypical Angina

This is how to differentiate "atypical chest pain" from a typically described "angina".

The American College of Cardiology (ACC) and the American Heart Association (AHA) have laid guidelines that the following pain descriptions are uncharacteristic of myocardial ischemia:[5]

- Pleuritic pain (i.e., sharp or knife-like pain brought by respiratory movements or coughing)
- Primary or sole location of discomfort in the middle or lower abdominal region
- Pain that may be localized by the tip of one finger, particularly over the left chest.
- Pain reproduced with movements or palpation of the chest wall or arms.
- Constant pain persists for many hours.
- Very brief episodes of pain that exist for a few seconds or less.
- Pain that radiates to lower limbs.[5]

Angina Equivalent

Myocardial ischemia may not always manifest as angina or typical chest pain in some groups of patients such as diabetes mellitus, women, and the elderly. These symptoms are known as "angina equivalent", such as dyspnea, faintness, fatigue, and frequent belching.[6]

Sites of Angina

The "various sites of angina" have been schematically shown in **Figure 1** (see below).

ACUTE CORONARY SYNDROME

One of the most important clinical presentations of cardiovascular diseases is "ACS". Almost 15–25% of all acute chest pain cases are due to ACS. A diagnosis of ACS is missed in approximately 2% of patients. The receiving physician in "emergency department" has a very crucial role to assess such patients for accurate interpretation. Angina persisting for >15 minutes with a crescendo pattern with a tendency to intensify on mild exertion and which may or may not be associated with sweating, dyspnea, nausea, vomiting, palpitation or giddiness is defined as "ACS". This usually occurs due to rupture or erosion of an atheromatous plaque. It can also occur due to in situ thrombosis and coronary embolism. ACS may be divided into three categories according to accompanying bedside parameters to facilitate to intervene for life-saving

TABLE 2: A short analysis of differential diagnosis of chest pain or angina.

System	Syndrome	Clinical description	Key distinguishing features
Cardiac	Angina	Retrosternal heavy chest pressure or squeezing, a burning feeling or a difficult breathing and radiates toward left shoulder and arm, epigastrium, back, and neck	Precipitated by exercise, cold weather or emotional stress, duration of 2–10 minutes
	Rest or unstable angina	Same as angina but may be more severe	Typically, <20 minutes, lower tolerance for exertion, crescendo pattern
	Acute myocardial infarction	Same as angina but may be more severe	Sudden onset, usually lasting >30 minutes, often associated with sweating, shortness of breath, weakness, nausea, and vomiting
	Pericarditis	Sharp, pleuritic pain aggravated by change in position, highly variable duration	• Pericardial friction rub • History of fever may be present
Vascular	Aortic dissection	Excruciating, ripping pain of sudden onset in either front or back of chest	Usually happens in a setting of hypertension or connective tissue disorder like Marfan syndrome
	Variant (Prinzmetal) angina	Severe chest pain often occurs in cycles, typically at rest and overnight, usually relieved by vasodilator like nifedipine	It is not due to coronary artery atherosclerotic disease and believed to be due to coronary spasm
	Pulmonary embolism	Sudden onset of dyspnea and pain, mostly pleuritic type	Dyspnea, tachypnea, tachycardia, and right-sided heart failure
	Pulmonary hypertension	Substernal chest pressure, exacerbated by exertion	Pain associated with dyspnea and sign of pulmonary hypertension
Pulmonary	Pleuritis and pneumonia	Pleuritic pain over the involved area	Pain pleuritic and lateral to midline associated with dyspnea
	Tracheobronchitis	Burning discomfort in the midline	Midline location with cough
	Spontaneous pneumothorax	Sudden onset of unilateral pleuritic chest pain with dyspnea	Abrupt onset of dyspnea and pain
Gastrointestinal	Esophageal reflux	Burning substernal and epigastric discomfort, 10–60 minutes duration	Aggravated by large meal and postprandial recumbency, relieved by antacid
	Peptic ulcer	Prolong epigastric or substernal burning	Relieved by antacid or food
	Gallbladder disorder	Prolong epigastric or right upper quadrant pain	Usually after 30 minutes of a fatty diet
	Pancreatitis	Prolonged, intense epigastric, left subcostal, and back radiating pain	Risk factors like alcohol or hypertriglyceridemia
Musculoskeletal Infectious	Costochondritis	Sudden onset of intense fleeting pain	Chest wall tenderness present
	Cervical disk disease	Sudden onset of fleeting pain	Reproduced by neck movement
	Trauma or strain	Constant pain	Tenderness on palpation and movements
	Herpes zoster	Prolong burning pain in a dermatomal distribution	Vesicular rash in dermatomal distribution
Psychological	Panic disorder	Chest tightness or aching, often accompanied by dyspnea and lasting >30 minutes, unrelated to exertion or movement	May have other evidences of emotional disturbances

methods. The first and most easily available tool is ECG. It may show ST elevation in contiguous leads with or without ST depressions in the opposite wall leads [ST-segment elevation myocardial infarction (STEMI)], only ST depressions, T wave inversion or even a normal ECG [non-STEMI or unstable angina (UA)]. The next commonly used tool is a myocardial enzyme level in the blood sample. It could be troponin I, troponin T, or creatine-kinase myocardial band (CK-MB). This is positive in all STEMI cases. If this enzyme is positive in such a case without the presence of ST elevation, it could be called non-STEMI. When an ACS case has ST depression or T inversion but the cardiac enzyme is negative, it is UA. But unfortunately, cardiac enzymes are detectable in most cases after 4–5 hours of the index angina. This is a sign of myocardial necrosis. Since "Time is Muscle" one cannot afford to wait till the cardiac enzymes are elevated.[5]

To substantiate this diagnosis, bedside echocardiography should be done to look for a relevant regional wall motion abnormality (RWMA). Once a diagnosis of STEMI is made, he/she should be thrombolyzed after ruling out any absolute contraindications. For non-STEMI or UA, heparin should be started. If the facility allows, such a patient has to be taken up

TABLE 3: Thrombolysis in myocardial infarction (TIMI) risk score.

Score	Risk of death/MI (%)
0–1	5
2	8
3	13
4	20
5	26
6–7	41

for coronary angiogram (CAG) within 24 hours to delineate the coronary anatomy and if necessary, an interventional procedure, angioplasty may be done to treat an obstructed coronary artery.

There are some clinical risk analysis scoring systems to determine the risk of subsequent events in a case of ACS in practice namely the "thrombolysis in myocardial infarction (TIMI)" risk score **(Table 3)** and Global Registry of Acute Coronary Events (GRACE) risk scoring system **(Tables 4 and 5)**.

Thrombolysis in Myocardial Infarction Risk Score

The TIMI score is used to determine the likelihood of ischemic events or mortality in patients with UA or non-ST-segment elevation myocardial infarction (NSTEMI).[7]

Each of the following criteria constitutes one point for TIMI scoring (total 7 points).

- Age ≥65 years
- Three or more risk factors for CAD (family history of CAD, hypertension, hypercholesterolemia, diabetes mellitus, and tobacco use)
- Known CAD (Coronary artery stenosis >50%)
- Aspirin use in the past 7 days
- Severe angina (≥2 episodes in 24 hours)
- ST deviation ≥0.5 mm
- Elevated cardiac marker level

DYSPNEA (BREATHLESSNESS)

Dyspnea is also described as "breathlessness" or "shortness" of breath. It is defined as—an abnormally uncomfortable awareness of one's own breathing.

This symptom is common for many pathological processes or diseases. Hence, meticulous history evaluation is needed to pinpoint or come close to a system(s) at fault. This is the cardinal symptom of the cardiovascular and respiratory systems. Sometimes an unaccustomed exercise can cause dyspnea in a normal healthy person. Basically, the following diseases can cause dyspnea in a patient.

- *Pulmonary*: Chronic obstructive pulmonary disease (COPD), bronchial asthma, pneumonia, pleural effusion, pneumothorax, pulmonary edema, restrictive lung diseases, and pulmonary embolism.

TABLE 4: Grace (Global Registry of Acute Coronary Events) risk score.

Variables	Points
Age (years)	
<30	0
30–39	8
40–49	25
50–59	41
60–69	58
70–79	75
80–89	91
≥90	100
Heart rate (beats/min)	
<50	0
50–69	3
70–89	9
90–109	15
110–149	24
150–199	38
≥200	46
Systolic blood pressure (mm Hg)	
<80	58
80–99	53
100–119	43
120–139	34
140–159	24
160–199	10
≥200	0
Initial serum creatinine (mg/dL)	
0.0–0.39	1
0.4–0.79	4
0.8–1.19	7
1.2–1.59	10
1.6–1.99	13
0.2–3.99	21
≥4	28
Killip class	
I	0
II	20
III	39
IV	59
Cardiac arrest at admission	39
Elevated cardiac markers	14
ST-segment deviation	28

TABLE 5: Interpretation of GRACE (Global Registry of Acute Coronary Events) risk score for in-hospital mortality.[8]

Score	Probability of in-hospital mortality (%)—hospital
≤60	≤0.2
70	0.3
80	0.4
90	0.6
100	0.8
110	1.1
120	1.6
130	2.1
140	2.9
150	3.9
160	5.4
170	7.3
180	9.8
190	13
200	18
210	23
220	29
230	36
240	44
≥250	≥52

- *Cardiovascular*: Congenital heart disease (cyanotic as well as acyanotic), valve diseases, coronary heart diseases, cardiomyopathy, pulmonary artery hypertension, and systemic arterial hypertension.
- *Anemia*: Severe anemia of any cause.
- *Metabolic derangements*: Uremia, acidosis, etc.
- *Obesity*: Gradually becoming obese persons usually do not complain of dyspnea. Persons becoming obese in a short period commonly become symptomatic.

Special Types of Dyspnea

Orthopnea: Dyspnea on lying down supine is called "orthopnea"; it is mostly seen in left heart failure situations.

Paroxysmal nocturnal dyspnea (PND): A classical symptom of heart failure, reported by the patient as sudden awakening with severe breathlessness after sleeping for 2–3 hours at night. This dyspnea gets settled after the patient takes fresh air in an erect posture for 15 minutes. This is mostly seen in MS and other valve diseases, "ischemic heart disease", and "cardiomyopathy".

Platypnea: Upright posture causes dyspnea and is usually seen in COPD and "cyanotic congenital heart diseases".

Trepopnea: By lateral decubitus posture the affected part of the lung becomes nonfunctional and the patient becomes dyspneic. Left atrial (LA) myxoma may obstruct flow by acquiring a lateral decubitus posture.[9]

TABLE 6: Differential diagnosis of dyspnea.

Acute	Acute on chronic	Chronic
Asthma	Infective exacerbation of COPD	COPD
Myocardial infarction	Decompensated chronic heart failure	Cardiac failure
Pulmonary embolism (PE)	PE complicating in CCF	Anemia
Cardiogenic pulmonary edema	Pneumothorax complicating COPD or asthma	Pulmonary hypertension
Pneumonia	Atrial fibrillation/flutter complicating COPD or heart failure	Parenchymal lung disease

(CCF: congestive cardiac failure; COPD: chronic obstructive pulmonary disease)

Clinically, dyspnea should be assessed in the following factors:

- Mode of onset
- Duration
- Progress
- Severity
- Functional class
- Special character
- Relieving factor
- Associated symptoms

The "differential diagnosis" has been narrated in **Table 6**.

Clinical Differentiation between Cardiac and Pulmonary Dyspnea

In both cases, there is some element of previous ailments. Sometimes it becomes easy to differentiate and sometimes it is very difficult.

Dyspnea due to pulmonary causes tends to develop gradually. But, at times it may come suddenly due to exacerbation factors such as infection of the lower respiratory tract, pneumothorax or exacerbation of bronchial asthma due to sudden exposure to its allergens such as cold, dust, paint, etc. Patients with COPD may also get awakened due to cough and dyspnea. Here patient may bring out a large amount of sputum and get relief.

The cardiac patient presenting with dyspnea has a specific scale, such as while exerting at a particular speed, gradient, or quantity. Cessation of such activities gives relief. But during the sudden development of dyspnea in cardiac disease patients, there is usually a background such as a history of myocardial infarction, valvular heart disease, sudden acceleration of hypertension, cardiomyopathy with heart failure, etc. In such acute cases, the patient also may bring out pink frothy sputum due to pulmonary edema. When both (cardiac and pulmonary) are present in one patient, it becomes a nightmare for the clinician to differentiate.

Paroxysmal nocturnal dyspnea occurs due to the development of pulmonary interstitial edema and typically occurs 2–4 hours after the onset of sleep. The patient usually stands up or sits at the edge of the bed till the symptoms resolve which usually takes 10–15 minutes. A patient with PND is

classified as the NYHA class 3. A history of PND or orthopnea is only present in 20% of patients with heart failure and its absence does not rule out the diagnosis of heart failure. The most common causes of PND are MS, other valvular heart diseases, ischemic heart disease, and dilated cardiomyopathy. Noncardiac causes which mimic PND are nocturnal asthma, COPD, obstructive sleep apnea, anxiety, and hyperventilation.

DYSPNEA IN A CHILD

Does the child have blue discoloration (central cyanosis) of lips, tongue, and nail beds during dyspnea which comes usually on exertion and the child prefers to squat to get relief?

If yes, then the possibility of a "congenital cyanotic heart disease" cannot be ruled out.

If the answer is no, i.e., the dyspnea is not associated with central cyanosis, one can think of a volume overload condition like a left to right shunt at the atrial, ventricular or pulmonary artery level, or a stenotic valve lesion.

If the child has an associated history of swelling of the periorbital area and legs, right heart failure has to be considered. If the dyspnea in a child is associated with a history of palpitations (tachycardia), the increased activity of breathing (tachypnea) and recurrent chest infection a left heart failure diagnosis has to be thought of.

FATIGUE

It is very often complained by the patients that they have severe weakness. It sometimes constitutes the first clinical manifestation of heart failure. Due to severe exertional dyspnea, the patient may express it as fatigue since there is incapacitation to perform at a regular norm. Fatigue is the manifestation of low cardiac output. This results from inadequate oxygen delivery to tissues due to low cardiac output. Chronic heart failure induces cachexia which leads to severe weakness and fatigue. Sometimes patients with heart failure being on large doses of diuretics may develop dehydration, hyponatremia or hypokalemia leading to severe weakness. Here, the history of medication is to be obtained if the patient passes a huge quantity of urine or visits urinals frequently after taking a particular medicine.[10]

Patients with pulmonary hypertension, pulmonary thromboembolism, and decreased pulmonary blood flow conditions like in cyanotic congenital heart disease may also often complain of fatigue.[11]

SYNCOPE

It is a transient episode of loss of consciousness (LOC) due to cerebral hypoperfusion. Its causes may be pathophysiologically different such as (1) neurally mediated, (2) orthostatic hypotension, (3) cardiac causes, (4) cerebrovascular, and (5) psychogenic.

Interrogation of a patient with syncope:

- Was the LOC complete (in incomplete or presyncope patient may lose postural tone and tend to fall due to blackout, but manages to protect from a fall on the ground)?
- Was LOC with rapid onset (occurs in cardiac arrhythmia) and short duration?
- Was recovery spontaneous, complete, and without any sequelae?
- Was postural tone lost? (In epilepsy usually tone is increased)

If the answers to the above questions are positive, the episode was most likely to be a cardiac syncope.[12] It is essential to know the common conditions that can cause syncope. It is also equally important to be aware of several of the less common but potentially lethal causes of syncope, such as the arrhythmogenic right ventricular cardiomyopathy, long-QT syndrome, short-QT syndrome, Brugada syndrome, idiopathic ventricular fibrillation, catecholaminergic polymorphic ventricular tachycardia (VT), hypertrophic cardiomyopathy (HCM), and massive pulmonary embolism.[13-15]

History Suggestive of Cardiac Syncope

History of Syncopal Episode

- Occurs during exertion.
- Occurs when supine suddenly.
- Associated with palpitation
- Associated with chest pain

Past Medical History

- Known structural heart disease
- Previous myocardial infarction
- History suggestive of heart failure
- History of valve disease

Family History

- Family history of sudden death
- Clinical differentiation between "seizure" and "syncope" has been illustrated in **Table 7**.

Common causes of cardiac syncope and presyncope:

- *Reduced flow*: HCM, aortic stenosis (AS), MS, pulmonary stenosis (PS), LA myxoma, and cardiac tamponade.
- *Vascular disease*: Pulmonary embolism, pulmonary hypertension, acute myocardial infarction (AMI), air embolism, and subclavian steal syndrome.

TABLE 7: Differentiation between seizures and syncope.

	Seizure	Syncope
Warning	>50% have some aura	Lightheaded, blackout, or blurring may be there
Onset	Sudden, any position	Usually occurs in sitting or standing, avoidable by changing the posture sometime
Features	Eyes open, rigidity, falls backward, convulsions present	Eyes closed and falls forward
Recovery	Confused, headache, sleepy, and focal deficit	Pale, washed out, sweating, and cold
Other features	Tongue bite and loss of sphincter control	Rarely loss of bladder control

- *Tachyarrhythmias*: Supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, atrial fibrillation with a rapid ventricular response, Wolff–Parkinson–White (WPW) syndrome, Brugada syndrome, and prolong QT syndrome (congenital, acquired, or drug-induced)
- *Bradyarrhythmias*: Atrioventricular block (complete and second degree, sick sinus syndrome, pacemaker malfunction, and severe hyperkalemia).
- *Drugs*: Sometimes drug-induced orthostatic hypotension may mimic syncope. Drugs like diuretics, α-adrenergic blocking agents (terazosin, prazosin, adrenergic ganglion blocking drugs), and antidepressants can cause syncope like features.[16]

PALPITATION

It is defined as an abnormal, uncomfortable awareness of one's own heart beating. The history of a palpitation should be carefully evaluated about the approximate rate, duration of symptoms, regularity of the rhythm and suddenness of the onset and offset. Also, it is noteworthy to evaluate the triggering factors such as exercise, alcohol, caffeine, drug (like β-agonists), etc. It may be useful to ask the patient to describe it by tapping his/her fingers on the table to describe their heartbeat during palpitations. Many times, patients misrepresent palpitation as shortness of breath to a house physician. One has to be very careful about it. Because, if the attending clinician is not careful and he/she treats this particular patient of palpitation as a case of "shortness of breath" and gives him/her an injection of bronchodilator the patient's condition will certainly aggravate and even it may lead to a critical situation. So leading question is always better in such cases to ask about the rapidity of the patient's heart rate, and whether it is beating very fast to cause him/her discomfort.

Palpitation may be reported due to:

- *Sinus tachycardia*: The gradual onset of rapid heart rate, usually associated with panic attacks, anxiety, β-agonist medications in asthmatic patients and thyrotoxicosis.
- *Premature or ectopic beats*: Patients may describe it as "missed beats" or "forceful beats". This, in fact, relates to the pause that follows the ectopic beat which does prolong diastolic filling and then a forceful contraction occurs giving a thrust to the chest. Benign ectopic is considered when (a) no family history of sudden death, (b) no other cardiovascular symptoms, (c) their occurrence more during rest and disappearance during exercise, and (d) a normal clinical cardiovascular examination and a normal ECG. A malignant ectopic is to be considered if multifocal ventricular ectopic occurs >20,000 in 24 hours (as evaluated in 24 hours Holter monitoring).
- *Atrial fibrillation (AF)*: This is the most common arrhythmia. It can present silently with intermittent palpitation or at times severe persistent palpitation depending on its response by the ventricle. This arrhythmia has to be picked up by tactful evaluation of history, like whether the patient can demonstrate it by tapping fingers irregularly.
- *Paroxysmal supraventricular tachycardia (PSVT)*: This arrhythmia has a sudden onset without any premonitory symptoms. Usually, it occurs in an apparently healthy person mostly in a structurally normal heart. It can persist for from minutes to hours. At times it resolves automatically or on taking rest or even sometimes warrants hospitalization for intervention. After this episode patient feels fatigued, dehydrated or even may pass more urine. This occurs due to the release of atrial natriuretic peptide consequent to atrial wall stretch. Sometimes congenital heart diseases like atrial septal defect (ASD) may make their first presentation in early or late adulthood.
- *Ventricular tachycardia*: This is the most fatal arrhythmia. It can cause palpitation with severe giddiness or syncope due to reduced cardiac output. This is usually preceded by chest discomfort since it is one of the most common complications of AMI. This can also be a presentation of hypertrophic obstructive cardiomyopathy (HOCM). This can also be observed in certain familial rhythm disorders like Brugada syndrome, arrhythmogenic right ventricular dysplasia (ARVD) or right ventricular outlet tract-ventricular tachycardia (RVOT-VT). Such patients need immediate evaluation to find out the cause and plan for treatment.

Patients with a regurgitant valve lesion often present with palpitation which is usually due to high volume causing forceful beats.

Sometimes patients with mitral valve prolapse (usually young females) may present with palpitation, anxiety, and atypical symptoms.

A careful drug and dietary history should also be sought; some nasal decongestants can provoke tachycardia episodes, whereas β-adrenergic blocking eye drops for the treatment of glaucoma can drain into tear ducts, be absorbed systemically, and precipitate syncope caused by bradycardia. The commonly used bronchodilators cause moderate palpitation along with tremors in asthmatic and COPD patients. Excessive consumption of beverages like coffee and tea can produce palpitation.

A considerable percentage of patients with palpitation are detected to have panic disorder. It is clinically difficult to rule out these groups of patients from a genuine cardiogenic cause.[17,18]

PEDAL EDEMA

Symmetric leg edema in older patients is commonly come across. The presence of leg edema does not always suggest cardiac symptoms (heart failure). The most probable cause of bilateral edema in older patients is chronic venous insufficiency. It is neither sensitive nor specific for the diagnosis of heart failure and has a low predictive value as an isolated variable.[19,20] However, when a patient with a background of risk factors such as diabetes, hypertension, CAD, rheumatic valvular heart disease or cardiomyopathy reports with history of leg edema it is indicative of heart failure. Apart from these, if a patient without a known history of the above risk factors presents with progressive leg edema with concomitant progressive dyspnea on exertion a preliminary diagnosis of "heart failure" cannot be ruled out.

Other common causes of peripheral or leg edema are cirrhosis of the liver, hypoproteinemia, hypothyroidism, renal disorder, anemia, hepatic vein congestion (Budd–Chiari syndrome), deep venous thrombosis, and drugs like calcium-channel blockers (dihydropyridine).

COUGH AND HEMOPTYSIS

Though cough is a respiratory symptom it is often observed in heart failure. Clinically this cough is missed and it presents to a cardiac clinic as a refractory cough after being treated with lots of antibiotics and cough syrups. At times this cough may be associated with pinkish frothy sputum in case of "mitral stenosis" or maybe positional while lying supine which is accompanied by shortness of breath or wheezing in case of chronic decompensated heart failure. Sometimes angiotensin-converting enzyme (ACE) inhibitors-induced nocturnal cough is confused with chronic allergic cough.

Cough with frank hemoptysis can occur in 5–7% of pulmonary infarction in 10–20% of submassive pulmonary embolism.[21,22]

OTHER UNCOMMON BUT SIGNIFICANT CARDIAC SYMPTOMS

Sudden onset of limb pain: This usually occurs in lower limbs in a case of "atrial fibrillation" due to thromboembolism in valvular heart disease. Patients present with acute onset of severe pain with cold and calm extremity which is pulseless. Sometimes this presentation brings the patient first time to the hospital.

Sudden onset of weakness in one-sided limbs presenting as cerebrovascular accidents (CVAs) in a case of rheumatic valvular heart disease (mitral stenosis) with "atrial fibrillation" is also not uncommon in India. Such presentations are also seen in "ischemic heart disease".

Sudden onset of blindness by "retinal vein occlusion" is caused by atrial fibrillation and myocardial infarction in up to 16% of incidences.[23]

After describing all the symptoms of cardiac origin, it is necessary to pinpoint the symptoms of heart failure in short **(Table 8)**.

TABLE 8: Symptoms of heart failure.[24,25]

Major symptoms	Minor symptoms
Dyspnea	Weight loss
Orthopnea	Cough
Paroxysmal nocturnal dyspnea	Nocturia
Ankle edema	Palpitations
Pulmonary edema	Peripheral cyanosis
Fatigue	Depression
Exercise intolerance	
Cachexia	

CONCLUSION

It is very important to properly interpret patients' cardiac symptoms, so as to form a clinical diagnosis based on history taking, which when coupled with clinical examination, will lead to the correct diagnosis. This will further help to streamline the diagnostic tests required to arrive at a definitive diagnosis and avoid unnecessary diagnostic testing.

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SECTION 2

GENERAL CARDIOLOGY

CHAPTER 12: **Clinical Approach to Resistant Hypertension**
PS Banerjee, Tanmay Mukhopadhyay, Gourav Bhattacharya

CHAPTER 13: **Recent Landmark Trials in Cardiology**
Vineet Bhatia, VK Bahl

CHAPTER 14: **Rheumatic Fever and Rheumatic Heart Disease: Recent Trends in India**
IB Vijayalakshmi

CHAPTER 15: **Stuck Prosthetic Valves: Diagnosis and Management Challenges**
Latchumanadhas Kalidoss

CHAPTER 16: **Atypical Infective Endocarditis: Challenges of Appropriate Antibiotic Strategies**
Vasant Nagvekar, Shalmali Inamdar

CHAPTER 17: **Clinical Assessment of the Severity of Valvular Heart Disease and Pitfalls**
Mandava Satya Sahitya, Rajesh Vijayvergiya

CHAPTER 18: **Sleep Apnea and Heart Disease: Management Strategies**
Amal Kumar Khan, Amartya Khan, Indrani Mandal

CHAPTER 19: **Left Ventricular Noncompaction**
Satyavir Yadav, Rakesh Yadav

CHAPTER 20: **Diagnosis and Management of Mid-cavitary Hypertrophic Obstructive Cardiomyopathy**
Vaibhav Bandil, Suman Bhandari

CHAPTER 21: **Environment and Cardiovascular Health**
Vivek Gupta, Chinmay Gupta, Chaitanya Gupta

CHAPTER 22: **Proteomics and Metabolomics**
Gopala Krishna Koduru, Venkata RS Subrahmanya Sarma Palaparthi

CHAPTER 23: **Epidemiology of Aortic Valve Disease in India**
Manik Chopra, Vyom Mori, Maqbool Sohil, Sumit Dheer

CHAPTER 24: **Dual Pathway Inhibition to Prevent Atherothrombotic Vascular Events: Current Status**
Vibhav Sharma, Nitish Naik

CHAPTER 25: **Renal Denervation Therapy, Is it the Way Forward?**
Sameer Gupta, Purshotam Lal, Prashant T Upasani

CHAPTER 26: **Diagnosis and Management of Acute Pulmonary Embolism**
Prashant T Upasani, Sameer Gupta, Purshotam Lal

CHAPTER 27: **Management of Primary Pulmonary Hypertension**
Dipankar Mukherjee, Subir Sen, Saikat Prasad Dutta

CHAPTER 28: **Anticoagulation, Dual Antiplatelet Therapy, and Perioperative Management**
Rathindra Nath Karmakar, Auriom Kar, Gaurav Agarwal, Sunandan Sikdar

CHAPTER 29: **Emerging Role of Impedance Cardiography: A New Tool**
Bhabani Prasad Chattopadhyay, Sudipta Ghosh, Nasim Mandal, Kalyan Saha

CHAPTER 30: **Women and Valvular Heart Disease**
Sujatha Vipperla

CHAPTER 31: **Women and Cardiomyopathy**
Meenakshi Subbiah

CHAPTER 32: **Meditation and Cardiac Health**
Ramajayram Govindaraj, Mohit D Gupta, Girish MP

CHAPTER 33: **Post-coronavirus Disease 2019 Long-term Cardiovascular Manifestations**
SN Routray, Shishu Shankar Mishra, Dipak Ranjan Das

CHAPTER 34: **Approach to Angiography in Cyanotic Congenital Heart Disease**
Jayranganath Mahimarangaiah, Varun Marimuthu

CHAPTER 35: **Antiplatelets in High Bleeding Risk Patients**
Dharmendra Jain, Umesh Kumar Pandey, Suyash Tripathi, Bhupendra Verma, Soumik Ghosh, Rajpal Prajapati, Abhijeet

CHAPTER 12

Clinical Approach to Resistant Hypertension

PS Banerjee, Tanmay Mukhopadhyay, Gourav Bhattacharya

ABSTRACT

Resistant hypertension (RH) is defined as blood pressure (BP) above-goal in a patient despite the simultaneous use of three classes of antihypertensive agents, including a long-acting calcium channel blocker, a renin–angiotensin system blocker (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), and a diuretic administered at maximum or maximally tolerated daily doses. RH also refers to patients whose BP reaches goal on ≥4 antihypertensive medications. The diagnosis of RH needs confirmation of drug adherence and exclusion of pseudoresistance such as the "white-coat effect," incorrect BP measurement, and treatment inertia. The importance of RH is due to the associated risk of adverse outcomes compared with non-RH. Exclusion of pseudoresistance, implementation of lifestyle interventions, and discontinuation of interfering substances are initial steps in approaching RH followed by screening for secondary hypertension, and assessment of hypertension-mediated organ damage (HMOD). Management of RH includes the use of long-acting thiazide-like diuretics (chlorthalidone or indapamide), addition of a mineralocorticoid receptor antagonist (spironolactone or eplerenone), and, if BP remains elevated, sequential addition of antihypertensive agents with complementary mechanisms of action to lower BP. If BP still remains uncontrolled, referral to a hypertension specialist is advocated.

INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading cause of global mortality, with an estimated 17.9 million attributable deaths, accounting for 32% of global deaths.[1] In accordance with the World Health Organization, India accounts for one fifth of these deaths worldwide, especially in younger population.[1] Indians experience CVD-related deaths almost a decade earlier than developed countries.[2] Hypertension (HTN) is the biggest contributor to these avoidable deaths. An estimated 1.28 billion adults aged 30–79 years worldwide have HTN, highest (two-thirds) being in low- and middle-income countries.[3] In India, 57% of stroke deaths and 24% of mortality in coronary artery disease (CAD) are directly related to HTN.[4] Recent national studies estimate the prevalence of HTN in India to be 10% in the rural settings and 25% in the urban areas. But surprisingly, only 25.6% have their blood pressure (BP) under control.[4,5]

The American College of Cardiology (ACC)/American Heart Association (AHA) has proposed new recommendations for the detection, evaluation, and management of HTN in their recently published 2017 clinical practice guideline. It also includes recommendations on resistant hypertension (RH). Among its recommendations, the 2017 guideline reduces both the BP threshold for initiating antihypertensive therapy and ≥130/80 mm Hg for adults with existing CVD or 10-year atherosclerotic CVD risk ≥10% and the BP goal of treatment to <130/80 mm Hg for most individuals. These recommendations affect the BP threshold for diagnosis of RH and thus will increase its prevalence in the hypertensive population.[6]

DEFINITION

Uncontrolled Hypertension

Uncontrolled HTN is defined as BP above goal.

Resistant Hypertension

Resistant HTN is defined as uncontrolled HTN in a patient despite the concurrent use of three antihypertensive drug classes, commonly including a long-acting calcium channel blocker (CCB), a blocker of the renin–angiotensin system [angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB)], and a diuretic. The drugs

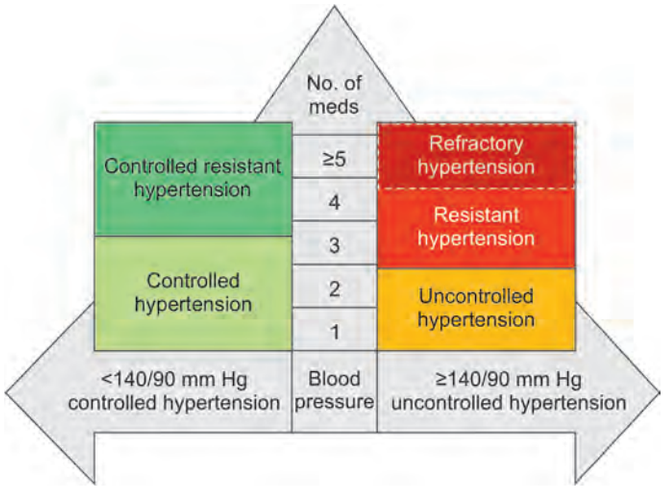


FIG. 1: Uncontrolled hypertension, resistant hypertension and refractory hypertension.

must be used at maximum or maximally tolerated doses daily according to the guidelines.

Resistant HTN also refers to patients whose BP reaches the goal on ≥4 antihypertensive medications.

The term RH thus includes hypertensive patients with both controlled and uncontrolled BP, on the basis of the number of antihypertensives used.

Refractory Hypertension

Uncontrolled HTN despite the use of ≥5 different classes of antihypertensive agents includes a long-acting thiazide or thiazide-like diuretic [i.e., chlorthalidone (CTDN)] and a mineralocorticoid receptor antagonist (MRA, i.e., spironolactone or eplerenone) **(Fig. 1)**.

The definition of RH has been modified in the 2017 ACC/AHA guideline in four important ways:[6] (1) BP should be measured accurately and the BP cutoff for the diagnosis and treatment should be according to current guidelines; (2) patients should be on ≥3 antihypertensive agents, commonly including a long-acting CCB, a blocker of the renin–angiotensin system (ACE inhibitors or ARB], and a diuretic at maximum or maximally tolerated daily doses; (3) patients with white-coat HTN should be excluded from the definition of RH; and (4) exclusion of medication nonadherence is a must for the diagnosis of RH.

WHY IS THERE A NEED FOR DEFINITION OF RESISTANT HYPERTENSION?

Resistant HTN is defined to find out patients who are having reversible causes of HTN and patients at high risk of target organ damage, who may benefit from advanced diagnostic and therapeutic measures.

EPIDEMIOLOGY OF RESISTANT HYPERTENSION

The term apparent treatment RH (aTRH) is used when ≥1 of the following data elements are missing: medication dose, adherence, or out-of-office BP; thus, pseudoresistance cannot be excluded.[7] On the basis of the previous cutoff of 140/90 mm Hg, the prevalence is approximately 13% in the adult population. Estimates suggest that the prevalence would be about 4% higher with the newly recommended control target of <130/80 mm Hg. Among treated adults with HTN, prevalent aTRH occurs in ≈12–15% of population-based[8,9] and 15–18% of clinic-based reports.[10,11] Prevalence of aTRH in adults with treated HTN as reported from selected population-, clinic-, and intervention-based studies is given in **Table 1**.

PROGNOSIS OF RESISTANT HYPERTENSION

In a retrospective study of >200,000 patients with incident HTN, those with RH were 47% more likely to suffer the combined outcomes of death, myocardial infarction, heart failure (HF), stroke, or chronic kidney disease (CKD) over a median follow-up of 3.8 years.[12] In another study of >400,000 patients, compared with patients without RH, patients with RH had a 32% increased risk of developing end-stage renal disease, a 24% increased risk of an ischemic heart event, a 46% increased risk of HF, a 14% increased risk of stroke, and a 6% increased risk of death.[13] Prospective studies with ambulatory blood pressure monitoring (ABPM) have revealed nearly twofold higher risk of CVD events in patients of true RH vis-à-vis treatment-responsive HTN.[14,15] In patients with CKD, RH is associated with a higher risk of myocardial infarction, stroke, peripheral arterial disease, HF, and all-cause mortality compared with patients without RH.[10] Similar rates of adverse events were seen in patients of ischemic heart disease (IHD). Conversely, RH is not associated with increased adverse clinical events in patients with HF with reduced ejection fraction and may lower the risk for HF-related rehospitalization.[16] In the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study, uncontrolled RH was associated with a twofold increased risk of coronary heart disease compared with controlled RH but no difference was seen in stroke or mortality.[17]

WHO IS AT RISK?

Age and Gender

Older age and male gender are at a higher risk of developing RH.

Race

People of African origin also tend to have more RH.[11]

Blood Pressure Level at Diagnosis

Degree of BP level at diagnosis and the peak BP level recorded at any time during the natural history correlate with a higher incidence of RH.[18]

Modifiable Risk Factors

Obesity, diabetes mellitus (DM), and CKD are the three main modifiable associations of RH. Thus, the basic triad of investigations in RH is formed by body mass index (BMI), glycated hemoglobin (HbA1c), and serum creatinine.[11,18]

TABLE 1: Prevalence of apparent treatment resistant hypertension in adults.

Population based	Time period	*n*	Uncontrolled with ≥3 BP medications, %	Controlled with ≥4 BP medications, %	aTRH, %
NHANES[13]	1988–1994	2,755	8.3	1.1	9.4
NHANES[13]	1999–2004	3,031	8.8	2.9	11.7
NHANES[14]	2003–2008	3,710	–	–	12.8
NHANES[13]	2005–2008	2,586	9.7	4.8	14.5
REGARDS[15]	2003–2007	14,731	9.1	5.0	14.1
REGARDS[16] (CKD)	2003–2007	3,134	–	–	28.1
Clinic based					
EURIKA[17] (diabetes mellitus)	2009–2010	5,220	13.0	3.1	16.1
Spanish ABPM[18]	2004–2009	68,045	12.2	2.6	14.8
CRIC (CKD)[19]	2003–2008	3,939	21.2	19.2	40.4
South Carolina[20]	2007–2010	468,877	9.5	8.4	17.9
Clinical trials					
ALLHAT[21]	1994–2002	14,684	11.5	1.2	12.7
ASCOT[22]	1998–2005	19,527	48.5	–	–
ACCOMPLISH[25]	2003–2006	10,704	39	–	–
INVEST[26]	1997–2003	17,190	25.1	12.6	37.8

(ABPM: ambulatory blood pressure monitoring; ACCOMPLISH: Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension; ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT: Anglo-Scandinavian Cardiac Outcomes Trial; aTRH: apparent treatment resistant hypertension; BP: blood pressure; CKD: chronic kidney disease; CRIC: Chronic Renal Insufficiency Cohort; EURIKA: European Study on Cardiovascular Risk Prevention and Management in Usual Daily Practice; INVEST: INternational VErapamil SR Trandolapril STudy; NHANES: National Health and Nutrition Examination Survey; REGARDS: Reasons for Geographic and Racial Differences in Stroke)

Obstructive Sleep Apnea

A total of 60–84% of individuals with RH have sleep apnea.[19] Obstructive sleep apnea (OSA) is often missed out in thin-built individuals or those without short neck. The patient should be asked about nighttime snoring and daytime somnolence. A complete sleep study is indicted in suspected cases.[18,19]

Hypertension-mediated Organ Damage

The presence of hypertension-mediated organ damage (HMOD) early in a hypertensive individual or HMOD out of proportion to the degree of HTN points toward RH.[19,20]

Lifestyle

Heavy intake of complex and refined carbohydrates including high fructose corn syrup and excess salt intake have been designated as a "driver" of RH. Excessive alcohol intake (>30–50 g/day) is a well-known risk factor for HTN.[21] Lesser physical activity and below-average physical fitness are separate risk factors for HTN. But there are very few studies that have suggested a correlation between physical inactivity and RH.

Physiological Aberration

The normal nocturnal decline in BP is also attenuated in a high proportion (43–65%) of individuals with RH.[13,22] Reverse dipping, in which nocturnal BP paradoxically rises, may be linked to subclinical organ damage and CVD events.

Metabolic

Resistant hypertension has also been linked to metabolic derangements, including hyperuricemia,[23] aldosterone excess,[12] and suppressed circulating renin levels (≈60% of those with RH have suppressed renin levels).[24]

Genetics

Disproportionately higher prevalence of RH among blacks[25] has been suggested to reflect a contribution by genetic factors. As much as 50–60% of BP variability can be attributed to additive genetic factors.[26] The majority of genetic studies of RH has been limited to candidate genes and has lacked adequate sample sizes to survive the multiple testing burdens across the many such candidate gene studies performed.

Medication-related Resistant Hypertension

Several classes of pharmacologic agents can increase BP and contribute to drug-induced RH as shown in **Table 2**.

Sleep Deprivation and Pseudopheochromocytoma

Once true pheochromocytoma is excluded, one should consider pseudopheochromocytoma, a syndrome characterized by the presence of paroxysmal HTN with three distinct features: sudden elevation of BP, similar abrupt onset of troublesome physical symptoms, and absence of described panic or anxiety at the start of such attacks.[27]

TABLE 2: Classes of pharmacologic agents that increase BP and contribute to drug-induced resistant hypertension.

Drug	Mechanism	Increase in BP
NSAIDs	Reduced vasodilation and Na excretion	2–5 mm Hg MAP
OCP (higher dose of estrogen or combination)	Increase in angiotensin biosynthesis	3–6 mm Hg SBP
HRT (lower dose of estrogen)	-do-	1.5 mm Hg SBP
Sympathomimetic amines	Activation of SNS	
Cyclosporine	Systemic and renal vasoconstriction and Na retention	
Antidepressants (MAO inhibitors, TCAs, SNRI, SSRI)	Increasing $t_{1/2}$ of NE at SNS terminals	
VEGF TK inhibitors	Reduction of NO and PGI2 bioavailability, increase in SVR and vascular stiffness	
EPO (erythropoietin)		

(BP: blood pressure; HRT: hormone replacement therapy; MAO: monoamine oxidase; MAP: mean arterial pressure; NE: norepinephrine; NO: nitric oxide; NSAID: nonsteroidal anti-inflammatory drug; OCP: oral contraceptive pill; PGI2: prostacyclin; SBP: systolic blood pressure; SNS: sympathetic nervous system; SNRI: serotonin–norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; SVR: systemic vascular resistance; TCA: tricyclic antidepressant; TK: tyrosine kinase; VEGF: vascular endothelial growth factor)

Poor sleep quality is often noticed in patients with pseudopheochromocytoma. It is not the result of just OSA but a host of sleep disorders, including restless leg syndrome and insomnia of various causes.[28] Poor sleep quality is defined as less than a minimum of 6 hours of uninterrupted sleep in patients without OSA. Paroxysmal bouts of very high BP relates to activation of both the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system due to reduced time in nonrapid eye movement (NREM) or slow-wave sleep affecting the nocturnal dip in BP.

There is a U-shaped association between sleep duration and HTN with the nadir being between 7 and 8 hours of uninterrupted sleep per night. Incident HTN is associated with a sleep duration of <5 hours in <60 years of age, whereas >9 hours per night in >60 years.[29,30]

Obstructive Sleep Apnea

Obstructive sleep apnea is extremely common in patients with RH, with prevalence rates as high as 70–90%, and when present, OSA is often severe.[31,32] Factors leading to the high incidence of OSA in patients with RH are increased fluid retention and accompanying upper airway edema, as revealed by studies positively correlating the presence and severity of OSA to aldosterone excess and high dietary sodium intake.[12,33] Treatment of patients with OSA and RH with continuous positive airway pressure (CPAP) induces significant but generally modest reductions in BP. Increasing CPAP adherence led to further reductions in BP. A well-conducted randomized controlled trial (RCT) recently demonstrated that CPAP plus usual care, compared with usual care alone, did not prevent CVD events in patients with moderate-to-severe OSA and established CVD.[34]

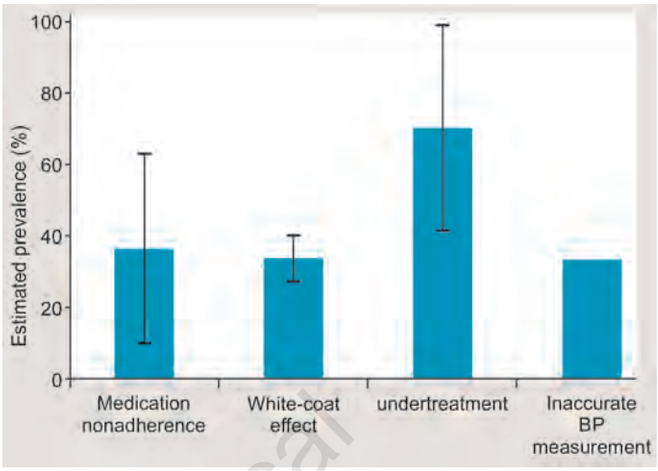


FIG. 2: Prevalence of each of the causes of pseudoresistant hypertension.

EVALUATION OF RESISTANT HYPERTENSION

Confirm Treatment Resistance

To confirm treatment resistance, clinic BP >130/80 and the patient taking three or more antihypertensive agents [long acting (LA) CCB, ACE inhibitors/ARB, diuretic (DU)] at maximal or maximally tolerated doses.

Exclude Pseudoresistance

One of the main hindrances to managing RH is accurate identification of pseudoresistance and correcting it first. In a study of 68,045 adults with RH by office BP measurement, 37.5% had pseudo-RH by ABPM. **Figure 2** shows the estimated prevalence of each of the causes of pseudoresistant HTN.

Challenge of Nonadherence

The term *adherence* is described as remaining affixed (to the medication regimen) and is distinct from *compliance*, which means conforming to an appeal, desire, or claim. Medication adherence is an important predictor of BP control. However, about one in four patients who are newly initiated on antihypertensive therapy fails to top up their first prescription.[35] During the initial year of treatment, the average patient has custody of antihypertensive agents only half of the time, and just 20% has sufficiently high adherence to achieve the benefits seen in clinical trials. Up to 40% patients continue to be nonadherent to BP medications.[35,36] Out of 2,325 patients who began using antihypertensive agents, only 39% used them continuously throughout the follow-up of 10 years. Also, 22% temporarily gave up and again resumed treatment, whereas

39% of patients stopped treatment permanently. Older patients and men were more persistent than younger patients and women respectively.[37]

Assessment of Nonadherence

There is no gold standard for measuring adherence.

Indirect methods:

- Patient self-report medication adherence assessment tools such as the Morisky Medication Adherence Scale and the Hill-Bone Compliance Scale
- Pharmacy databases for medication possession and refills provide a valid measure of adherence
- Measurement of pharmacodynamic parameters [e.g., heart rate (HR) for β-blockers, lack of rise of plasma renin activity (PRA) for renin–angiotensin inhibitors, *N*-acetyl-seryl-aspartyl-lysyl-proline measurements for ACE inhibitors]

Direct methods:

- Witnessed drug intake
- Medication event monitoring system
- Drug monitoring in body fluids

Factors Responsible for Nonadherence

Patient-level barriers:

- Multiple comorbid conditions
- Resource constraints
- Suboptimal health literacy
- Lack of involvement in the treatment decision-making process

Clinician-level barriers:

- Prescription of complex drug regimens
- Communication barriers
- Ineffective communication of information about adverse effects
- Provision of care by multiple providers
- Clinician inertia

Healthcare system-level barriers:

- Office visit time limitations
- Limited access to care
- Lack of team-based approaches and health information technology

Interventions to Improve Adherence

So the need of the hour is proper education and counseling regarding consequences of RH and importance of both lifestyle modifications and antihypertensive medication. A simple once-a-day single-pill combination (SPC) with minimal side effects as well as cost-effective is more likely to be taken by the patient regularly.

White-coat Effect

The white-coat effect is the observations of continual BP elevations within the workplace with controlled or considerably lower BP outside the workplace in a hypertensive patient on medication. It is attributed to an alerting reflex triggered by the healthcare provider or the clinic environment that activates the SNS. A clinically significant white-coat effect may be present in 28–39% of individuals with aTRH by office BP measurement.[14,38]

The white-coat effect can be easily identified by 24-hour ABPM which may not be readily available. So, the next best option is automated office BP. Home-based BP monitoring (with accurate instruction in the BP measuring technique) relates to the average daytime BPs and may be used to diagnose white-coat HTN.

Physician Inertia

It has been meticulously shown in studies that doctors/physicians often do not uptitrate the dose of the antihypertensive drug on patients' review despite suboptimal BP control. During 2007–2010, only 49.6% of patients with uncontrolled aTRH identified in a community-based practice network in the United States were prescribed an optimal antihypertensive regimen. Antihypertensive medications were administered at <50% of their maximally recommended dose in 42.1% of patients with uncontrolled aTRH. Patients more likely to be prescribed an optimal regimen were black, CKD, DM, or CAD.[11]

Analysis of large electronic health data from the United States reveals that only 4.7% of hypertensive patients eligible for a three-drug regimen were prescribed three drugs despite being clinically indicated and the doctor being aware of it. Overcoming clinician treatment inertia can be accomplished through an integrated health system model of care such as the Kaiser Permanente and Veterans Affairs health systems, where the approach to BP control is systematic and multidisciplinary.

Inaccurate BP Measurement

Imprecise measurement of BP can consequently give rise to treatment resistance. In a study of patients referred for RH, inaccurate BP measurement was estimated at 33%.[39] A proper BP measurement technique entails: (1) Preparing the individual by emptying a full urinary bladder and then sitting in a quiet room with back, arm, and feet supported and legs uncrossed, preferably 5 minutes prior to the first reading; (2) selecting a sphygmomanometer cuff with a bladder length no <80% and width no <40% of the arm circumference; (3) keeping the cuff directly on the skin of the upper arm at the heart level on the supported arm; and (4) taking at least two readings 1 minute apart.[1,3] BP measured by cuff may vary from intra-arterial pressure. Severe stiffness of arterial wall or calcification of intima media of the brachial artery may outturn in an imprecise detection of Korotkoff sounds. The unsuitable raised cuff pressure in patients with severe arterial disease is described as pseudohypertension.

Screen for Secondary Hypertension

Patients of RH more often suffer from secondary HTN but not all RH are secondary ones. One should suspect secondary causes if one of the following is present:

- Young age of onset <30 years
- Severe HTN
- Sudden accelerated HTN
- Unprovoked hypokalemia
- Labile HTN
- Asymmetric kidney in ultrasonography (USG)
- Nondipping pattern in 24 hours ABPM
- Renal Doppler suggesting renal artery stenosis

TABLE 3: Important causes of secondary hypertension which need further evaluation.

Disorder	Major symptoms	Clinical findings	Screening tests	Confirmatory tests
Primary aldosteronism	Generalized weakness, dizziness	Hypertension, hypokalemia, metabolic alkalosis, and advanced cardiovascular and renal disease	ARR >30 or ARR >20 if plasma aldosterone concentration is ≥16 ng/dL and PRA <0.6 ng/mL/h	• Saline suppression test • Oral salt-loading test • Captopril test • Fludrocortisone suppression test • Adrenal venous sampling
CKD	Polyuria/Anuria, anasarca, SOB	Pedal edema, crepitations	Urea, creatinine, urine R/M, USG	
Renal artery stenosis	Headache	Hypertension	Duplex imaging to identify increased peak systolic velocity in the renal arteries	CTA or MRA
Pheochromocytoma/Paraganglioma	Headache, palpitations, pallor, and piloerection ("cold sweat")	Paroxysmal HTN, sustained in 50%	Plasma-free or urinary fractionated metanephrines	• Clonidine-suppression testing • CT scan/MRI/MIBG
Cushing syndrome	Mood disorders, menstrual irregularities, muscle weakness	Weight gain, abdominal striae, hirsutism, dorsal and supraclavicular fat, fragile skin	Morning cortisol levels	
Hypothyroidism	Dry skin, cold intolerance, constipation, hoarseness, weight gain	Delayed ankle reflex, periorbital puffiness, coarse skin, cold skin, slow movement, goiter	• High TSH, low or normal • fT4	
Hyperthyroidism	Warm, moist skin; heat intolerance; nervousness; tremulousness; insomnia; weight loss; diarrhea; proximal muscle weakness	Lid lag, fine tremor of the outstretched hands, warm, moist skin	• Low TSH, high or normal • fT4 and T3	Radioactive iodine uptake and scan

(ARR: aldosterone-to-renin ratio; CKD: chronic kidney disease; CT: computed tomography; CTA: computed tomography angiography; fT4: free thyroxin; HTN: hypertension; MIBG: metaiodobenzylguanidine; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; PRA: plasma renin activity; SOB: shortness of breath; TSH: thyroid-stimulating hormone; urine R/M: urinary routine and microscopic examination; USG: ultrasonography)

- Abnormal aldosterone–renin ratio

The important causes of secondary HTN which need further evaluation are as follows **(Table 3)**:

- Primary aldosteronism
- Renal parenchymal disease
- Renal artery stenosis
- Pheochromocytoma/Paraganglioma
- Cushing syndrome
- Coarctation of the aorta
- Hypo/Hyperthyroidism

Assess for Hypertension-mediated Organ Damage

- *Eye*: Fundoscopy to look for retinal changes
- *Heart*: Left ventricular hypertrophy, CAD, hypertensive heart disease
- *Kidney*: Proteinuria, reduced estimated glomerular filtration rate (eGFR)
- *Peripheral arteries*: Ankle brachial index

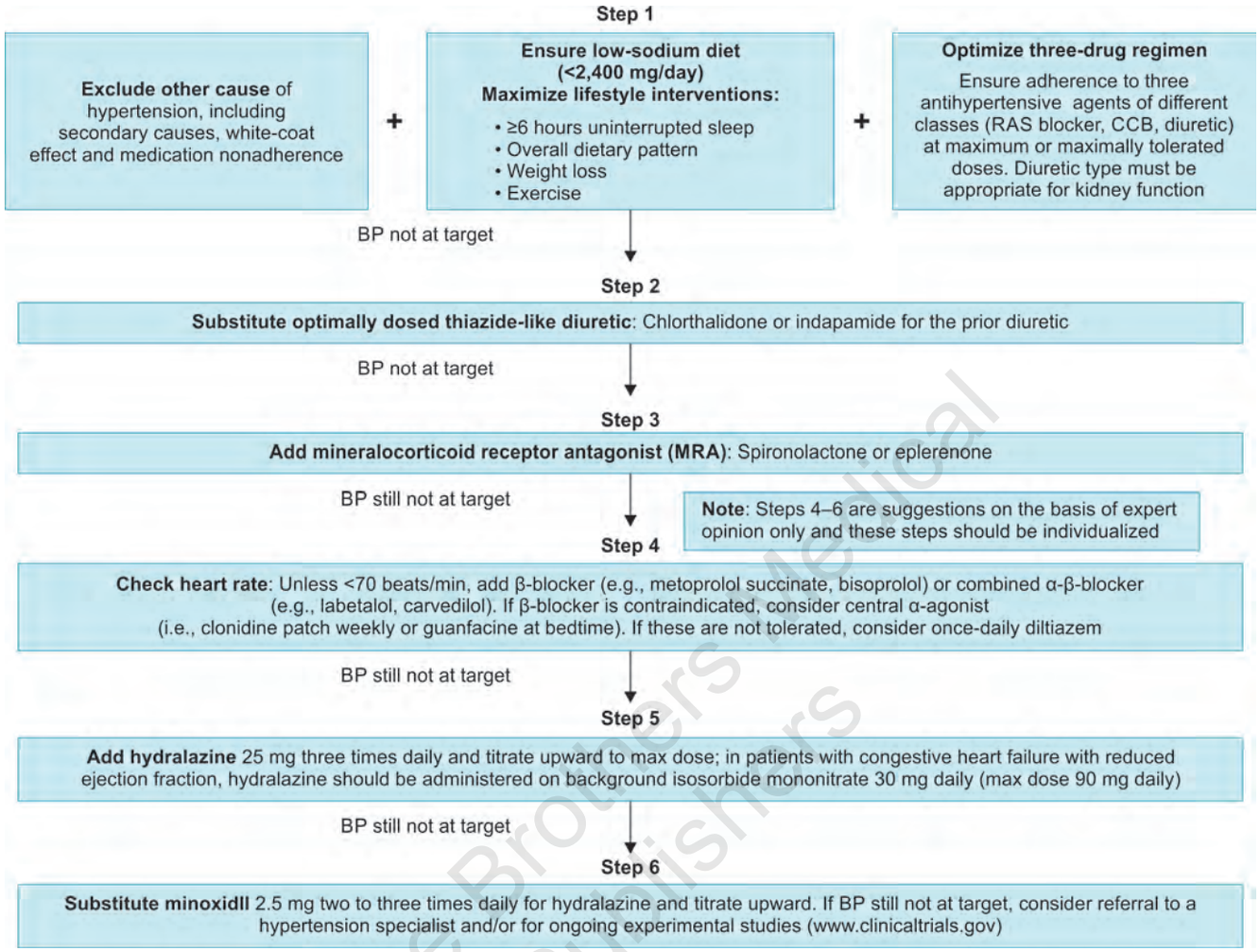
MANAGEMENT OF RESISTANT HYPERTENSION

An algorithm depicting the management of RH is show in **Flowchart 1**.

Lifestyle Interventions

Weight Loss

Weight-reducing diets are well established to lower BP among patients with HTN, by 4.5/3.2 mm Hg in the most recent meta-analysis.[40] Conversely, the effect of medicine-supported weight loss is mixed, with some agents showing prudent improvements (e.g., orlistat), whereas others (sibutramine) may even elevate BP.[41] A meta-analysis of 25 RCTs consisting of 4,874 participants showed a net weight reduction of –5.1 kg (95% confidence interval) by means of energy restriction, increased physical activity, or both reduced systolic blood pressure (SBP) by –4.44 mm Hg and diastolic blood pressure (DBP) by –3.57 mm Hg.[42] Guidelines consistently promulgate a healthy



FLOWCHART 1: Algorithm depicting the management of resistant hypertension.
(BP: blood pressure; CCB: calcium channel blocker; RAS: renin–angiotensin system)

lifestyle (including caloric restriction), aiming for a >5–10% body weight loss among overweight and obese adults to help lower BP.

Dietary Salt Restriction

It is a well-proven fact that BP is lowered by a reduced-sodium diet. Low-compared to high-salt diet decreased office SBP and DBP by 22.7 and 9.1 mm Hg, respectively. A recent meta-analysis showed that an estimated 1g (43.5 mmol) reduction in daily sodium intake produces a 2.1 and 1.2 mm Hg decrease in SBP among hypertensive and normotensive patients, respectively.[43] In patients with RH, recent small studies have proved the efficacy of dietary sodium restriction for reducing BP. A U-shaped relationship may exist between salt restriction and CVD risk, with the greatest risk reductions resulting from moderate restriction in sodium intake of 173–217 mmol/day (4–5 g/day) despite BP decreasing linearly with further salt restriction to <65 mmol/day (1.5 g/day).[43] The AHA recommends to lower daily sodium intake to <100 mmol/day (2.3 g/day) and to consider more rigorous reductions to <65 mmol/day (1.5 g/day) on an individual case basis.

DASH Diet and Other Dietary Factors

DASH (dietary approaches to stop hypertension) diet → 2,100 calorie diet: It is low in saturated fat, cholesterol, and total fat and rich in fruits, vegetables, and fat-free or low-fat milk and milk products. It consists of whole grains, nuts, poultry, and fish. It is reduced in lean red meat, sweets, added sugars, and sugar-containing beverages. It has higher contents of potassium, magnesium, calcium, and also protein and fiber. Besides, alcohol restriction to <10 g/day (women) and <20 g/day (men) can yield significant reductions in BP. Dietary intervention studies specific to patients with RH are missing.

Exercise

In the largest meta-analysis to date, BP was lowered by 8.3/5.2 mm Hg over several weeks by a variety of endurance (aerobic) exercise programs in patients with HTN.[44] Moreover, dynamic resistance exercise reduced BP by 1.8/3.2 mm Hg among patients with HTN. The 2017 ACC/AHA guideline recommends at least 150 min/week (in 3–5 sessions of 30–40 minutes) of moderate-to-intense aerobic activity, properly reinforced

with two to three sessions of endurance training each week. In sedentary individuals, low-intensity physical activity of 6 min/h over an 8-hour period can reduce BP (14/8 mm Hg) and can ameliorate metabolic syndrome.

Alternative Approaches

Despite many treatment modalities having insufficient scientific basis (e.g., acupuncture, yoga), several methods, including isometric handgrip exercise, device-guided slow breathing, and transcendental meditation, were shown to be of some benefit. The recently published meta-analysis showed that isometric handgrip, typically executed for 12 minutes for 3–5 times/week, decreases BP by 5.2/3.9 mm Hg.[45]

The recently published TRIUMPH (TReatment for ImmUne-Mediated PathopHysiology) trial showed that a 4-month structured program of diet and exercise as adjunctive therapy delivered in a cardiac rehabilitation setting results in significant reductions in the clinic and ambulatory BP and improvement in selected CVD biomarkers.[46]

Pharmacological Treatment of Resistant Hypertension

Step 1: *Ensure treatment resistance*–Three mechanistically complementary antihypertensive agents, commonly including a long-acting CCB, a blocker of the renin–angiotensin system (ACE inhibitors or ARB), and a diuretic, should already be prescribed and taken by the patient in maximally tolerated dose to ensure a proper diagnosis of RH. The choice of ARB and CCB is also important. Specifically, 24-hour ABPM trial data showed that azilsartan medoxomil ensures an additional 4–8 mm Hg (on average) SBP reduction over other ARBs such as, valsartan and olmesartan, or the ACE inhibitors ramipril.[47] Some studies suggest that long-acting preparations of nifedipine may have a bit more antihypertensive actions than amlodipine but results in more pedal edema.[48]

Step 2: *Substitute optimally dosed thiazolidinedione (TZD) like diuretic* → Hydrochlorothiazide (HCTZ) does not induce a predictable natriuresis below a GFR of 45, but CTDN and indapamide induce natriuresis down to an eGFR of 25–30. Below this eGFR level or in hypoalbuminemic states (i.e., serum albumin <3.0 g/L), a long-acting loop diuretic such as torsemide should be used over shorter-acting agents such as bumetanide or furosemide. The greatest evidence base for reducing cardiovascular (CV) outcomes are the TZD like diuretic, namely CTDN and indapamide.[49] Comparative studies show an additional SBP reduction of 7–8 mm Hg simply by switching from HCTZ to the same daily dose of CTDN.[50]

Step 3: *Add MRA*–In patients who are not overtly volume overloaded but who have evidence of low renin status or salt sensitivity of BP, MRAs are more successful than α- or β-blockers. ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) and ASPIRANT (Addition of Spironolactone in Patients with Resistant Arterial Hypertension) trials have shown the effectiveness of spironolactone in BP reduction when added as a fourth-line agent. The PATHWAY2 trial which compared between spironolactone, doxazosin, and bisoprolol as the fourth drug clearly demonstrated superiority of spironolactone in reducing SBP. Approximately 70% of adults with RH are candidates for MRAs based on eGFR and serum K^+, yet only a small fraction receive these effective agents.[51] Spironolactone has the advantage of once-daily administration and can be initiated at doses of as little as 12.5–25 mg daily. Owing to its shorter half-life in comparison to spironolactone, eplerenone may be given twice daily for satisfactory result.

Step 4: *Add α/β-blockers*–The choice of a fifth drug (to add) depends on sympathetic drive as assessed in part by HR. In two post hoc analyses from large outcome trials, patients with HRs >80 bpm had higher mortality.[52,53] So, in case of HR in excess of 70 bpm, β-blockers (metoprolol succinate/bisoprolol) or combined α/β-blocker (carvedilol, labetalol) should be added and if there is a contraindication to β-blocker, central alpha agonists (clonidine patch, guanfacine) should be considered. Clonidine in tablet form should be precluded as it requires frequent administration and carries the chance of rebound HTN at the time of nonadherence and after sudden discontinuation. If these are not tolerated, once-daily diltiazem should be tried.

Step 5: *Add hydralazine*–If BP is still not controlled with the above-described measures, the addition of hydralazine (25 mg TDS, max 150 mg) should be considered and combined with nitrates [isosorbide mononitrate (ISMN) 30 mg OD, max dose 90 mg/day] in cases of HF. Nitrates are preferred in this setting because they help restore calcium (Ca^{2+}) cycling and cardiac contractile performance and control superoxide production in isolated cardiomyocytes.[54] Moreover, hydralazine reduces nitrate tolerance in this setting.[55] Hydralazine causes increased sympathetic tone and sodium avidity and therefore, should be used in the presence of background-appropriate diuretic and β-blocker therapy. Hydralazine in doses >150 mg has a high risk of developing drug-induced lupus.

Step 6: *Add minoxidil*–Last, minoxidil (2.5 mg BD-TDS) is substituted for hydralazine. It also requires concomitant diuretic and β-blocker administration due to SNS activation and profound sodium avidity leading to fluid retention. However, minoxidil lowers BP effectively in most cases.[56] Minoxidil is not well tolerated. It induces hirsutism, which in women can lead to discontinuation of the agent. If BP is still above goal, the patient should be referred to an HTN specialist.

Step 7: *Consider newer agents*–Although this step is not included in the 2018 AHA scientific statement on RH, there is some evidence to add angiotensin receptor-neprilysin inhibitor (ARNI)/sodium-glucose cotransporter-2 (SGLT-2) inhibitors/new nonsteroidal MRA in treatment-resistant cases.

Angiotensin Receptor-neprilysin Inhibitor

Post hoc analysis of the *PARAGON-HF* trial on the effect of neprilysin inhibition on "apparent RH" in patients with heart failure with preserved ejection fraction (HFpEF) demonstrated that ARNI as compared to ARB valsartan may be useful in treating apparent RH in patients with HFpEF. Newer ARNI specifically designed for RH is under trial.

Sodium-glucose Cotransporter-2 Inhibitors

In the *CREDENCE* (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation)

trial, canagliflozin recipients showed an early and sustained reduction in BP (–3.5 mm Hg vs. baseline); this was consistent across all patient subgroups. Although statistically significant, the reduction in office BP in this trial can really be described as "modest" and certainly is not of a magnitude to fully account for the 30% reduction in primary endpoint event.

New Aldosterone Antagonists

New nonsteroidal MRA, finerenone promises a safer option for mineralocorticoid suppression.

Specialist in Clinical Hypertension

This certification is offered by the American Society of Hypertension. Three subspecialties, namely cardiology, nephrology, and endocrinology, qualify for this program. The specific purpose is to identify and recognize physicians with expert skills and knowledge in the management of clinical HTN and related disorders. These physicians can be posted as regional consultants for complex and difficult cases and also provide input regarding formulation of guidelines and process improvement. Referral to an HTN specialist improves BP control in over 50% patients with RH.

DEVICE-BASED TREATMENT OF RESISTANT HYPERTENSION

Sympathetic nervous system dysfunction plays an important role in the development and progression of HTN, HF, and CKD. In the 1940s, surgical sympathectomy demonstrated dramatic improvement in BP control and accompanying reduction in cardiac size, improved renal function, and a decrease in the rate of CV events before the availability of antihypertensive drugs. These successes were soon diminished by the occurrence of severe orthostatic hypotension, erectile dysfunction, and bowel and bladder incontinence and increasing availability of antihypertensive agents.

Renal Sympathetic Denervation

Early studies (e.g., *SYMPLICITY HTN-2*) in this field were quite promising and showed large reductions of clinic BP in patients not controlled with four or five antihypertensive agents. However, most of these studies did not study ambulatory BP as the primary endpoint. Also, these studies were not sham controlled. Later research demonstrated that in uncontrolled studies, effect sizes using ABPM were much lower (one-third) than the changes obtained in the clinic setting.

SYMPLICITY HTN-3 is the first sham-controlled prospective randomized study in the arena of renal ablation therapy. This study demonstrated little/no benefit of renal denervation (RDN) therapy in severely drug-resistant patients. The disappointment of this trial to fulfill the efficacy endpoints raised many technical concerns, such as inadequate denervation resulting from technical failure of the catheter, the interventional cardiologist, or both and nonadherence to multidrug pharmacological regimens. Subsequent review of the SYMPLICITY HTN-3 trial revealed that BP decreased in patients with more complete renal nerve ablation vis-à-vis lesser degrees of ablation. Moreover, the *DENERHTN* (Renal Denervation for Hypertension) study recently showed a statistically significant fall in daytime ambulatory SBP (–5.9 mm Hg; $p = 0.03$) in subjects on three antihypertensive agents randomized to RDN as compared to those on four antihypertensive agents.

A meta-analysis of 15 RCTs showed no statistically significant benefit of renal nerve ablation on BP control in patients with RH. A modest benefit in 24-hour ambulatory SBP at 6 months with RDN was shown in a subgroup analysis of sham control studies.[57] Another meta-analysis showed RDN significantly reduced (modest reduction) ambulatory and office BP readings as compared to placebo controls both for patients taking and those not taking antihypertensive medications.[58] However, these trials largely excluded patients with RH.

Carotid Baroreceptor Stimulation

Carotid baroreceptor activation therapy is a system that consists of baroreflex activation leads placed adjacent to the carotid sinus, an implantable pulse generator, and an external programming system. Effects of carotid sinus stimulation include enhanced vagal activity and reduced SNS activity. Hence, the HR falls, allowing more left ventricular filling and decreasing cardiac preload and energy demands. Besides, arterial dilation leads to reduced cardiac afterload and improved renal blood flow, augmenting natriuresis. So there is a multisystemic response for disorders associated with sympathetic overactivity such as HTN, HF, and arrhythmias.

The first large randomized trial in 322 patients of RH 410 with the first-generation implantable pulse generator (Rheos) was unsuccessful in fulfilling the primary endpoint of the trial, a combination of five separate efficacy and safety endpoints. But it demonstrated persistent BP-reducing efficacy (and SNS blockade) with some procedural and long-term safety concerns.[59] A second-generation unilateral device (BAROSTIM NEO™) has been developed to address these issues. A propensity score-matched comparison of the first- and second-generation devices showed that BP at 1-year postimplantation was similar, with a better safety profile for the second-generation device.[60] The ongoing trial *NORDIC BAT* will throw more insight into this device for its use in both RH and refractory HTN.

Complex surgical intervention involved in implanting BAT devices has led to the development of an endovascular carotid baroreflex amplification device using a dedicated stent-like device (*MobiusHD*) designed to stretch the carotid bulb and increase baroreflex sensitivity. It substantially lowered BP with an acceptable safety profile in the CALM FIM_EUR (Controlling and Lowering Blood Pressure with the MobiusHD first-in-man European) study.[61] CALM-FIM_US[62] (Controlling and Lowering Blood Pressure with the MobiusHD first-in-man United States) is an ongoing study that should provide results in 1–2 years.

Randomized, sham-controlled, double-blind trials are needed to study the use of this treatment further.

Creation of an Arteriovenous Fistula

The ROX arteriovenous coupler is a stent-like nitinol device which creates a fixed-caliber (4-mm) conduit between the external iliac artery and vein (arteriovenous anastomosis). Device deployment is reversible and can be confirmed. It results

in the deflection of arterial blood (0.8–1 L/min) into the venous circuit with prompt, demonstrable decrease in BP. In the *ROX CONTROL HTN* trial, subjects with RH were randomized to receive either standard medical therapy or insertion of an arteriovenous coupler in combination with standard medical therapy. At 6 months, both ambulatory and office BP were significantly lowered in the coupler group vis-à-vis the control group.[63]

Other devices on the horizon are the ReCor endovascular ultrasonic renal denervation device,[64] and median nerve stimulation that uses an electroacupuncture technique to reduce sympathetic outflow.

In conclusion, device therapy for RH is investigational at present and has been given a class III recommendation for the treatment of HTN in the guidelines unless in the context of clinical studies and RCTs.

CONCLUSION

Resistant HTN is defined as uncontrolled BP with three drugs at therapeutic dosage, one of them being a diuretic. It is like a triple threat due to difficulty in diagnosing true RH, due to ineffective treatment despite the availability of potent drugs, and due to difficulties in adherence and persistence. Exclusion of pseudoresistance, implementation of lifestyle interventions, and discontinuation of interfering substances are initial steps in approaching RH. Common comorbidities such as CKD, obesity, DM, and OSA should be diagnosed and treated. Workup for secondary causes of RH should be reserved for patients with appropriate clinical clues. Referral to HTN specialists can help to improve BP control. Newer agents such as ARNI and SGLT-2 inhibitors should be tried. Device therapy for RH is still investigational.

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CHAPTER 13

Recent Landmark Trials in Cardiology

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ABSTRACT

It was a great year for clinical trials. We saw data released on sacubitril/valsartan, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and antithrombotic strategies. Understandably, coronavirus disease 2019 (COVID-19) was a hot topic this year, and overall it was a great year of informative trials. In this chapter, we shall discuss few important recent clinical trials.

INTRODUCTION

Well designed and meticulously executed clinical trials go a long way in shaping the future of modern medicine. Their results help pave the path for further research in real world settings and formulation of practice guidelines. Despite the global pandemic of COVID-19 over the past 2 years the quest for medical excellence has not dampened the spirits of researchers from all over the world. Several landmark trials have been completed. This chapter shall discuss some of the important recent clinical trials.

TRIALS IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

EMPEROR-preserved: Empagliflozin in Heart Failure with a Preserved Ejection Fraction[1]

Taming heart failure with preserved ejection fraction (HFpEF): Treating HFpEF has been an uphill task for clinicians. The beneficial effects of sodium-glucose cotransporter-2 (SGLT-2) inhibitor (empagliflozin) in reducing the risk of hospitalization for heart failure (HHF) in patients with heart failure and a reduced ejection fraction (HFrEF) in the EMPEROR-Reduced trial prompted investigators to study their effects in the HFpEF patient population subset.

In this double-blind trial, 5,988 patients at 622 centers across 23 countries with class II–IV heart failure (HF) and an ejection fraction (EF) ≥40% were randomized in a 1:1 fashion to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular (CV) death or HHF.

The patients were followed-up for over 2 years (median 26.2 months). A primary outcome event occurred in 13.8% patients in the empagliflozin group and 17.1% patients in the placebo group [hazard ratio (HR) 0.79; 95% confidence interval (CI) 0.69–0.90; $p < 0.001$). The beneficial effects of empagliflozin were primarily driven by lower rates of HHF in the SGLT-2 inhibitor group (407 with empagliflozin and 541 with placebo; HR 0.73; 95% CI 0.61–0.88; $p < 0.001$). Benefits of SGLT-2 inhibitors were similar in diabetic and nondiabetic patients. Adverse events such as hypotension, uncomplicated urinary tract, and genital infections were more frequent in the empagliflozin group.

Pharmaceutical major AstraZeneca recently (5th May, 2022) reported that the results from the *DELIVER Phase III trial*[2] showed that Farxiga (dapagliflozin) reached a statistically significant and clinically meaningful reduction in the primary composite endpoint of CV death or worsening HF in patients with HF with mildly reduced or preserved EF [defined as left ventricular ejection fraction (LVEF) ≥40%]. The detailed results are due for announcement in the near future.

These two landmark trials help establish the role of SGLT-2 inhibitors in reducing the combined risk of CV death or HHF in patients with HFpEF, regardless of the presence or absence of diabetes.

HEMODYNAMIC-GUIDED MANAGEMENT OF HEART FAILURE (GUIDE-HF): A RANDOMIZED CONTROLLED TRIAL[3]

Previous studies using implantable pulmonary artery pressure monitoring devices in the management of patients with chronic HF (NYHA class III) and required had to be hospitalized in the past 1 year, irrespective of EF have shown favorable results. With this background the present trial was undertaken to look into the utility of these devices across the spectrum of HF (NYHA CII-IV). The GUIDE-HF trial was a multicenter, single-blind study at 118 centers in the USA and Canada. About 1,022 patients were enrolled in the trial and 1,000 devices were implanted successfully. The patients were randomized in a 1:1 fashion to either hemodynamic-guided HF management based on pulmonary artery pressure or a usual care control group. All-cause mortality and total HF events which included HHF and urgent HF were the primary endpoints at 12 months. Safety assessment was done in all patients. A pre-COVID impact analysis was prespecified for primary and secondary outcomes.

The hemodynamic-guided management did not result in lower composite endpoints of mortality and total HF events compared to the control group. The primary endpoints were nonsignificantly lower in the hemodynamic-guided management group (0.563 per patient-year) than the control group (0.640 per patient-year) (HR 0.88; 95% CI 0.74–1.05; $p = 0.16$).

EXPLORING THE ROLE OF ARNI IN ACUTE MI SETTING: EXPANDING INDICATIONS

Prospective ARNI versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction: PARADISE-MI[4]

This trial was designed to study the efficacy and safety of sacubitril/valsartan [angiotensin receptor neprilysin inhibitor (ARNI)] compared with ramipril in patients with acute myocardial infarction (AMI) with LVEF ≤40% with or without pulmonary congestion. In addition, the patients also satisfied one of the following criteria: age ≥70 years, atrial fibrillation, estimated glomerular filtration rate (eGFR) <60, diabetes mellitus (DM), prior MI, LVEF <30%, Killip class ≥III, and ST-segment elevation MI (STEMI) without reperfusion.

The primary outcome of CV death, first HF hospitalization, or outpatient HF for ARNI versus ramipril was 11.9% versus 13.2% ($p = 0.17$), for CV death 5.9% versus 6.7% ($p = 0.20$), and for HF hospitalization 6% versus 6.9% ($p = 0.17$). The secondary outcomes like the primary also showed trends in favor of ARNI but none of them reached statistical significance.

This head-to-head comparison garnered a lot of discussion at American College of Cardiology meeting in 2021 about whether the trial was negative (the *p* value for the primary endpoint was not statistically significant) or positive (examination of recurrent and not just first HF events was significant). Regardless of these interpretations, this long-awaited trial provided important insights into where sacubitril/valsartan fits into clinical practice and generated substantial interest.

INFLUENZA VACCINATION AFTER MYOCARDIAL INFARCTION: IAMI TRIAL[5]

A positive association of influenza with the risk of CV events was described in a study of influenza epidemics in the early part of the 20th century and later observational studies confirmed a temporal association. A few clinical trials of influenza vaccine versus no vaccine or placebo in high-risk patients with CV disease observed lesser CV events in the vaccinated population.

With this background, 2,571 patients were randomized in a 1:1 fashion at 30 centers across 8 countries to receive the influenza vaccine of placebo (saline) shortly after acute MI (99.7% patients) or high-risk stable coronary artery disease (CAD) (0.3%). The primary endpoint was the composite of all-cause death, MI, or stent thrombosis at 12 months. All-cause death, CV death, MI, and stent thrombosis were key secondary endpoints.

Over the 12-month follow-up, the primary endpoint occurred in 5.3% patients assigned to the influenza vaccine and 7.2% patients assigned to the placebo group ($p = 0.040$). Rates of all-cause death were 2.9 and 4.9% ($p = 0.010$), rates of CV death were 2.7 and 4.5% ($p = 0.014$), and rates of MI were 2.0 and 2.4% ($p = 0.57$) in the influenza vaccine and placebo groups, respectively.

The authors concluded that the administration of influenza vaccine shortly after AMI resulted in a lower rate of all-cause death, MI, stent thrombosis, all cause, and CV death as compared to placebo.

COMPARING EFFECTIVENESS OF CT AND INVASIVE CORONARY IMAGING IN THE MANAGEMENT OF CAD TO REDUCE THE FREQUENCY OF MAJOR ADVERSE CORONARY EVENTS

With rapid refinements in CT coronary angiography, it is rapidly being adopted as an alternative to invasive coronary angiography (ICA). This randomized trial (CT or ICA in stable chest pain—the DISCHARGE trial group)[6] was undertaken to compare the effectiveness of these two techniques in the management of CAD to reduce the frequency of major adverse coronary events (MACE) in patients with stable chest pain who had an intermediate pretest probability of obstructive CAD.

The primary outcome was major adverse CV events (CV death, nonfatal MI, or nonfatal stroke) over a period of 3.5 years. Procedure-related complications and angina pectoris were the secondary outcomes.

Major adverse coronary events occurred in 2.1% in the CT group and in 3.0% in the ICA group ($p = 0.10$). Major procedure-related complications occurred in 0.5% in the CT group and in 1.9% in the ICA group. Angina during the final 4 weeks of follow-up was reported in 8.8% of the patients in the CT group and in 7.5% of those in the ICA group.

The trial results showed that in this prespecified subgroup of patients the risk of MACE was similar in the CT and ICA groups while the risk of procedure-related complications was lower in the CT group.

MASTER DAPT TRIAL[7] COMPARING ABBREVIATED VERSUS STANDARD ANTIPLATELET THERAPY AMONG PATIENTS UNDERGOING PERCUTANEOUS INTERVENTION WITH A BIODEGRADABLE POLYMER SIROLIMUS-ELUTING STENT

About 4,579 patients undergoing percutaneous coronary intervention (PCI) for acute or chronic coronary syndrome using a biodegradable-polymer sirolimus-eluting stent (Ultimaster, Terumo) in whom no further revascularization was planned and who had ≥1 criterion for high bleeding risk were divided into two groups. In the first group (abbreviated therapy group), dual antiplatelet therapy was discontinued after the run-in period of 30–44 days and single antiplatelet was continued. In the standard therapy group, participants continued DAPT for 5 months then remained on single antiplatelet therapy. The patients were followed-up over a period of 12 months.

Net adverse clinical events (all-cause mortality, MI, stroke, or major bleeding) were lower in the abbreviated therapy group as compared to the standard therapy group (7.5% and 7.7% respectively) ($p < 0.001$ for noninferiority).

Major adverse cardiac or cerebral events (all-cause mortality, MI, or stroke) were lower in the abbreviated therapy group as compared to the standard therapy group (6.1% and 5.9% respectively) ($p = 0.001$ for noninferiority).

Similarly, major or clinically relevant nonmajor bleeding were lower in the abbreviated therapy group 6.5% compared with 9.4% in the standard therapy group ($p < 0.001$ for superiority).

The MASTER DAPT trial showed that abbreviated antiplatelet therapy was noninferior to standard antiplatelet therapy with regard to net adverse clinical events. These results however, are specific to patients who received a biodegradable-polymer sirolimus-eluting stent.

FLOWER MI TRIAL: FLOW EVALUATION TO GUIDE REVASCULARIZATION IN MULTIVESSEL ST-ELEVATION MYOCARDIAL INFARCTION TRIAL[8]

This was undertaken to investigate whether the use of fractional flow reserve (FFR) in complete revascularization results in a better clinical outcome than the use of angiography in patients with STEMI and multivessel disease.

About 1,171 acute MI patients with nonculprit multivessel CAD were randomized to FFR-guided revascularization versus angiography-guided revascularization. The mean age of the patients was 63 years and they were followed-up for 12 months. Nonculprit PCI was generally performed in a staged fashion (97%).

The mean number of stents per patient for nonculprit lesions were lower (1.01) in the FFR-guided group while it was 1.50 in the angiography-guided group.

The rates of primary outcome of death, MI, or urgent revascularization at 12 months of follow-up was 5.5% of the FFR-guided group and 4.2% of the angiography-guided group ($p = 0.31$).

Rates of nonfatal MI at 12 months were not significantly different in the two groups: 3.1% versus 1.7% in the FFR-guided group compared and the angiography-guided respectively.

There need for urgent revascularization at 12 months were more or less similar in both groups and did not reach statistical significance: 2.6% for the FFR-guided group compared with 1.9% for the angiography-guided group.

Present day guidelines recommend that patients admitted with STEMI who have multivessel PCI be subject to complete revascularization during the index hospitalization itself. This trial showed that while dealing with residual disease in such patients a FFR-guided strategy is not superior to an angiography-guided strategy and both are acceptable choices for the management of residual disease after primary PCI.

UNGUIDED DE-ESCALATION FROM TICAGRELOR TO CLOPIDOGREL IN STABILIZED PATIENTS WITH ACUTE MYOCARDIAL INFARCTION UNDERGOING PERCUTANEOUS CORONARY INTERVENTION (TALOS-AMI): AN INVESTIGATOR-INITIATED, OPEN-LABEL, MULTICENTER, NONINFERIORITY, RANDOMIZED TRIAL[9]

Antiplatelet therapy always carries a bleeding risk which is of major concern for patients and treating physicians. In this trial conducted at 32 institutes in South Korea, acute MI patients receiving aspirin and ticagrelor without major ischemic or bleeding events during the first month after index PCI were randomly assigned in a 1:1 ratio to a de-escalation (clopidogrel plus aspirin) or active control (ticagrelor plus aspirin) group. No loading dose of clopidogrel was used in the former group.

The primary endpoint was a composite of CV death, MI, stroke, or bleeding type 2, 3, or 5 according to Bleeding Academic Research Consortium (BARC) criteria from 1 to 12 months. A noninferiority test was done to assess the safety and efficacy of de-escalation DAPT compared with standard treatment.

A total of 2,697 patients were included in the trial and 1,349 patients were randomly assigned to the de-escalation group and 1,348 to active control groups. The primary endpoints occurred in 4.6% in the de-escalation group and 8.2% patients in the active control group [p noninferiority <0.001; HR 0.55 (95% CI, 0.40–0.76); p superiority = 0.0001] at 12 months of follow up. There was no significant difference in composite of CV death, MI, or stroke between de-escalation (2.1%) and the active control group ($p = 0.15$). Predefined bleeding rates were also lower in the de-escalation group ($p = 0.0012$).

In stabilized patients with AMI after index PCI, a uniform unguided de-escalation strategy significantly reduced the risk of net clinical events up to 12 months, mainly by reducing the bleeding events.

Exploring the Role of Percutaneous Transluminal Pulmonary Angioplasty in Treating Patients with Takayasu Arteritis with Pulmonary Hypertension

Percutaneous treatment of patients with chronic thromboembolic pulmonary hypertension using percutaneous transluminal pulmonary angioplasty (PTPA) has shown satisfactory results. Taking cue from these findings the present trial[10] was undertaken to look into the feasibility of PTPA in nonspecific aortoarteritis [Takayasu arteritis (TA)], another chronic obstructive pulmonary vascular disease.

Over a period of 3 years, 50 patients underwent PTPA while 21 refused to undergo the procedure. They were followed up for 37 ± 14 months. The primary endpoint was all cause mortality. Safety monitoring was carried out by looking out for procedure-related complications.

Similar base line characteristics and medical therapies were noted between the PTPA group and the non-PTPA group. Three patients (6%) died in the PTPA group while six died in the non-PTPA group (28.6%) at follow-up, contributing to the 3-year survival rate of 93.7% in the PTPA group and 76.2% in the non-PTPA group ($p = 0.0096$ for log-rank test). Statistical analysis showed that PTPA was associated with a significantly reduced hazard of all-cause mortality in TA-PH patients ($p = 0.017$). The PTPA procedure was found to be safe with no periprocedural deaths. Severe complications requiring noninvasive positive pressure ventilation occurred rarely (0.7%).

This modality seems to be a safe and effective option for TA patients with PH and offer a ray of hope for patients with this otherwise frustrating disease with limited treatment options.

CONCLUSION

This chapter has highlighted and summarized the key cardiology trials that were published and presented recently. Many of these trials will guide clinical practice and influence guideline development. Others have shown encouraging early data which will guide future study.

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CHAPTER 14

Rheumatic Fever and Rheumatic Heart Disease: Recent Trends in India

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ABSTRACT

Acute rheumatic fever (ARF) and its long-term sequel, rheumatic heart disease (RHD), are major problems in children, adolescents, and young adults. This young population who is affected with rheumatic fever (RF)/RHD is in their prime and productive phase of life. It is essential to make an accurate and precise diagnosis because in 35–40% of the cases, timely management can make the heart almost normal by initiating secondary prophylaxis to prevent further damage to the valves in the future. Balloon mitral valvotomy during pregnancy and in juvenile mitral stenosis (JMS) is safe and effective. New Jones criteria with echo as a major criterion (2015) will take the biting teeth from ARF, so the old sayings—"RF licks the joints and bites the heart and 50% of RHD patients do not have past H/O ARF"—will be obsolete. The present trend in India shows that we have skilled doctors but lack of will to control ARF.

INTRODUCTION

Acute rheumatic fever (ARF) and its consequence chronic rheumatic heart disease (RHD) continue to be the major cause of morbidity and mortality with a huge disease burden in India. School-going children, adolescents, and young adults are more often affected. This young population who is affected with rheumatic fever (RF)/RHD is in their prime and productive phase of life. Unfortunately, India is in the phase of "epidemiological transition." On the one hand, there is a substantial burden due to RHD; on the other hand, resources are scarce to treat the full-fledged RHD. Hence, it is very important to know the current trends and contemporary issues to take the teeth out of the disease licking the joint and biting the heart.

BACKGROUND

The prevalence of RF/RHD varies in studies conducted in different states of India because of the inclusion of different populations at different points of time and using different screening methods for the diagnosis. Data on the incidence and prevalence of nationally represented samples are lacking in India. There is a need to establish a population-based surveillance system in India for monitoring trends, management practices, and outcomes to formulate informed guidelines for initiating appropriate interventions for the prevention and control of RF/RHD in India.

EPIDEMIOLOGY

The annual incidence of ARF ranges from <0.5/100,000 in developed countries to >100/100,000 in developing countries as shown in the map in **Figure 1**. Annually, approximately 500,000 new cases of ARF occur worldwide, and RHD affects more than 40 million people and claims nearly 300,000 lives each year.[1,2] India has the highest prevalence rate globally (27%) and contributes nearly 25–50% of newly diagnosed cases, hospitalizations, and deaths due to RHD, according to the World Health Organization (WHO) bulletin of 2015. The overall prevalence estimated to be about 1.5–2/1,000 in all age groups in India (total population of about 1.3 billion) suggests that there are about 2.0–2.5 million patients with RHD in India. The worldwide map shows a prevalence of >10/1,000 in India.[3]

Trends of change in the prevalence of RF/RHD in Indian Council of Medical Research (ICMR)-led multicentric survey studies across the country in the last 40 years clearly show a decline in the prevalence of RF/RHD **(Fig. 2)**.

METHODS OF DETECTION

The detection of RF/RHD in the population is very challenging in a heterogeneous country like India. Detection is done by various methods such as hospital admission data collection, population-based survey studies, school-based surveys, and echocardiography-based screening studies in school children

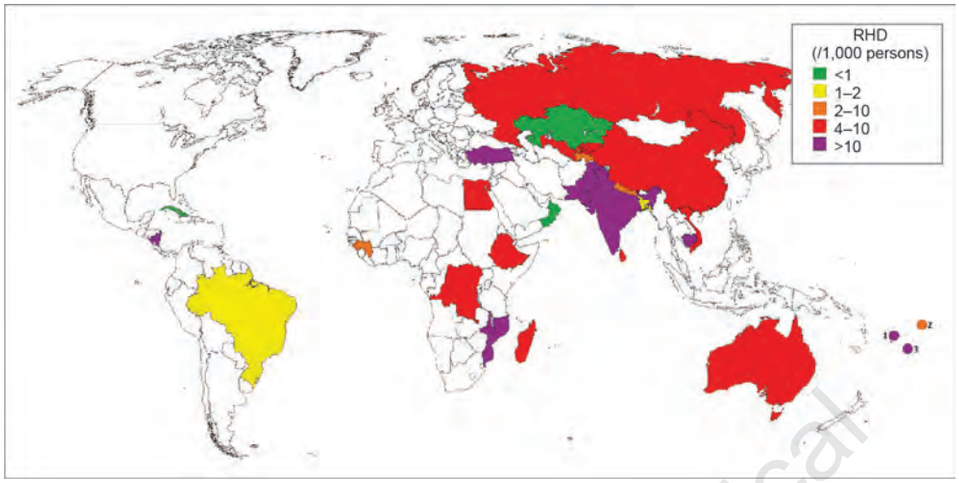


FIG. 1: Map showing reported worldwide prevalence of rheumatic heart disease (RHD)[3] from 1991 to 2011.

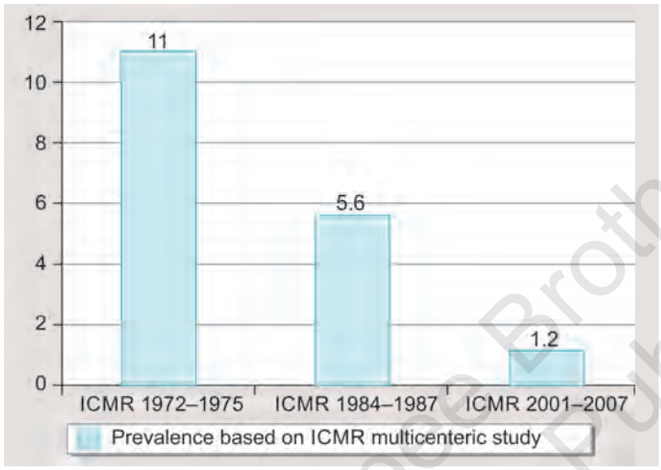


FIG. 2: Prevalence based on Indian Council of Medical Research (ICMR) multicentric study.

post year 2000.[4] If RF/RHD is detected on the basis of signs and symptoms and auscultation in crowded health checkup camps, then there will be gross underdiagnosis. Even if the well-qualified pediatricians detect RF, depending on earlier Jones criteria, then also there is a chance of both underdiagnosis and overdiagnosis.[5] Echocardiographic study of RHD in Indian school children using the World Heart Federation criteria showed that the prevalence of RHD is several fold higher using echocardiographic screening compared with clinical examination. The prevalence is higher among girls and children of lower socioeconomic status.[6] In the majority of cases, subclinical carditis appears to be nonprogressive on medium-term follow-up. Hence, the present trend in India is to do routine echocardiographic screening in populations at high risk of RHD.

Recent Echocardiographic Criteria

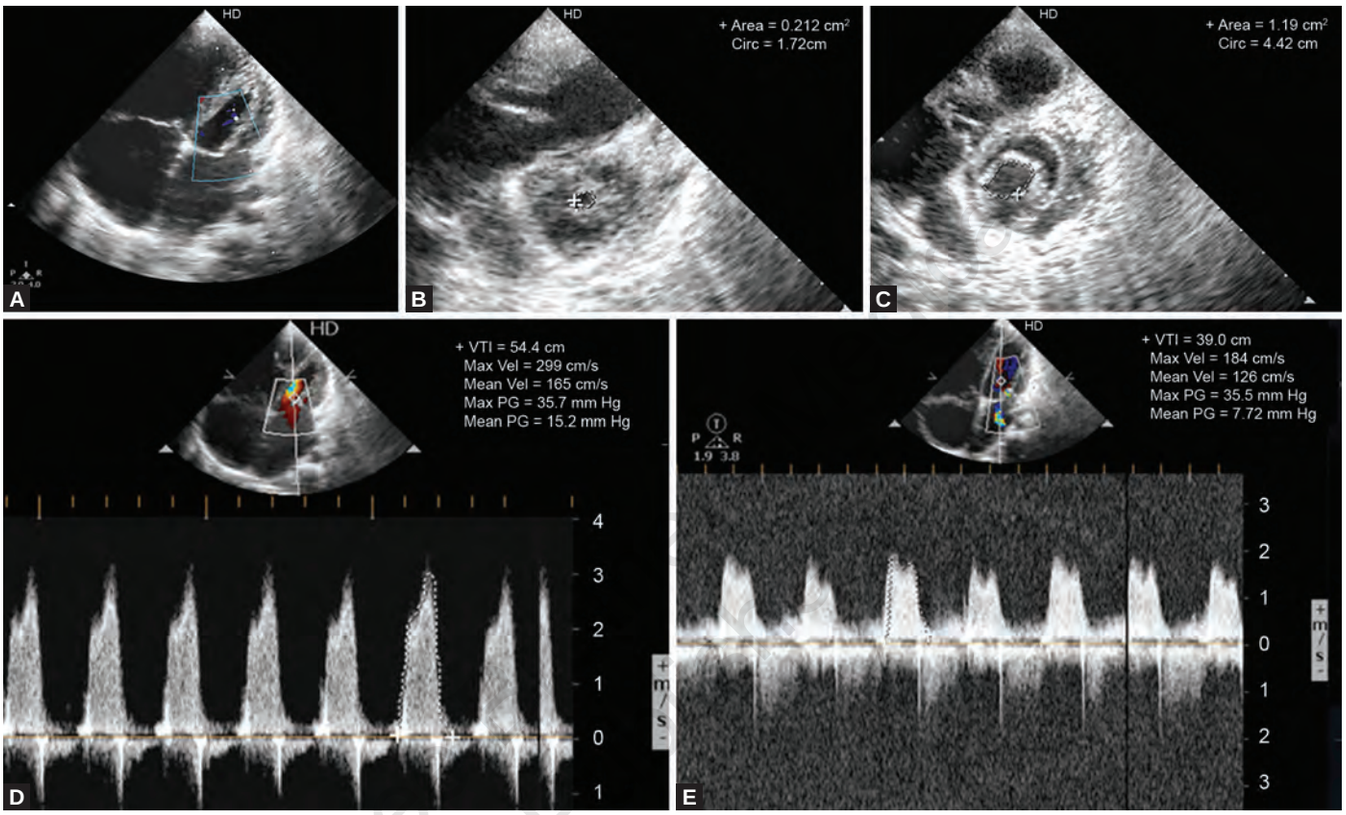
Duckett Jones established diagnostic criteria in 1944. They were first modified in 1955, revised in 1965, edited in 1984, updated in 1992, and later revised by WHO in 1988 and then again in 2003.[7-12] Despite all these modifications, revisions, and re-revisions of the Jones criteria several times, "carditis" in ARF was either underdiagnosed or overdiagnosed[13] and still worse, many patients went undiagnosed. The WHO bulletin (1981) shows that in ARF/RHD detected in surveys and health checkup camps, >50% of the patients were unaware of the disease and >70% were not receiving regular secondary prophylaxis.[14] Hence, in the past, it was taught that 50% of the RHD patients do not have a history of ARF. The diagnosis of ARF based on Jones criteria depending only on traditional characteristic auscultatory findings can lead to underdiagnosis in many patients with arthralgia and subclinical carditis.[13] It is essential to make an accurate and precise diagnosis as in 35–40% of the cases, timely management can make the heart almost normal and prevent recrudescence of rheumatic activity by initiating secondary prophylaxis to prevent further damage to the valves.

The double-blind study in 542 patients from three best pediatric centers in Bengaluru showed that echo interrogation can prevent both overdiagnosis and underdiagnosis.[13] Only 59.4% of the clinically diagnosed patients had echo evidence of carditis and 40.6% had functional murmur, tachycardia, fever, and anemia, and some even had congenital heart diseases. This clearly shows how echo can prevent both overdiagnosis and underdiagnosis of carditis. At the same time, polyarthralgia (70%) was a minor criterion, but echo evidence of carditis/valvulitis was present in 46.9%, demonstrating underdiagnosis of carditis if polyarthralgia is taken as a minor criterion and echo is not done in them. Now in high prevalence states of India, both monoarthritis and polyarthralgia are taken as major criteria.

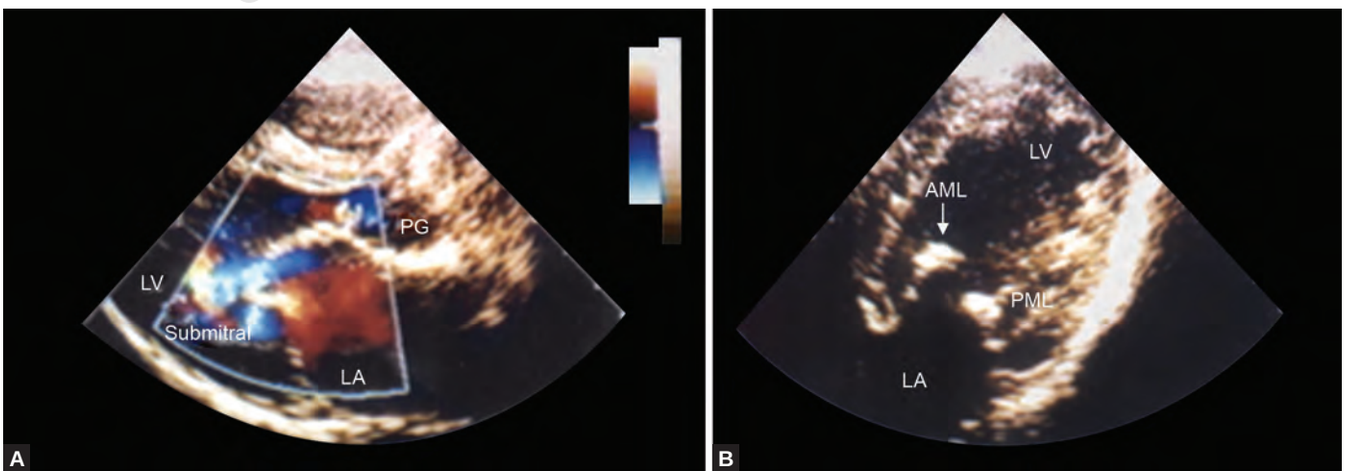
Echocardiography has become widely available and evolved over the past two decades, and several papers documenting the utility of early diagnosis of carditis, even in the absence of apparent clinical findings (subclinical carditis), have been published.[13-15] The study titled "The efficacy of echocardiographic criteria for the diagnosis of carditis in acute rheumatic fever"[16] is quoted in the 2015 revised Jones

criteria.[17] Any patient getting <6 scores is unlikely to be a case of ARF **(Figs. 3A and B)**. Only if valvular regurgitation is associated with other features such as thickened valves, reduced mobility, beaded appearance, hyperechogenic submitral structures **(Figs. 4A and B)**, and chordal tear, with an echo score of >6, it is taken as carditis of rheumatic etiology. Vijaya's echo criteria have 81% sensitivity and 93% specificity as shown in **Table 1**.

The sixth revision of the Jones criteria in 2015 is historic as it included subclinical carditis, diagnosed by echocardiography, as a major criterion. For the first time, transthoracic echocardiography (TTE) is included as a major criterion in



FIGS. 3A TO E: (A) Dilated right atrium (RA) and right ventricle (RV) due to severe pulmonary arterial hypertension (PAH) and small underfilled left ventricle (LV) due to critical mitral stenosis (MS). (B) Parasternal short axis shows that mitral valve orifice area (MVOA) measurement by planimetry was just 0.21 cm^2. (C) MVOA increased from 0.2 to 1.2 cm^2 after balloon dilatation with 18–20 Inoue balloons passing through 10F sheath. The stretched profile of the balloon was 3.6 mm. (D) Doppler interrogation shows mitral valve (MV) gradient of 35/15 mm. (E) After balloon mitral valvotomy (BMV), the MVOA is better with gradient of 13/7 mm Hg.



FIGS. 4A AND B: (A) Transthoracic echocardiography (TTE) in parasternal long axis with color Doppler turbulence in submitral area. (B) Modified view shows thick club-like AML and PML.
(AML: anterior mitral leaflet; PML: posterior mitral leaflet)

TABLE 1: Vijaya's echo score for the diagnosis of carditis in acute rheumatic fever.

Echo feature	Score
MV and AV thickness ≥4 mm	2
MV regurgitation and AV/TVR	2
Mitral valve prolapse	2
Rheumatic nodules	2
Pancarditis	2
Chordal tear	2
Reduced mobility of valves	2
↑ Echogenicity of submitral structures	2
Total score	16

Note: Echo score ≥6 is diagnostic of rheumatic carditis.
(AV: aortic valve; MV: mitral valve; TVR: tricuspid valve repair)

Jones criteria, as auscultation-based methods of screening RF/RHD have limited sensitivity and specificity. Two-dimensional (2D) TTE is a noninvasive, essential key tool for the diagnosis and evaluation of carditis in ARF.[16-19]

Valve Involvement in Rheumatic Heart Disease

The incidence and patterns of valvular heart disease in the Indian population are not available. But a single center experience of the incidence of various valve involvements among the RHD cases referred to a high-volume tertiary care cardiac center is available.[20] In this study, out of the 13,289 first-time echocardiograms performed, 60.2% had involvement of mitral valves, followed by aortic, tricuspid, and pulmonary valves. Mitral stenosis (MS), predominantly seen in females, was almost exclusively of rheumatic etiology (97.4%). The predominant form of isolated mitral regurgitation (MR) was rheumatic in 41.1% followed closely by myxomatous or mitral valve prolapse in 40.8%. Isolated aortic stenosis (AS), more common in males, was the third most common valve lesion seen in 7.3% of the cases. Degenerative calcification was the most common cause of isolated AS (65.0%) followed by bicuspid aortic valve (BAV) (33.9%) and RHD (1.1%). Multiple valves were involved in more than a third of all cases (36.8%). Overall, 9.7% of the cases had organic tricuspid valve disease. Isolated MS was the most common (25%), and an additional 40% had combined MS and MR. Multivalve involvement was seen in 38% of the MS patients, aortic valve in 35%, and tricuspid valve in about 6% of the patients. However, tricuspid stenosis (TS) has been reported to be about 15%, and pulmonary valve involvement was extremely rare.

JUVENILE RHEUMATIC HEART DISEASE

Juvenile MS is very often seen in the Indian subcontinent. The younger age of onset of RHD (juvenile) seen in India is special for both public health and clinical importance. Patients with juvenile MS have much more severe submitral fusion with a significantly reduced mitral valve orifice area (MVOA) than

TABLE 2: Comparison of percutaneous transvenous mitral commissurotomy (PTMC) results in adult mitral stenosis versus juvenile mitral stenosis.

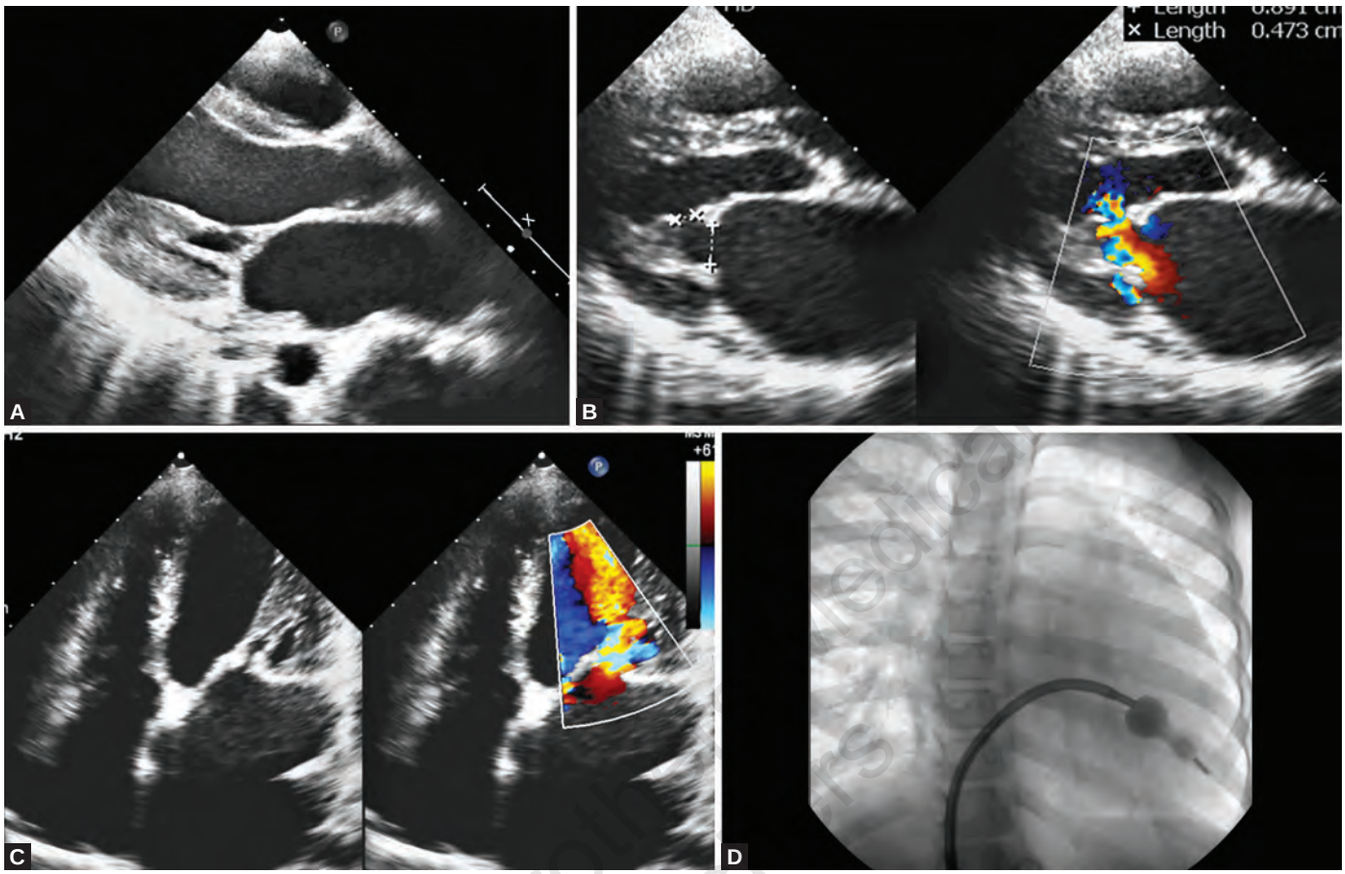
	Mean age (years)	MVOA (cm^2)		PASP (mm Hg)		Peak MV Gat. (mm Hg)	
		Pre	Post	Pre	Post	Pre	Post
Adult MS 18,334	32.7	0.8 ± 0.18	2.3 ± 0.25	54.8 ± 20.16	30.6 ± 10.6	18.5 ± 6.12	3.8 ± 3.1
JMS 3,450	14.39	0.73 ± 0.164	1.85 ± 0.32	72.38 ± 23.03	42.95 ± 14.54	28.46 ± 7.18	11.47 ± 4.04

(JMS: juvenile mitral stenosis; MS: mitral stenosis; MV: mitral valve; MVOA: mitral valve orifice area; PASP: pulmonary arterial systolic pressure)

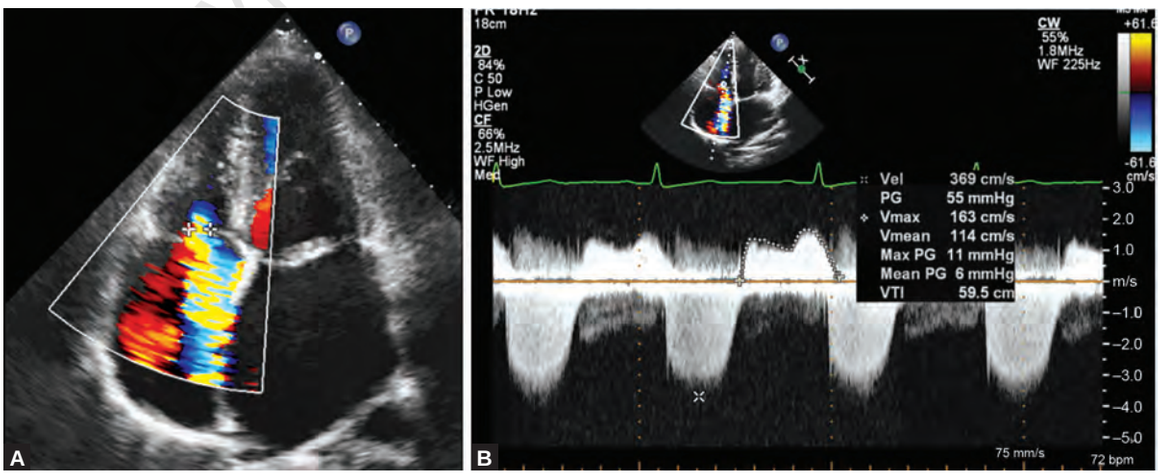
adults. The result of balloon mitral valvotomy (BMV) in juvenile MS/malignant MS in a 12-year-old girl with RHD, severe MS, trivial aortic regurgitation (AR), severe tricuspid regurgitation (TR), and severe pulmonary hypertension (PH), with reduced right ventricle (RV) function, is shown in **Figures 3A to E**. The BMV is feasible and safe, but the results are suboptimal compared to BMV in adults **(Table 2)** because, though commissurotomy is successful and the MVOA achieved is good for the body surface area, there is a gradient at the valve level due to damaged, thicker, club-like valves with reduced mobility **(Figs. 4A and B)** and significant submitral stenosis with gradient **(Figs. 5A and B)**. BMV is quite challenging as the set, including puncture needle, has to be smaller. Sometimes, the distal portion of the balloon can be trapped in fused submitral structures in juvenile mitral stenosis (JMS) **(Figs. 5C and D)**. If balloon deformity is not noticed and the balloon is inflated forcibly, then chordal tear with post-BMV severe MR can occur. Apart from this, despite the good splitting of commissure, symptoms persist due to persistently high pulmonary artery pressure with severe TR and RV dysfunction **(Fig. 6A)** and what is worse, the patient may have organic TR with TS **(Fig. 6B)**. Hence, it is also called "malignant MS." However, BMV in JMS significantly reduces the morbidity and mortality in the otherwise undernourished children and postpones surgery.[21] To our utter disbelief, the youngest child with MS in our experience was a 2-year and 3-month-old boy who presented with a history of breathlessness; his echo showed RHD with severe MS and TS **(Figs. 7A and B)**, continuous-wave (CW) cursor on mitral valve showed MS, and cursor on tricuspid valve showed TS and TR **(Figs. 7C and D)**.

PREGNANCY AND RHEUMATIC HEART DISEASE

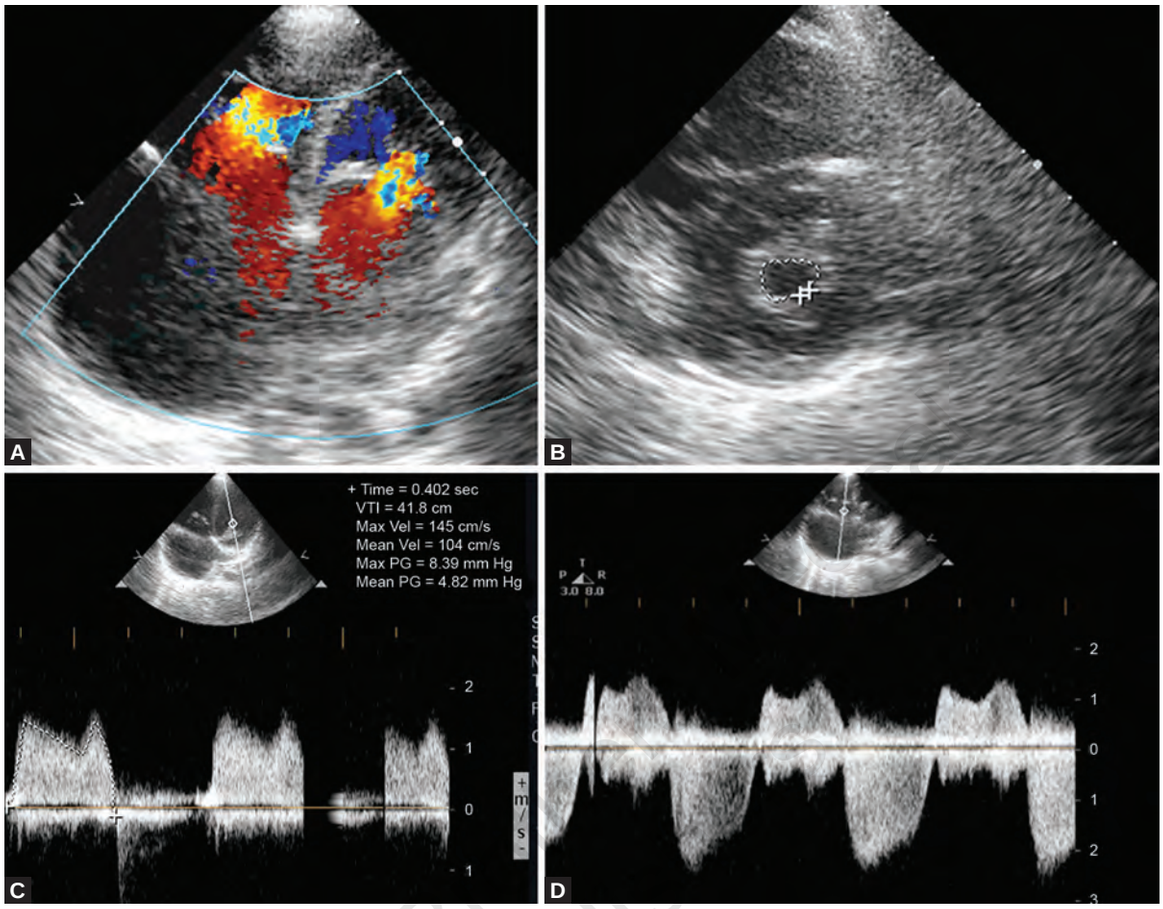
Rheumatic heart disease may increase maternal and fetal risks during pregnancy. Patients with RHD respond differently to the hemodynamics of pregnancy depending on the type and severity of maternal valvular disease, the resulting abnormalities of functional capacity, left ventricle (LV) function, and pulmonary pressure. Pregnancy increases the heart rate, blood volume, and cardiac output (CO), and this is poorly tolerated by women with left-sided obstructive lesions such as MS or AS. On the other hand, the decrease in systemic vascular



FIGS. 5A TO D: (A) Transthoracic echocardiography (TTE) in parasternal long-axis view shows hyperechogenic submitral apparatus; (B) Parasternal long axis (PLX) in diastole with color compare shows submitral opening narrower than the stenotic mitral orifice in a 12-year-old boy with juvenile mitral stenosis (JMS); (C) Apical four-chamber view shows severe submitral fusion appears almost like single papillary muscle, and with color Doppler comparison shows candle flame appearance due to severe mitral stenosis (MS); (D) Fluoroscopy during mitral balloon valvuloplasty (MBV). Notice that submitral fusion has deformed the distal portion of the balloon.



FIGS. 6A AND B: (A) Apical four-chamber view with color Doppler shows severe tricuspid regurgitation (TR) with 6 mm vena contracta; (B) Doppler interrogation shows both tricuspid stenosis (TS) and TR in a 14-year-old girl with juvenile rheumatic heart disease (JRHD).



FIGS. 7A TO D: Transthoracic echocardiography (TTE) in a 2-year and 3-month-old boy. (A) Apical four-chamber view with color Doppler shows mitral stenosis (MS) and tricuspid stenosis (TS); (B) In short-axis planimetry, mitral valve orifice area (MVOA) is 0.4 cm^2; (C) Continuous-wave (CW) cursor on mitral valve shows MS; (D) CW cursor on tricuspid valve demonstrates TS and tricuspid regurgitation (TR) in this case of malignant juvenile rheumatic heart disease (RHD).

resistance often benefits women with regurgitant lesions such as MR and AR until delivery, when the abrupt increase in vascular resistance may precipitate pulmonary edema at the time of delivery. Hence, valve replacement and cesarean section are done simultaneously in such cases to save the lives of mother and child. Women with PH are particularly intolerant of the hemodynamic changes of pregnancy and represent an exceptionally high-risk group.

Out of 17,398 patients who underwent BMV in our hospital at Sri Jayadeva Institute of Cardiovascular Sciences and Research (SJICS), 605 were pregnant. Majority were in New York Heart Association (NYHA) classes III and IV. 47 patients were of acute pulmonary edema. A single balloon (Inoue or Acura) was used in all the patients. The average fluoroscopy time was 5.1 + 2.5 minutes. The procedure was successful in 95.2% of the patients. The mean left atrial (LA) pressure dropped from 32 + 16 to 14 + 5 mm Hg and MVOA increased from 0.8 ± 0.4 to 1.85 ± 0.03 cm^2. One 22-year-old full-term pregnant woman presented with severe hemoptysis of about half liter daily (pulmonary apoplexy). TTE showed 0.4 cm^2. This woman underwent successful emergency BMV in the morning and in the evening, she had a safe normal delivery **(Fig. 8A)**. The current trend in India is to perform safe echo-guided BMV in the second trimester with minimal fluoroscopy, that too after covering the abdomen with a lead sheet **(Fig. 8B)** so that both mother and child are safe.

Retrospectively analyzed BMV during pregnancy performed between January 2008 and July 2018. BMV was carried out in 97 pregnant women. It is a safe and effective treatment for severe MS during pregnancy.[22] Long-term maternal outcomes after BMV done during pregnancy are good and comparable to that of BMV done in nonpregnant patients. BMV during pregnancy is safe and provides excellent symptomatic relief and hemodynamic improvement. This should be considered as the treatment of choice when managing pregnant women with severe MS.

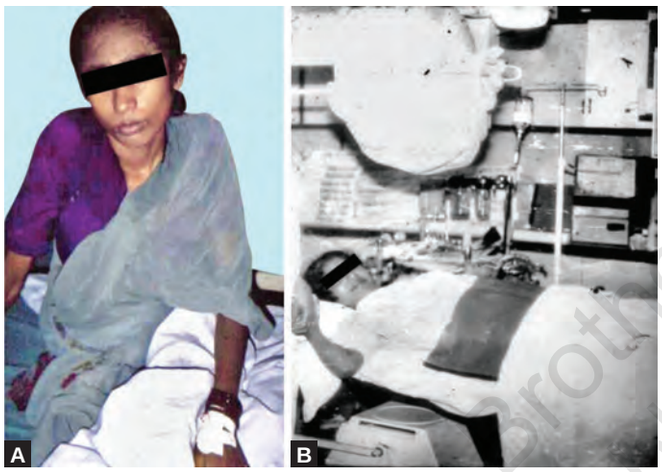
MANIFESTATIONS OF HEART FAILURE IN RHEUMATIC HEART DISEASE

Irrespective of which valve is involved, the first manifestation of congestive heart failure (CHF) is usually tachycardia. Invariably recent onset of atrial fibrillation with fast ventricular rate precipitates CHF. Left-sided heart failure is generally

associated with signs of pulmonary venous congestion and pulmonary edema, often seen in patients with MS and MR, whereas right-sided heart failure is associated with signs of systemic venous congestion as in cases with TS and TR or severe pulmonary arterial hypertension (PAH). Later stages of CHF are characterized by signs and symptoms of low CO. Generally, CHF with normal CO is called compensated CHF, and CHF with inadequate CO is considered decompensated.

Early and precise diagnosis of RHD with appropriate management can prevent or postpone the occurrence of CHF and reduce both morbidity and mortality, and the cost of repeated hospitalizations. For example, a 12-year-old boy presented with exertional dyspnea for the past 6 months, in NYHA class III symptoms. He was medically treated as dilated cardiomyopathy (DCM) with failure in another hospital. His pulse rate (PR) was 110/min (collapsing), blood pressure (BP) was 112/50 mm Hg, jugular venous pressure (JVP) was raised, RS: Bilateral basal crepts ++ CVS, and gallop rhythm was present. Long soft blowing early diastolic murmur (EDM) in Erb's area was missed by the treating clinician. Emergency TTE showed EF 15% vegetation on AV **(Figs. 9A and B)**. Thickened beaded MV with reduced mobility was missed by the echocardiographer. Had the child been diagnosed as RHD and put on secondary penicillin prophylaxis, the boy would not have been in the state where it is high risk for surgery/inoperable. With the facilities available today, no child should reach this stage in India.

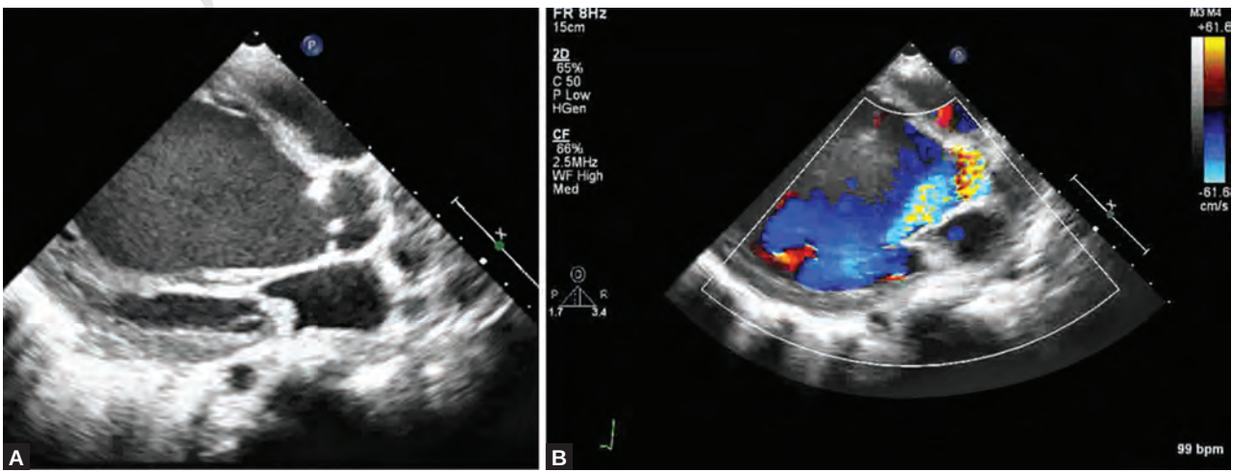
In just 3 months, 212 RHD patients were admitted to intensive care unit (ICU) at SJICS. The majority of them (166 patients, 78%) were with heart failure, 27 patients with infection, 10 with anemia, 8 patients with cerebrovascular accident (CVA), 4 patients with peripheral embolism and acute coronary syndrome, 3 patients with pericardial effusion, 3 patients with prosthetic valve thrombosis, and 1 patient with complete heart block. Out of these 212 patients admitted to ICU, 37 patients (17.45%) expired despite the optimal treatment. This hospital data of just 3 months show that RHD is a neglected giant in India.



FIGS. 8A AND B: (A) A 22-year-old full-term pregnant woman presented with pulmonary apoplexy who underwent emergency balloon mitral valvotomy (BMV) and safe normal delivery. (B) Pregnant woman in the second trimester with mitral stenosis (MS) underwent elective BMV with abdomen covered with lead coat.

SURGERY IN RHEUMATIC HEART DISEASE

According to the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) guidelines 2012, mitral valve repair should be the preferred technique when it is expected to be durable. Surgery is indicated in symptomatic patients with left ventricular ejection fraction (LVEF) > 30% and left ventricular end-systolic diameter (LVESD) <55 mm. Surgery is indicated in asymptomatic patients with LV dysfunction (LVESD ≥45 mm and/or LVEF ≤60%). Surgery should be considered in asymptomatic



FIGS. 9A AND B: (A) Transthoracic echocardiography (TTE) in parasternal long-axis view shows dilated left ventricle (LV), hyperechogenic submitral structure, and thickened aortic valve (AV) with healed vegetation; (B) Parasternal long axis (PLAX) with color Doppler shows severe aortic regurgitation (AR) in a 12-year-old boy with rheumatic heart disease (RHD).

patients with preserved LV function and new onset of atrial fibrillation or PH (systolic pulmonary pressure at rest >50 mm Hg). Surgery should be considered in asymptomatic patients with preserved LV function, high likelihood of durable repair, low surgical risk and flail leaflet, and LVESD ≥40 mm. It should be considered in patients with severe LV dysfunction (LVEF <30% and/or LVESD >55 mm) refractory to medical therapy with a high likelihood of durable repair and low comorbidity. MV repair, annuloplasty, valvuloplasty, chordal shortening, and release were done in more than 1,500 cases at SJICS with excellent results and avoided complications of anticoagulation **(Figs. 10A to C)**. Out of 1,686 MV repairs done over 18 years by Dr Prasanna Simha at SJICS, only 10 cases required redo surgery in RHD; 5 replacements were done for late endocarditis, whereas 3 redo repairs were for post-endocarditis and repair failure in non-rheumatic cases.

Roadmap for the Prevention and Control of Rheumatic Fever and Rheumatic Heart Disease

The patterns of RF and RHD in India may be similar to those in other developing countries and underscore the importance of effective public health strategies for their prevention and control **(Flowchart 1)**. Unfortunately, we do not have a national RF/RHD control program. Hence, it is important to have the following programs:

- Regular school surveys to be conducted uniformly in all states covering both rural and urban children with portable echo and skilled interpretation of the echo, followed by specialist referral for those with abnormalities.
- Teach the methods of preventing the droplet infection by covering the face while sneezing, coughing, washing the hands, and improving oral hygiene.
- Primordial prevention is difficult, but family physicians can attempt primary prevention by giving penicillin within 9 days of the onset of sore throat.
- Secondary prevention, by extending penicillin prophylaxis to all the cases of RF/RHD, including subclinical carditis detected by ECHO that includes even suspected cases as per 2015 Jones criteria.
- Tertiary prevention is expensive and requires skilled cardiologists and cardiac surgeons to do BMV, timely valve repair, and/or replacement before the patient develops CHF. A stitch in time saves precious lives. For this, regular echo monitoring of all the RHD cases is of paramount importance.
- It is high time we in India have a national RF control program.
- Vaccine production and trial should be done on priority.

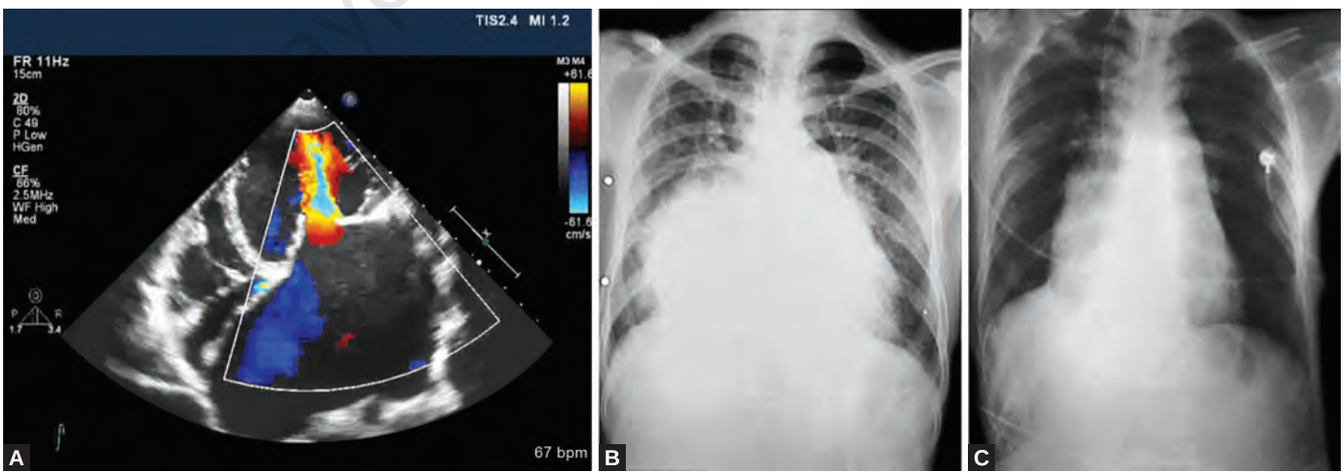
Prevention at different levels is shown in **Flowchart 1**.

Decline of Rheumatic Heart Disease in India: Is it Real? Or a Neglected Giant?

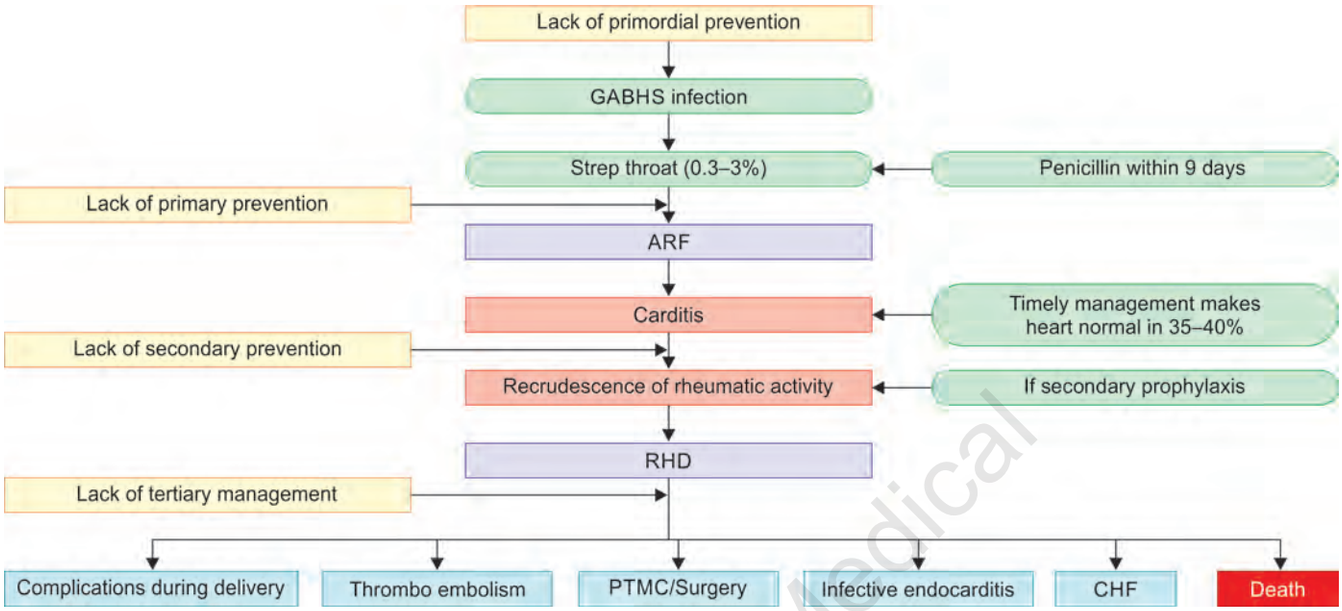
A systematic review of the available data across the country by individual authors and ICMR-led multicentric survey studies suggest declining trends, especially after the year 2000.

FUTURE

With the advent of technological advances in antigen delivery and vaccine developmental strategies, it is important to design and test the immunogenicity and protective potential of various synthetic peptide-based immunogens, including non-M protein vaccine candidates, with a view to the development of a gas vaccine that can be delivered intranasally and stimulate mucosal immunity. This is important as a primary portal of entry of gas is the upper respiratory tract and



FIGS. 10A TO C: (A) Transthoracic echocardiography (TTE) in apical four-chamber view shows a giant left atrium (LA) in a 16-year-old child with rheumatic heart disease (RHD) with mitral stenosis (MS) and mitral regurgitation (MR); (B) Plain X-ray of the chest in posteroanterior (PA) view shows giant LA extending beyond the right cardiac border; (C) Postsurgical X-ray following mitral valve (MV) repair and LA plication shows normal-sized cardia.



FLOWCHART 1: Strategies for prevention and control of rheumatic fever.

(ARF: acute rheumatic fever; CHF: congestive heart failure; GABHS: group A β-hemolytic streptococcal pharyngotonsillitis; PTMC: percutaneous transvenous mitral commissurotomy; RHD: rheumatic heart disease)

nasopharyngeal group A *Streptococcus* (GAS) infections are thought to be critical in the pathogenesis of RF/RHD.

CONCLUSION

Rheumatic fever/rheumatic heart disease is a neglected giant in India. Patients with clinical and subclinical carditis are more likely to be detected during their first attack of ARF if echo criteria are applied. Detecting subclinical carditis will prevent a more relaxed and inappropriate secondary prophylaxis. New Jones criteria with echo as a major criterion (2015) will take the biting teeth from ARF so that old sayings—"RF licks the joints and bites the heart and 50% of RHD patients do not have past H/O ARF" will be obsolete. The present trend in India shows that we have skilled doctors but lack the will to control ARF.

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CHAPTER 15

Stuck Prosthetic Valves: Diagnosis and Management Challenges

Latchumanadhas Kalidoss

ABSTRACT

Mechanical valves are known for its durability for left-sided valvular heart diseases especially in younger population <60 years of age. Prosthetic valve thrombus (PVT) with significant obstruction leads to redo surgery even in the first year after valve replacement. Fluoroscopy and computed tomography (CT) scan are the key in diagnosing and differentiating thrombus and pannus. Transesophageal echocardiogram (TEE) is ideal for diagnosing PVT of mitral prosthetic valve. Recently fibrinolytic therapy gains confidence of physicians in managing PVT in the scenario of high risk of redo surgery. Although ultraslow infusion fibrinolytic therapy showed 90% success rate and <2% complications, still robust long-term data are lacking. Transcatheter balloon dilatation with cerebral embolic protection is the new upcoming treatment option for PVT. Identification of ideal annular plane view is the key to success for transcatheter therapy.

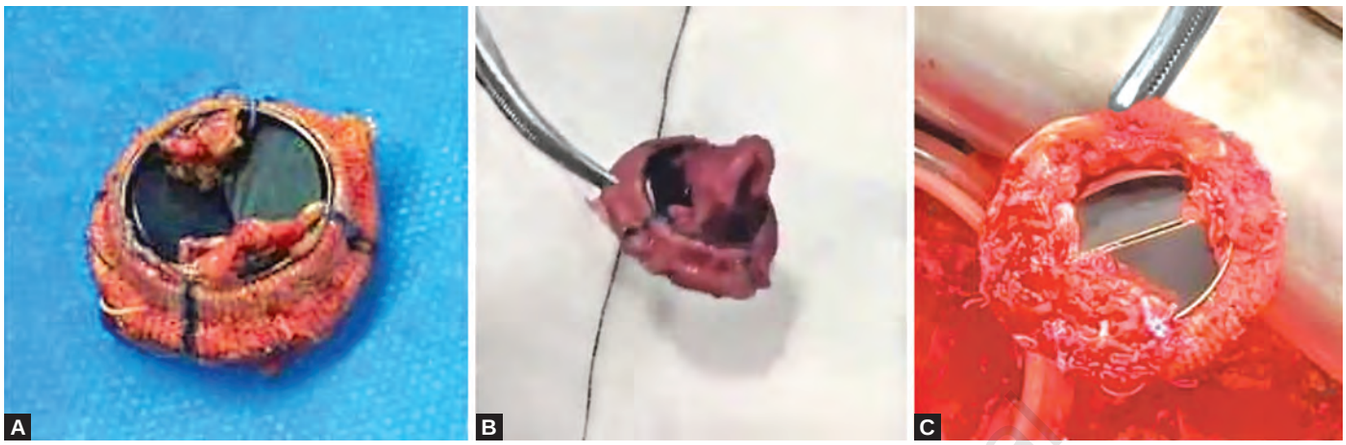
INTRODUCTION

History and evolution of mechanical valves are cornerstone to understand the mechanisms of prosthetic valve thrombosis and its therapeutic options. The history of prosthetic valves was born with Charles Hufnagel, MD (1916–1989) after he got into a position as professor of experimental surgery in Georgetown University in Washington, DC in 1950. The first artificial valve contained a methacrylate ball in a methacrylate tube which was successfully implanted into the descending thoracic aorta for severe aortic insufficiency in 1952. This heterotopic valve was a sutureless valve with plastic leaflets and that was implanted with beating heart approach.[1] Surprisingly these are the expected features of modern-generation surgical valves apart from the hemodynamics and durability.

Modification of the Hufnagel valve leads to development of various ball and cage valves. Lateralization of forward flow due to the central ball occluder, limited effective orifice area (EOA) due to high profile and large sewing ring, and left ventricular outflow tract obstruction at mitral position are considered as the poor hemodynamic performances of this valve. The need for a more physiological central flow led to the invention of tilting-disk prosthesis in late 1960s. Yet the blood flow is not completely laminar, more turbulence across the minor orifice leads to blood stagnation and thrombus formation. To address this issue, bileaflet valve, the St Jude Medical was introduced in 1977, has three flow areas with a more uniform and laminar central flow compared to the tilting disk design.[2] With its better EOA, hemodynamics, lower profile and less blood stagnation, bileaflet design remains the better choice till now even after 45 years among the mechanical valves. Thromboembolic complications due to inadequate anticoagulation and anticoagulation related bleeding events are the main drawbacks of mechanical valves. The evolution of biological tissue valves, homograft cadaveric valves, porcine xenograft valves, and bovine pericardial valves though removed the problems of mechanical valves, durability became the main concern. Structural valve deterioration was detected in the first 5 years' follow-up itself.[2]

BACKGROUND

Mechanical valves are known for its durability for left-sided valvular heart diseases especially in younger population <60 years of age. Although valve replacement surgery is considered as the definitive treatment for valvular heart diseases, essentially it is the exchange of the native valve dysfunction with the potential complications of prosthetic mechanical valves namely, prosthetic valve thrombus (PVT), pannus ingrowth, valve dehiscence, hemolysis, systemic thromboembolism, stroke, paravalvular leak, and infective endocarditis. PVT can happen any time after implantation if anticoagulation is not



FIGS. 1A TO C: Pannus in-growth. (A) 13-year-old mitral bileaflet valve shows pannus in-growth at the hinge regions. (B) 13-year-old mitral bileaflet valve shows extensive pannus in-growth completely occluding half of the valve orifice. (C) 9-year-old aortic bileaflet valve shows pannus in-growth at ventricular side hinge regions.

optimal. Rather than the individual international normalized ratio (INR) values, time in therapeutic range (TTR) is more meaningful to know the anticoagulation status. For the same TTR level, in a patient TTR calculated for 1 year with 18 INR levels is better than in another patient TTR calculated for 1 year with 12 values. The incidence of PVT is estimated to be 0.03% and 0.13% per patient-year.[3]

MECHANISMS OF MECHANICAL VALVE DYSFUNCTION

Mechanical valves are preferred over the bioprosthetic valves in the contemporary era in two scenarios, (a) younger age of the patient for durability and (b) pre-existing indication for anticoagulation like atrial fibrillation. In the first scenario, though the mechanical valves are considered durable, in reality earlier mechanical valve dysfunction was noted mainly because of PVT even within the first year of surgery due to one of the following reasons.[4]

Surface Causes

- Malpositioning of the valve
- Leaflet damage
- Incomplete endothelialization

Hemodynamic Causes

- Low cardiac output
- Malpositioning of the valve
- Anatomical position
- Inherent hemodynamic profile of the mechanical valve

Hemostatic Causes

- Poor time in therapeutic range
- Platelet reactivity
- Hypercoagulable state
- Heparin-induced thrombocytopenia
- Hyperviscosity

One of the unique mechanisms of late dysfunction of mechanical valve is pannus ingrowth. The pannus is the result of excessive biological response to the mechanical valve material. Histologically, pannus consists of fibroblasts and extracellular matrix. Usually, the pannus is located in subannular region, atrial side of the mitral mechanical valve, and ventricular side of the aortic mechanical valve **(Figs. 1A to C)**. The pannus is unaffected by thrombolysis or therapeutic anticoagulation because of its fibrotic nature. But, thrombus can form as a consequence of reduced leaflet motion due to pannus. Another scenario where subclinical thrombus forms earlier which later organizes into pannus.[5,6] PVT occurred during perioperative withdrawal of anticoagulation for other surgeries in 26% of patients.[7]

CLINICAL PRESENTATION

Since the ball and cage valves are long back discontinued, the further discussion is about tilting disk and bileaflet mechanical valves only. Presently surgeons stopped implanting tilting disk valves also. Yet those tilting disk valves implanted in the previous decade are still seen by the cardiologists in their follow-up. Hence, it is worthwhile to include tilting disk valves in the discussion. The incidence of PVT ranges from 0.1 to 5.7% in various studies.[4] The presentation of PVT according to the anatomic position was mitral (67%), aortic (15%), both mitral and aortic (15%) and tricuspid (1%). Essentially the mechanical valves are implanted on the left side in the contemporary era. Hence, the low-flow position of mitral valve site is the most common victim for PVT. The mean age of PVT was 58 ± 11 years. Up to 41% of the PVT patients were in atrial fibrillation before the valve replacement. Though left ventricular dysfunction and atrial fibrillation were presumed to be the risk factors for PVT, no robust data available to prove its association.[7]

The mean interval from the valve replacement to PVT was 39 ± 42 months. The mechanical valve which was presumed to be a long-durable valve compared to bioprosthetic valve needs to be replaced at 3–4 years after surgery in PVT patients. The most common symptom was dyspnea in 56% of patients.

Cardiogenic shock was noted in 13% of PVT patients during their presentation. Change in murmur was documented in 13% of patients. Muffling of closing clicks or disappearance of closing clicks is generally appreciated by both patients and physicians. Stroke, syncope, or abdominal pain were the other miscellaneous symptoms noted in 15% of patients. Thromboembolic events before PVT was documented in 23% of patients in the form of stroke, limb ischemia, or organ ischemia.[7]

DIAGNOSIS OF MECHANICAL VALVE DYSFUNCTION

The first step in diagnosing PVT is by transthoracic echocardiogram (TTE). Obstruction is defined as >50% increase in mean transvalvular gradient or an increase of >10 mm Hg across the aortic prosthesis compared to baseline. Exclusion of high-output states such as fever, anemia, hyperthyroidism, and beriberi needs to be excluded before the assessment. The next step is to document the leaflet motion by fluoroscopy or computed tomography (CT). Alternatively, transesophageal echocardiogram (TEE) can be used to assess the leaflet motion for mitral prosthesis but it is difficult to assess the aortic prosthesis. Long fluoroscopy for 10 cycles may be needed during atrial fibrillation or frequent premature ventricular contractions to document intermittent obstruction following short R-R cycles alone. Isolated valvular leak is due to stuck leaflet in open position is diagnosed by the routine criteria for native valve regurgitation, although it is rare. The visualization of thrombus or pannus and its quantification is possible with CT (mitral and aortic prosthesis) or TEE (mitral prosthesis).[8,9] Gunduz et al. measured the mean attenuation value of thrombus was 87 ± 59 HU and pannus was 322 ± 122 HU. A cutoff point of >145 HU has got the high sensitivity (87.5%) and specificity (95.5%) in discriminating pannus from thrombus was noted in the study.[8] One needs to be careful not to mistake the beam hardening artifact beneath the prosthetic ring for thrombus and bright blooming artifact near the metallic ring for pannus.

Fluoroscopic evaluation of mechanical leaflets opening is more objective and feasible. Opening and closing angles of both leaflets in bileaflet valve and major orifice opening and closing angles in tilting-disk valves are meaningful. Though the measurements of closing and opening angles in literature are of different kinds, authors of this chapter found the following methodology more useful. **Figure 2** shows the closing and opening angles of aortic valve in stuck position and in normal functioning position. **Figure 3** shows the closing and

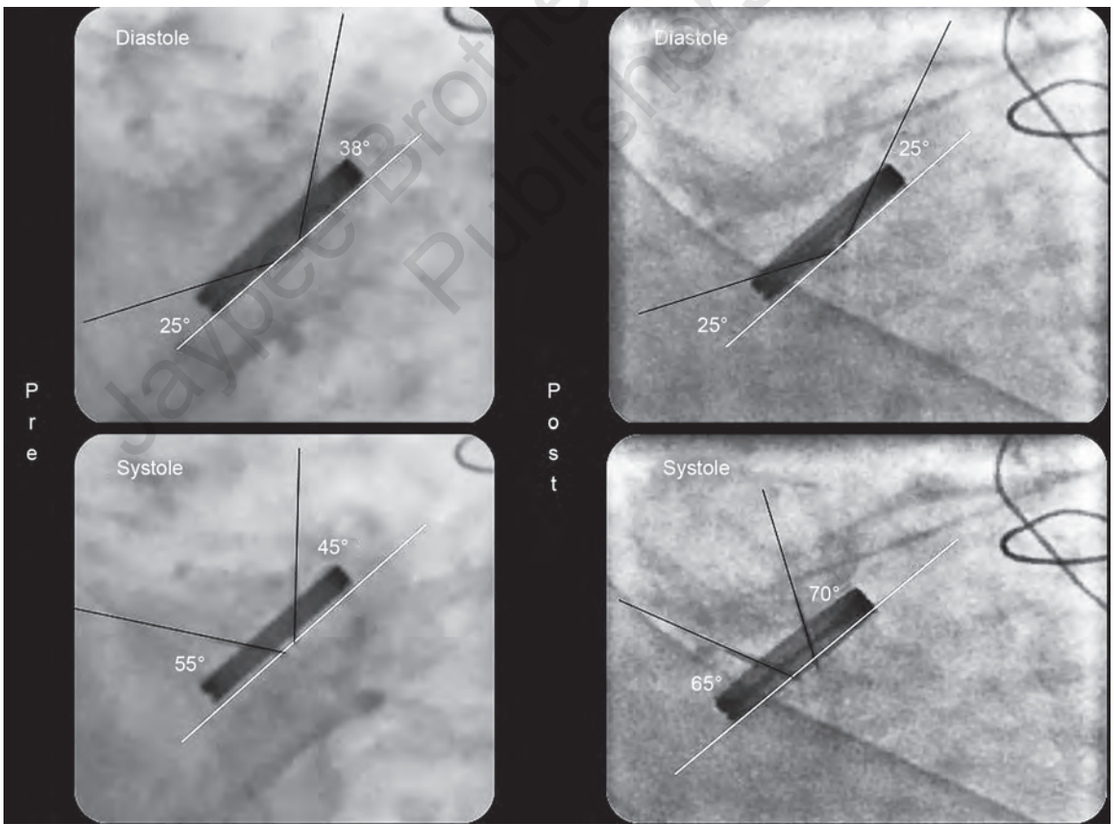


FIG. 2: ATS-AP 360, 20-mm valve in aortic position. Annular plane view obtained in left anterior oblique (LAO) caudal view. Left-side images show the closing angle of inferior leaflet as 25°, whereas the stuck superior leaflet due to thrombus closes at 38° angle in diastole. The opening angle of stuck superior leaflet is 45° against the inferior leaflet opening angle 55°. Right-side images show after the transcatheter release both leaflets closing angle become 25° in diastole. Opening angle of superior leaflet improved to 70° and inferior leaflet opening angle improved to 65°.

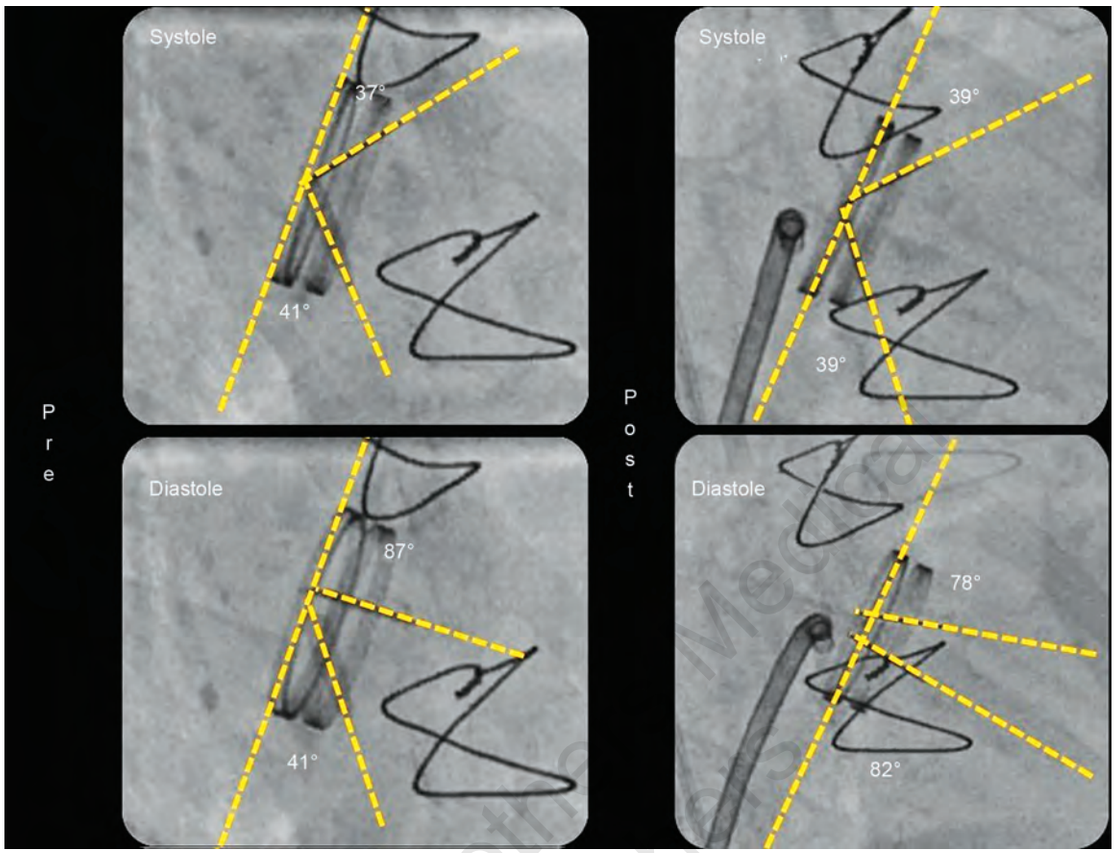
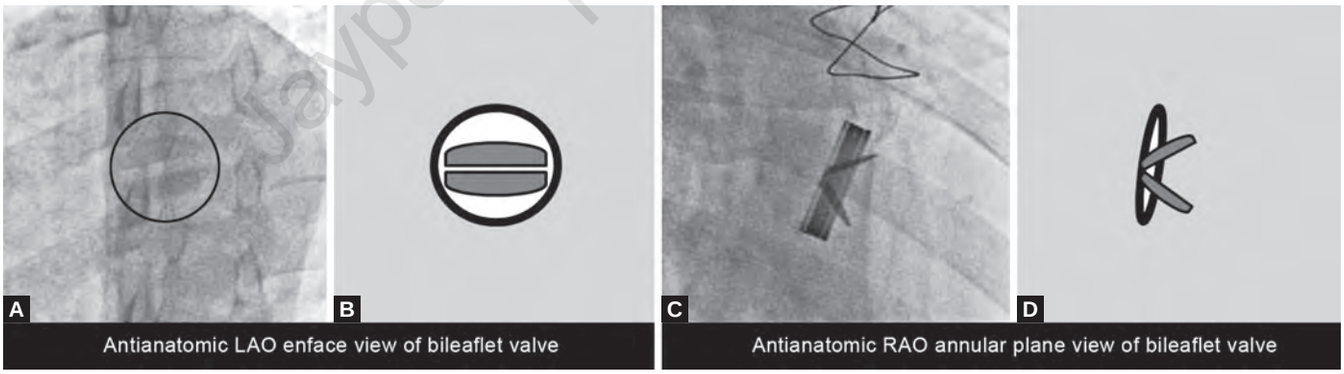


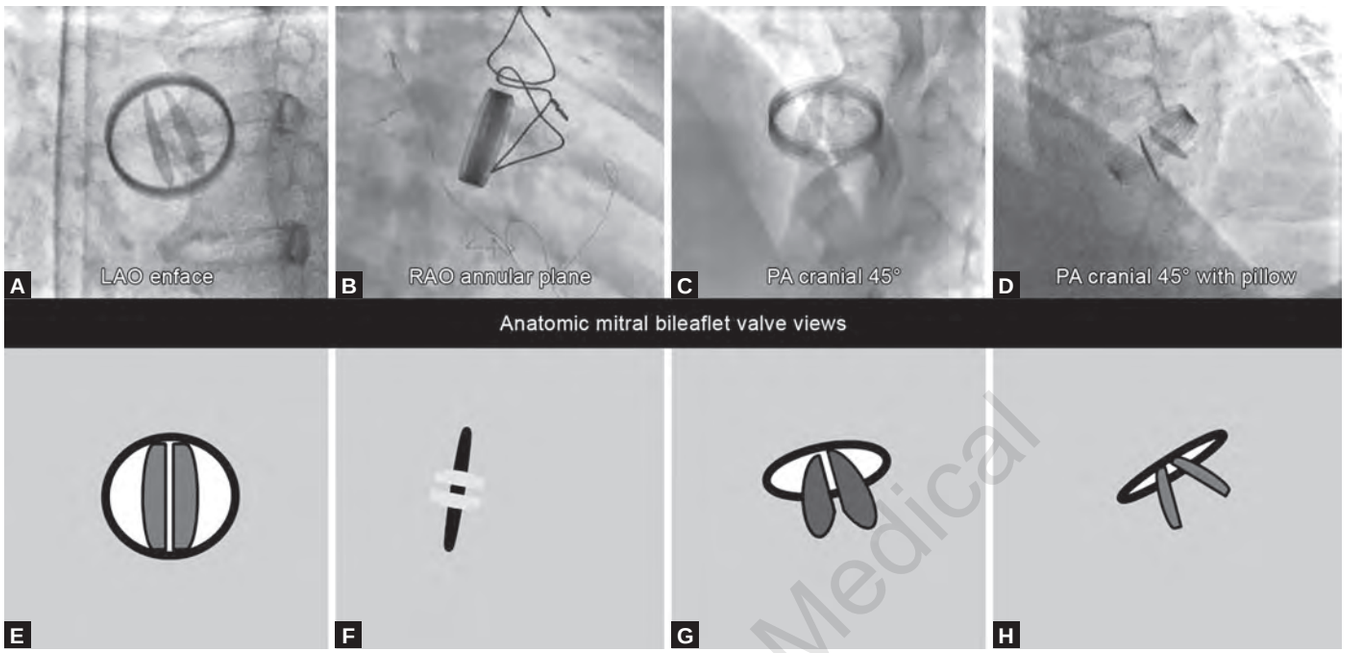
FIG. 3: On-X® valve, 27 mm in mitral prosthesis implanted in antianatomic position. Annular plane view obtained in right anterior oblique (RAO). Left-side images show the closing angle of inferior leaflet and superior leaflet as 41° and 37° respectively in systole. The opening angle of stuck inferior leaflet is 41° against the superior leaflet opening angle 87° in diastole. Right-side images show after the transcatheter release both leaflets closing angle become 39° in systole. Opening angle of superior leaflet decreased to 78° and inferior leaflet opening angle improved to 82°. This because of decrease in pressure gradient and more laminar blood flow after the release of stuck inferior leaflet.



FIGS. 4A TO D: Bileaflet valve at mitral position. (A) Enface view in left anterior oblique (LAO) shows horizontal position of the leaflets in open position. (B) Cartoon representation of panel-A. This indicates antianatomic orientation of mitral prosthetic leaflets. (C) 90° perpendicular right anterior oblique (RAO) view from the enface view shows the ideal annular plane view with leaflets seen as single line in open position. (D) Cartoon representation of panel-C.

opening angles of mitral valve in stuck position and in normal functioning position. Fluoroscopic image needs to be obtained in annular plane. To identify the right annular plane for mitral prosthesis, the first step is to identify whether the implanted position is anatomic or anti-anatomic.

For that left anterior oblique (LAO) view is the best. In the range of plain LAO 35° to 60° we can see the enface view of the prosthetic valve **(Figs. 4A and B, 5A and E)**. If the open bileaflet valves or tilting disk leaflet are seen in vertical position **(Figs. 5A and E)**, it indicates that the valve was implanted in anatomic



FIGS. 5A TO H: Bileaflet valve at mitral position. (A) Enface view in left anterior oblique (LAO) shows vertical position of leaflets in open position. (B) 90° perpendicular right anterior oblique (RAO) view from the enface view shows the annular plane, but leaflets are not visible in open position. (C) 45° cranial tilt (maximum by fluoroscopic gantry) from enface view shows the open leaflets, but annuls did not align in a single line. (D) 45° head end elevation with 45° cranial tilt from enface view (equivalent to 90° cranial tilt) shows the ideal annular plane view. (E) Cartoon representation of panel-A. Anatomic orientation of mitral prosthetic leaflets. (F) Cartoon representation of panel-B. Annular plane without visible leaflet opening. (G) Cartoon representation of panel-C. Semi-annular plane view with visible leaflets. (H) Cartoon representation of panel-D. Ideal annular plane view with visible leaflets.

position. Whereas if the enface view shows leaflet in horizontal position **(Figs. 4A and B)**, it means that prosthetic valve was implanted in antianatomic position.

The next step is to identify the annular plane view which is usually perpendicular to the enface view. From the enface view two perpendicular projections are of our interest. One view is 90° from LAO to right anterior oblique (RAO), whereas another view is obtained from 90° angulation in caudal-cranial direction by maintaining the same LAO angulation.

For antianatomic position the RAO perpendicular annular plane view shows the leaflets in single line **(Figs. 4C, D and 5B)**, whereas for the anatomic position cranial perpendicular annular plane view shows the leaflet in single plane **(Figs. 5D and H)**. The fluoroscopic gantry maximum moves up to 45° cranial angulation. In order to obtain additional gain of 45° (total of 90°) two to three pillows can be used at the head end of the bed to make the patient in semirecumbent position. This identification of right annular plane view is the key to measure the exact excursion of leaflets and for intervention. The right annular plane view for aortic prosthesis will be obtained usually in plain posteroanterior (PA) or with little cranial or caudal tilt **(Figs. 2, 5C and 6)**. The normal in vivo excursion of bileaflet valve is 70° during full opening, although in vitro up to 90° is possible. The opening angle range depends on the pressure gradient between the chambers at the beginning of systole or diastole for aortic prosthesis and mitral prosthesis respectively, the angle at which the prosthetic valve is implanted compared to the angle between the long axes of two chambers. If the annular plane of the prosthetic valve is right angle to the long axes of two chambers, the leaflet opening will be maximum and symmetrical. If the right angle is decreased during implantation and become more acute angle, asymmetrical opening of leaflets will result with one leaflet opens more and the other may open with little excursion.

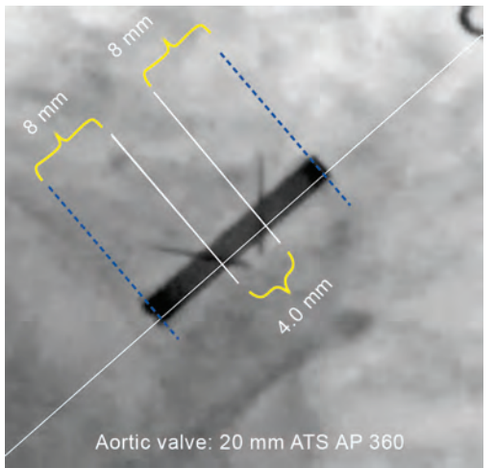
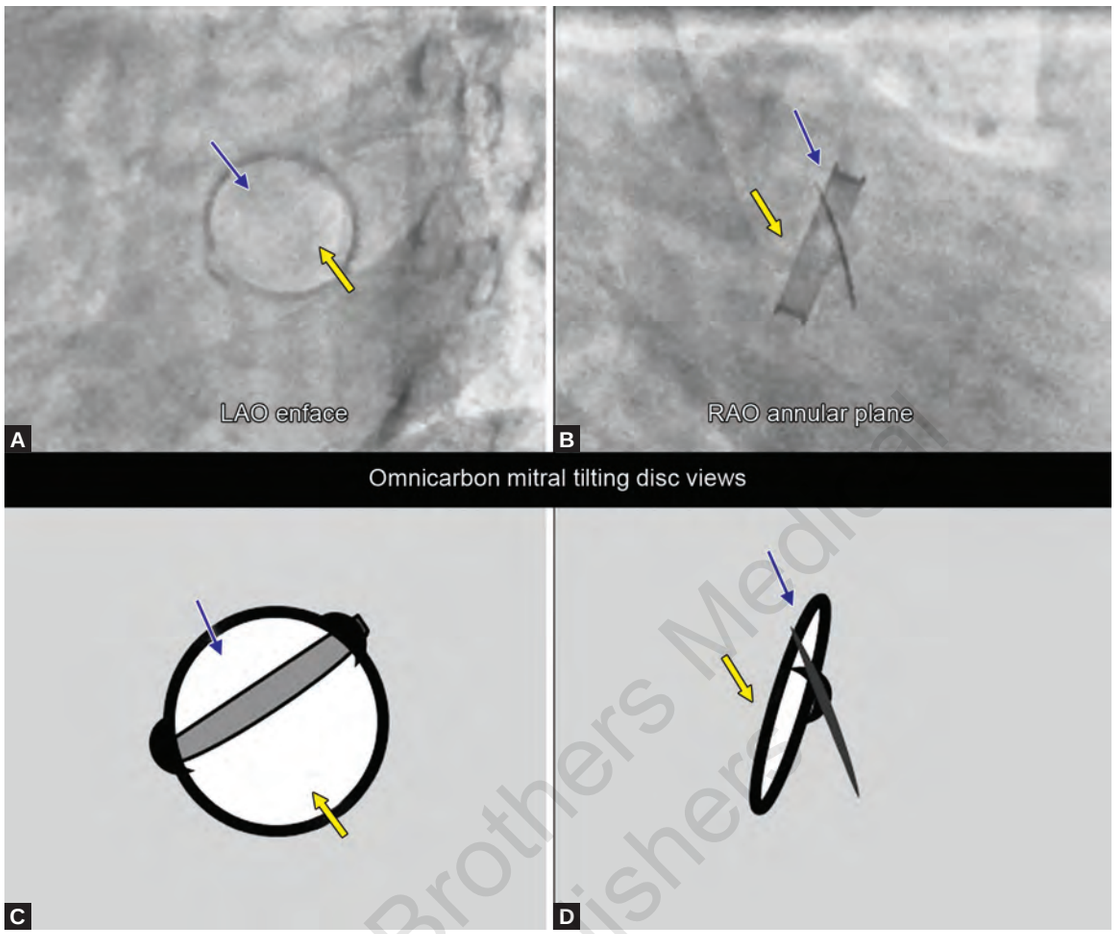


FIG. 6: 20 mm ATS-AP 360 valve in aortic position. Ideal annular plane view in open leaflets position. Quantitative analysis shows 4 mm single central orifice diameter and 8 mm of two lateral orifices diameters.



FIGS. 7A TO D: Omnicarbon tilting disk valve in mitral position. Broad yellow arrows indicate major orifice and blue lean arrows indicate minor orifice. (A) Left anterior oblique (LAO) view shows the enface view of the valve. (B) Right anterior oblique (RAO) annular plane view shows the full excursion of leaflet in a single line. (C) Cartoon representation of panel-A. Imaginary nonvisible leaflet shown in enface view. (D) Cartoon representation of panel-B.

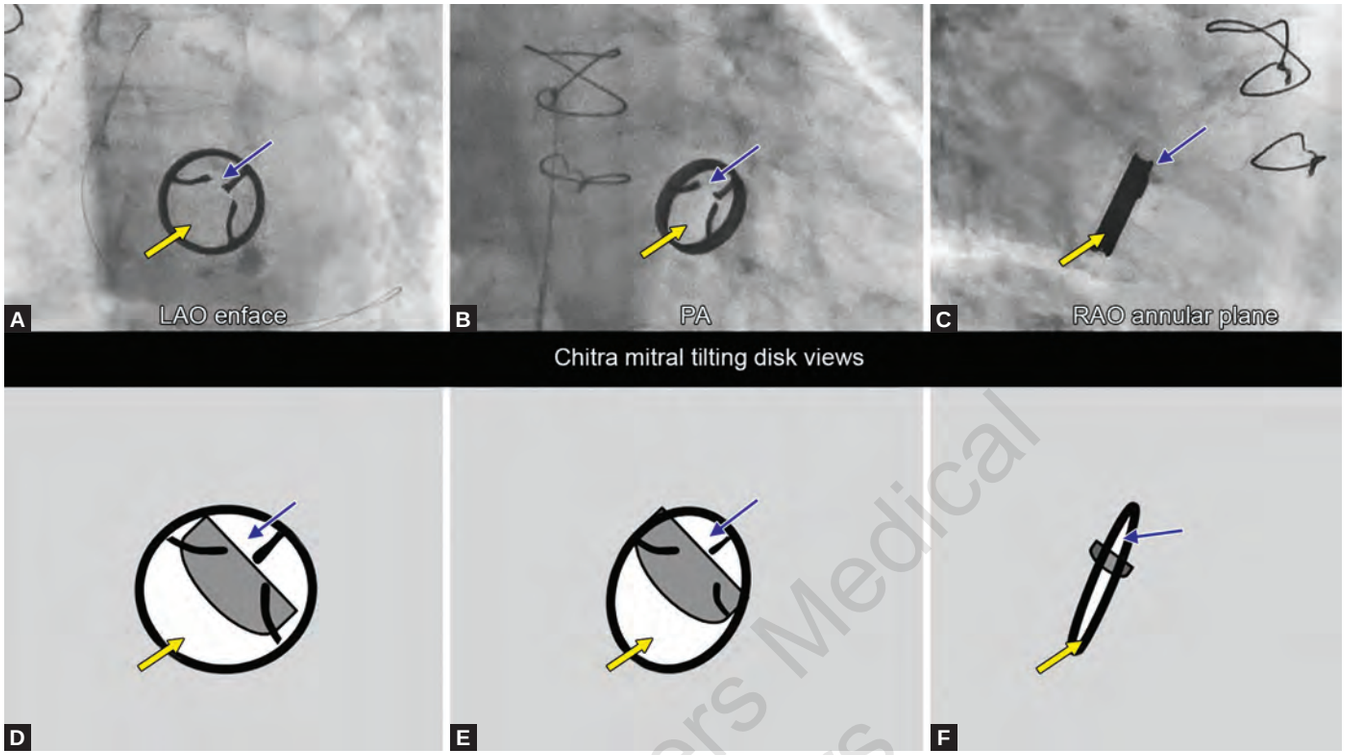
Figures 7A to D demonstrates the minor and major orifices of titling disk valve in enface view and annular plane view. TTK chitra valve is the only mechanical valve with radiolucent leaflets. But, the annular ring is radiopaque. **Figures 8A to F** demonstrate how to identify the major and minor orifices of TTK chitra valve fluoroscopically in enface and annular plane views.

MANAGEMENT OF PROSTHETIC VALVE THROMBOSIS

Emergency Surgery versus Fibrinolytic Therapy

Reoperation by replacing the previous valve with a newer one, either another mechanical valve or a bioprosthetic valve has been the standard of care. But, the mortality rates were reported from 6 to 69% in various scenarios.[10-13] When the PVT patients present in cardiogenic shock the mortality rate may even go further higher with redo surgery. Hence, establishing a more effective strategy is crucial in saving the PVT patients. Thrombolytic therapy recently has become the first-line therapy with good outcomes.[14-17] The European Society of Cardiology (ESC) 2021 guidelines suggest surgery for obstructive PVT as class I recommendation in low risk for surgery patients, whereas thrombolytic therapy is recommended in high risk for surgery population. For patients with nonobstructive thrombosis with <10 mm thrombus size optimization of anticoagulation and follow-up for disappearance of thrombus is recommended. For large nonobstructive thrombus ≥10 mm surgery is the class I recommendation. But patients with large nonobstructive thrombus and high risk for surgery thrombolytic therapy is recommended.

Thrombolytic therapy is considered as class IIa recommendation by the ESC.[18] The choice and regimen of fibrinolytic therapy is as follows. (1) Recombinant tissue plasminogen activator 10 mg bolus followed by 90 mg in 90 min with unfractionated heparin. (2) Streptokinase 150,00,000 units units in 60 min without unfractionated heparin.[11] The use of fibrinolytic therapy is generally discouraged in nonobstructive thrombus because of the increased risk of bleeding and embolization. The TROIA trial showed that slow infusion



FIGS. 8A TO F: TTK chitra tilting disk valve in mitral position. Only the annulus ring is visible. Leaflets are radiolucent. Broad yellow arrows indicate major orifice and blue lean arrows indicate minor orifice. (A) Left anterior oblique (LAO) view shows the enface view of the valve. Note the three hinges on which the disk is mounted are visible. (B) Posteroanterior (PA) view shows the transition of major and minor orifices between enface and annular plane views. (C) Right anterior oblique (RAO) annular plane view did not show the leaflet as it is radiolucent. (D) Cartoon representation of panel-A. Imaginary nonvisible leaflet shown in enface view. (E) Cartoon representation of panel-B. Imaginary nonvisible leaflet shown in PA view. (F) Cartoon representation of panel-C. Imaginary nonvisible leaflet shown in RAO annular plane view.

regimen of 25 mg t-PA without a bolus over 6 hours, repeat once 24 hours later up to six times if needed with the maximum total dose of 150 mg, results in superior success rate of >80% with lower complications and mortality.[15]

The American College of Cardiology (ACC)/the American Heart Association (AHA) 2020 guidelines suggest class I recommendation for both fibrinolytic therapy or emergency surgery for obstructive PVT.[19] But, the thrombolytic regimen recommended by the ACC/AHA was slow infusion of 25 mg t-PA without a bolus over 25 hours. Thrombolytic therapy was repeated up to eight times (maximum total dose of 200 mg) with TTE/TEE guidance. With this regimen success rate was >90%, embolic event rates <2%, and major bleeding rates <2%.[20]

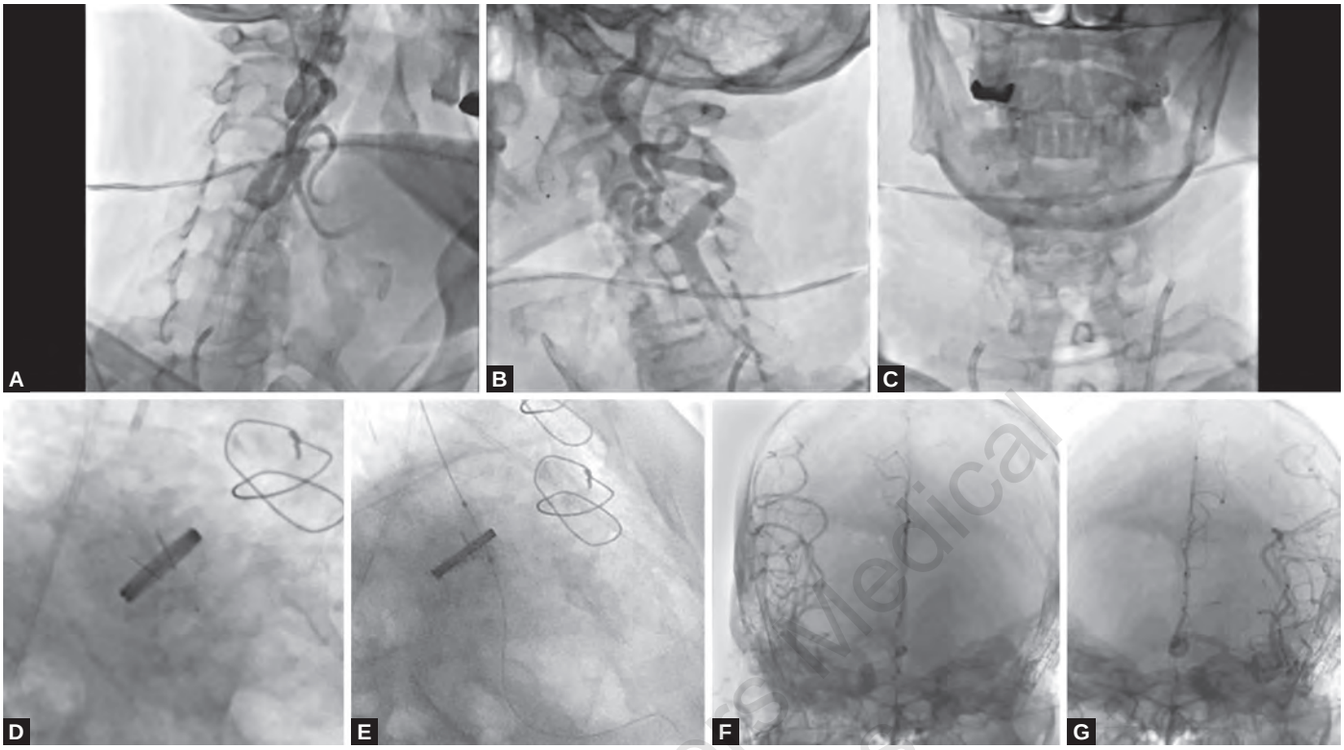
Transcatheter Management of Mechanical Valve Obstruction

Need for Alternative Therapy

Most common two reasons of mechanical valve obstruction are PVT or pannus ingrowth. The ultra-slow PROMETEE trial recently has given encouraging results of ultra-slow infusion fibrinolytic therapy for PVT. The exclusion criteria of this study consist of contraindication to thrombolytic treatment, nonobstructive thrombus with <10 mm thrombus diameter and PVT with ischemic stroke <3 weeks. But in reality, these population consists of significant proportions of PVT patients, where the option is only high-risk redo surgery. The criteria for complete success in this study was reduction in thrombus major diameter by ≥75%, clinical improvement and Doppler resolution of increased gradient or decreased valve area. But, how much resolution of gradients was not defined in the protocol of the study. Hence, >90% success rate as per the definition of the study based on the above-mentioned criteria may not be the ideal outcome which we expect. No follow-up data available for recurrence of PVT in those successful cases. Fluoroscopic documentation of opening and closing angle was not performed which must be one of the most important endpoints of any PVT study. Hence, a newer alternative therapy should be applicable in majority of population without much exclusion criteria, more robust in terms of success rate, less complications, and good long-term outcome.

Transcatheter Release of Stuck Prosthetic Valve

Transcatheter release of stuck leaflets due to PVT or pannus by balloon dilatation with cerebral embolic protection is the upcoming and promising alternative therapy. The technical details of the procedure has been elaborated recently by Kalidoss et al.[21] Just before the procedure Doppler study of both common carotid arteries, internal carotid arteries (ICA) and external carotid arteries were analyzed for atherosclerosis, tortuosity, and feasibility of carotid filter deployment and to choose the ideal filter size. Tortuous ICA may be really



FIGS. 9A TO G: (A) Tortuous right internal carotid artery. (B) Tortuous left internal carotid artery. A 6-mm carotid filter in right internal carotid artery is seen. (C) Both internal carotid arteries show deployed 6 mm carotid filters. (D) A 5 mm x 20 mm coronary balloon dilatation up to 14 atm in the central orifice of bileaflet aortic mechanical valve. (E) A 9 mm x 18 mm peripheral balloon dilatation in the lateral orifice of a bileaflet aortic mechanical valve. (F) Right cerebral angiogram shows patent right middle cerebral and anterior cerebral arteries after removal of the filter. (G) Left cerebral angiogram shows patent left middle cerebral and anterior cerebral arteries after removal of the filter.

challenging to deploy and retrieve the carotid filters **(Figs. 9A to C)**.

Since stroke is the major complication of PVT, cerebral embolic protection is of the utmost important. Doppler study of both vertebral arteries, upper limb, lower limb arterial systems, celiac, renal, and superior mesenteric systems is must to document baseline velocity of blood flow. So that either during or after the procedure it would be easy to rule out clinically significant systemic embolism.

The procedure will be done under local anesthesia except in the New York Heart Association (NYHA) class IV patients, where general anesthesia and mechanical ventilation are required. Two 6-F common femoral artery (CFA) accesses are needed for 5- to 6-mm carotid filters in each ICA **(Fig. 9C)**. Both accesses can be taken on single side with ultrasonogram guidance or for mitral cases it can be taken bilaterally (right CFA for right ICA and left CFA for left ICA). Since the mitral intervention is done through transvenous transseptal access, right common femoral vein (CFV) is the main interventional access. Whereas for aortic intervention, we need arterial access for intervention hence either both ICA filters could be deployed through left CFA via two separate 6-F access or both CFA accesses can be used for cerebral protection and right radial artery (RRA) access can be used for intervention. But 6/7 slender glide sheath is required via RRA. 7F access is must since lateral orifices accommodate 8- or 9-mm peripheral balloons **(Fig. 9E)**.

During the mitral intervention transseptal access is taken from right CFV and an 8.5-F agilis steerable sheath (Abbott, St Jude Medical, Saint Paul, MN) is placed in the left atrium. A 7F JR guide catheter is introduced inside the agilis sheath and the curve of the JR tip is kept perpendicular to the steerable curve, so that three-dimensional (3D) maneuverability is possible. This 3D maneuverability is important to precisely direct a 0.014 coronary wire into the required orifice. During stuck valve, the central orifice may be as small as 1–2 mm. Once the coronary wire is placed across the required orifice (central or one of the lateral orifices for bileaflet valves/minor or major orifices of the tilting disk valves), based on the quantitative measurement of the orifices from fluoroscopic views the balloon size is chosen **(Figs. 6 and 10)**.

Central orifice of bileaflet valve or minor orifice of tilting disk valve usually requires 4.5 mm or 5.0 mm coronary balloons, whereas lateral orifice of bileaflet valve or major orifice of tilting disk valve requires 8–9 mm peripheral balloons **(**see **Figs. 9D and E)**. After the balloon dilatation, the thrombus disintegrates and stuck leaflets start functioning normally. During the balloon dilatation through the central orifice of bileaflet valve, systolic equalization of aortic and left atrial pressure was observed along with 90° opening of both leaflets **(Figs. 11A and B)**.

Postprocedure Doppler study of the previously assessed arterial systems before the procedure is done to rule out clinically significant systemic embolism. If visceral or

peripheral embolism is identified, transcatheter removal of embolism or Fogarty balloon embolectomy of upper or lower limbs are done **(Figs. 12A, C, and F)**. Cerebral embolism should be ruled out after ICA filter retrieval on both sides by doing cerebral angiogram **(**see **Figs. 9F and G)**. If cerebral embolism is documented immediate transcatheter embolectomy could be performed. Coronary embolism can be ruled out by absence of ECG changes or by obtaining coronary angiogram at the end of the procedure. **Figure 12** shows the embolized thrombus caught by the carotid filters **(Figs. 12B, D, and E)**. Without cerebral protection patient could have developed major stroke.

The authors of this chapter reported a case series of transcatheter release of stuck leaflets with short-term outcomes.[21] Data and technique of this therapy is evolving, although presently few concerns and limitations are existing.

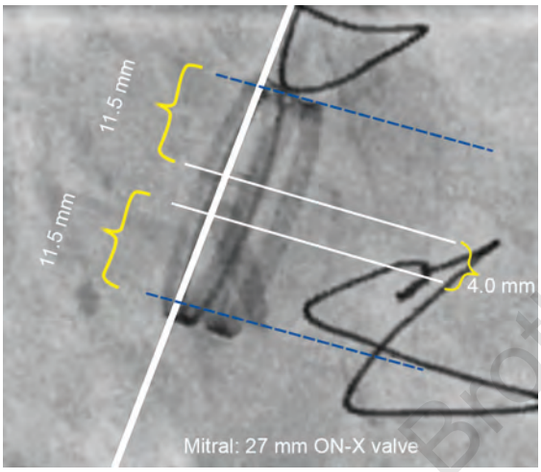


FIG. 10: A 27-mm On-X® valve at mitral position. Ideal annular plane view shows open superior leaflet and stuck inferior leaflet in diastole. Quantitative analysis shows 4 mm single central orifice diameter and 11.5 mm of two lateral orifices diameters.

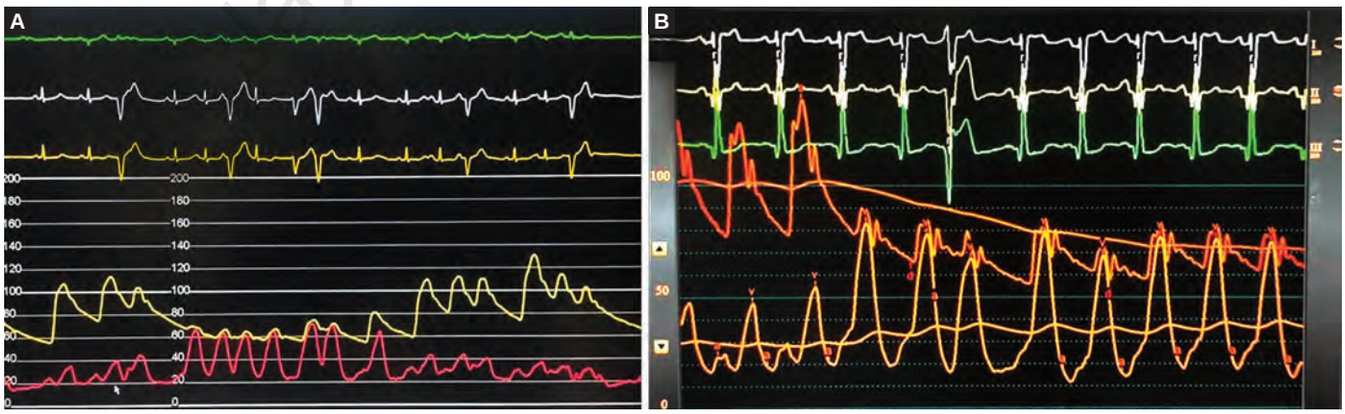
PREVENTION OF PROSTHETIC VALVE THROMBOSIS

Atrial fibrillation, left ventricular ejection fraction <35%, mitral or tricuspid valve replacement, previous thromboembolism and mitral stenosis of any degree are considered as risk factors for PVT. The ideal INR value depends on the risk factors. Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St Jude Medical and Sorin Bicarbon valves are considered as low thrombogenic valves and the target INR is 2.5. Other bileaflet valves are considered as medium thrombogenic in nature and the recommended target INR is 3.0. Lillehei–Kaster, Omniscience, Starr–Edwards ball-cage, Björk–Shiley and other tilting disk valves are considered highly thrombogenic, hence target INR should be kept at 3.5. If one or more risk factors of PVT are present then 0.5 more than the recommended INR value to be maintained in all categories.[18]

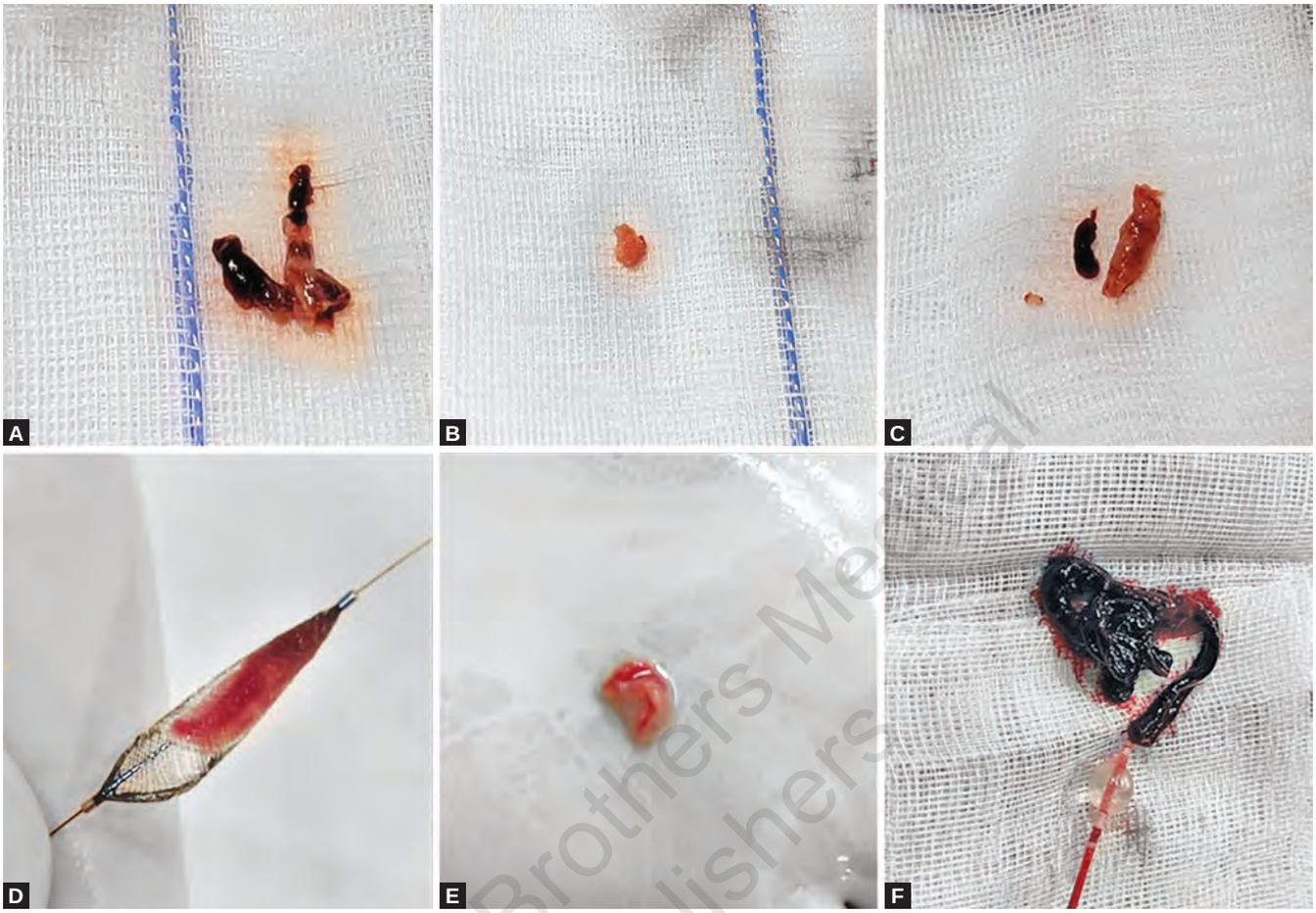
Dedicated valve clinics, patient education, social media group formation among prosthetic valve patients, and regular electronic notification to patients from healthcare workers, improvising the quality of peripheral laboratories that measure INR, are some of the ways to maintain the recommended anticoagulation level steadily.

CONCLUSION

Prosthetic valve malfunction is an important clinical emergency. Acute obstructive prosthetic valve thrombosis can be treated with emergency fibrinolysis or surgery, whichever is quickly and easily available. Nonobstructive thrombus requires proper anticoagulation protocol. Chronic obstructions are usually dealt with surgery. In future catheter interventions may help in selected cases.



FIGS. 11A AND B: Hemodynamics during balloon dilatation across the central orifice of bileaflet mitral valve. (A) Frequent coronary wire induced premature ventricular contractions noted in electrocardiogram (ECG). Systolic equalization of aortic and left atrial pressures was documented during balloon dilatation. Improvement of aortic systolic pressure after the release is shown. (B) Ventricularization of the left atrial V waves during balloon dilatation indicates free mitral regurgitation via the completely open lateral orifices during balloon dilatation.



FIGS. 12A TO F: Embolized thrombus and pannus during fibrinolysis and transcatheter release. (A) Thrombus retrieved via fogarty balloon from right superficial femoral artery after fibrinolytic therapy. (B) Fibrous pannus bit captured by the internal carotid filter after transcatheter release of stuck valve. (C) Thrombus retrieved via fogarty balloon from left popliteal artery after fibrinolytic therapy. (D) Thrombus captured by the internal carotid artery filter after transcatheter release of mitral stuck valve. (E) Pannus bit captured by the internal carotid artery filter after transcatheter release of mitral stuck valve. (F) Thrombus retrieved via fogarty balloon from left common iliac artery after fibrinolytic therapy.

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CHAPTER 16

Atypical Infective Endocarditis: Challenges of Appropriate Antibiotic Strategies

Vasant Nagvekar, Shalmali Inamdar

ABSTRACT

Typical organisms causing endocarditis are *Streptococcus viridans, Staphylococcus aureus, Enterococcus faecalis*, and coagulate negative *Staphylococcus*. Other organisms, that also cause endocarditis but are not a common pathogen, are HACEK group of organisms, *Pseudomonas aeruginosa, Klebsiella, Burkholderia capaciae, Burkholderia pseudomallei, Corynebacterium diphtheriae*, non-tuberculous mycobacteria and brucellosis. These organisms are usually slow growing and cause varied presentations which are different from typical presentations of infective endocarditis (IE). Therefore, IE occurring secondary to these organisms would be classified as atypical IE. The term *atypical IE* can be extrapolated as atypical clinical presentation of a case of IE or also can be understood as atypical organisms causing IE. Atypical presentations are more available in literature as case reports.

INTRODUCTION

Infective endocarditis (IE) carries a high risk of morbidity and mortality. Rapid diagnosis, effective treatment, and prompt recognition of complications are essential to good patient outcome. Therapy of IE caused by the more commonly encountered organisms including streptococci, enterococci, staphylococci, and the HACEK organisms [*Haemophilus parainfluenzae, Haemophilus aphrophilus, Actinobacillus (Haemophilus) actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species, and *Kingella* species].

As IE varies in clinical presentation, a strategy for diagnosis is needed, which is sensitive for detection of disease as well as specific for its exclusion for all types of the disease.[1]

The term *atypical IE* can be extrapolated as atypical clinical presentation of a case of IE or also can be understood as atypical organisms causing IE.

OVERVIEW

Among patients with classic Oslerian manifestations such as fungemia or bacteremia, peripheral emboli, evidence of active valvulitis, and immunologic vascular phenomena, the diagnosis of IE is simple and clear. However, among some patients, there are few or lack of classic peripheral stigmata.[2]

There is an important role of echocardiography in the diagnosis and management of IE. Along with other clinical parameters, new regurgitation, abscesses, characteristic vegetations, or new prosthetic-valve dehiscence are considered to be four potential identifiers of IE. Transthoracic echocardiography (TTE) is a technique that can be performed rapidly, and with noninvasive nature, and comprises excellent specificity for vegetations (98%).[3] However, the overall sensitivity for vegetations is reported to be <60%.

One of the significant major diagnostic criteria for IE is positive blood culture, which is important for recognizing the causative agent as well as its antimicrobial susceptibility. The typical characteristics of this infection include continuous bacteremia and increase in presence of positive blood cultures.

It is difficult to perform isolation of some IE pathogens from blood cultures. Prolonged incubation as well as subcultures is needed for recovering the HACEK organisms.

Approximately 5–7% of the cases of streptococcal IE are caused due to the nutritionally variant streptococci, which are presently classified to be *Abiotrophia* species. On subculturing the blood cultures onto standard blood agar media, frequent failure of growth occurs in these strains.

Till now, *Coxiella burnetii* (which is the agent of Q fever) cannot be recovered from blood cultures until recently and is recognized through serological tests. High titers of antibody

directed against the phase I antigen (IgG titers >1:400 by complement fixation or ≥1:800 by microimmunofluorescence, or IgA titer ≥1:100) in blood culture–negative patients with echocardiographic evidence of IE is diagnostic in Q-fever IE. The presumptive diagnosis of *Brucella, Bartonella*, or chlamydial endocarditis can also be made serologically.

Due to prolonged central catheters, Permacath, Ports, Hickman's catheters, peripherally inserted central catheters (PICCs) lines, nosocomial endocarditis due to multidrug-resistant (MDR) Enterobacteriaceae, *Pseudomonas*, *Acinetobacter* and nonfermenters such as *Burkholderia cepacia* which have varied susceptibility and limited options for treatment. Infact there are no guidelines specific for MDR pathogens and except a few case reports and all are experimental treatments with high mortality.

RARE OR ATYPICAL ORGANISMS CAUSING INFECTIVE ENDOCARDITIS

Infective endocarditis due to atypical (not the common organisms causing endocarditis) organism is on the rise and are predominantly hospital acquired due to devices or poor infection control practices.

Nowadays due to Permacath, Hickman's catheter, Chemoports, etc., MDR gram-negative bacilli (GNB) are on the rise. Also individuals treated with dialysis are at high risk for healthcare-associated infections. For dialysis patients, water and dialysate have been the source of healthcare-associated pathogens, including nontuberculous mycobacteria (NTM) and GNB as well as systemic reactions due to GNB–associated endotoxin. Common being MDR GNB, NTMs, and other water carried pathogens such as *Ralstonia, B. cepacia* and candida species as all these devices remain for months and at times to 1 or 2 years predisposing them to endocarditis due to the biofilm formation. It is important for healthcare personnel to adhere to infection prevention guidelines in hemodialysis patient care, especially hand hygiene, aseptic technique, cleaning/disinfection, and water management. Also chemoports handling and PICC with strict aseptic precautions are important, failure of it causes bacteremia or candidemia or at times endocarditis.

Pandrug-resistant (PDR) *K. pneumoniae* refractory to conventional treatment has been reported worldwide, causing a huge burden on the healthcare system, patient safety and the economy. *K. pneumoniae* is a prominent opportunistic pathogen causing hospital-acquired and community acquired infections, but is rarely associated with IE. Currently, there are sparse data guiding the optimal regimen when commonly used antibiotics fail, notably for the treatment of endocarditis infections.[4]

Burkholderia cepacia rarely causes endocarditis in community settings, but it is known to cause IE particularly in intravenous heroin users, and in patients with prosthetic valve replacement. However, IE caused by *B. cepacia* in patients without predisposing factors is rare.[5]

Treatment of some or majority is challenging due to the resistance, poor choice of antibiotics and poor penetration of some of these only available antibiotics for those particular organisms, e.g., if we have *Elizabethkingia* endocarditis only susceptible to Minocycline becomes a challenge and so *Candida auris* which is a MDR *Candida* with limited antifungals available. All these prolonged device-related who develop endocarditis are either immunocompromised or sick patients where surgery also may not be an alternative and neither adequate antimicrobials available.

Few examples:

1. *Klebsiella*: *Klebsiella pneumoniae* complex encompasses the group of organisms which includes *K. pneumoniae* and *K. variicola*.

Pathogen detected and in vitro susceptibility reported, specific/directed therapy—specific therapy based on the pattern of in vitro susceptibility which can provide hints as to the mechanism(s) of antibiotic resistance.

For sensitive strains: Ceftriaxone IV 2 g × 12 hourly + IV Tobramycin 1.5–2.0 mg/kg 8 hourly

Cefepime 2 g IV × 12 hourly + IV Tobramycin 1.5–2.0 mg/kg 8 hourly

For extended-spectrum beta-lactamase (ESBL) strains: Class A beta-lactamases—narrow spectrum penicillinases and ESBLs and serine carbapenemases (KPCs, *K. pneumoniae carbapenemases*) that hydrolyze selected advanced generation cephalosporins and carbapenems, respectively.[6]

Confer resistance to advanced generation cephalosporins (e.g., ceftriaxone, ceftazidime, cefepime) and aztreonam (AZT).

- Meropenem IV 1–2 g × 8 hourly + IV Tobramycin 1.5–2.0 mg/kg 8 hourly
- Piperacillin + Tazobactam 4.5 g 6 hourly + IV Tobramycin 1.5–2.0 mg/kg 8 hourly.

Adding an aminoglycoside is important when it comes to management of gram negative endocarditis.

For carbapenem resistant (CR) strains: Important is to know the mechanism of resistance and the sensitivity.

- *Serine carbapenemases*: Confer resistance to all beta-lactams
- *Class B*: Metallo-beta-lactamases, zinc metalloenzymes, e.g., New Delhi metallo, Verona integron–encoded metallo-β-lactamase 1 (VIM-1), IMP-1
    - Hydrolyze all penicillins, cephalosporins, and carbapenems, but not AZT.
        - However, since most metallo-beta-lactamase producing strains also produce ESBLs, AZT, which is inactivated by ESBLs, is not active against the vast majority of these strains. AZT in combination with ceftazidime-avibactam (CZA) may be active because the avibactam inactivates the ESBL and other serine carbapenemases, and thereby protecting the antibacterial activity of the AZT.[7]

About 30–40% of CR *Klebsiella* have OXA 48 as the mechanism of resistance and another 40–50% will have OXA 48 + NDM as mechanism of resistance and the rest 10% would have variable apart from carbapenemeses enzymes causing resistance. It is important to know as we can use a carbapenem sparer drug for its treatment.[8]

OXA-48:

- *OXA-48 and OXA-48-like*:
    - Hydrolyze penicillins efficiently, carbapenems slowly, and extended cephalosporins poorly
    - OXA-48 and some others are inactivated by avibactam (e.g., CZA)

- In contrast vaborbactam and relebactam are poor inhibitors of OXA-48 and other OXA enzymes and meropenem-vaborbactam and imipenem-relebactam have unreliable activity.[7,9]

Ceftazidime-avibactam 2.5 g 8 hourly + IV Tobramycin 1.5–2.0 mg/kg 8 hourly *or* IV Gentamicin 3–5 mg/kg/day

- *OXA-48+NDM*:

Option 1: CZA 2.5 h 8 hourly + IV AZT 2 g 8 hourly (ideally AZT Avibactam, but not available in India as of now) + IV Tobramycin 1.5–2.0 mg/kg 8 hourly or IV Gentamicin 3–5 mg/kg/day.[10,11]

OR

Option 2: IV Colistin/Polymyxin B with combination of high dose Meropenem 1–2 g 8 hourly.[12]

Choice of carbapenems would depend on the lowest MICs of the carbapenem.

Polymyxin B and polymyxin E (Colistin) are parenteral antibiotics in the polymyxin class. Their spectrum of activity and toxic potentials are similar. However, their pharmacology is dramatically different. Polymyxin B is administered as an active sulfate salt; it is not excreted by the kidneys. Hence, polymyxin B should be avoided in the treatment of urinary tract infections (UTIs). Polymyxin E is administered as a prodrug; the active drug formed in vivo is excreted in the urine.

As with Colistin, Polymyxin B has a "detergent effect" on the cell membrane that allows restoration of antibacterial activity of drugs considered resistant as monotherapy. *Acinetobacter, Pseudomonas,* or *E. coli,* or *Klebsiella* isolates may be resistant to carbapenems in vitro due to carbapenemase activity. When concomitantly exposed to a polymyxin, the cell permeability increases dramatically so as to allow rapid penetration of the carbapenem to its antibacterial target before the carbapenem is rendered inactive by the carbapenemase.

Colistin: Colistin base activity [CBA 1 mg = 2.4 mg of CMS (Colistimethate) = 30,000 IU CMS]

Loading dose of CBA (mg) = Colistin targeted average steady state serum concentration (Css), average target (mg/L) Å (2) × 2.0 × ideal body weight (kg)

To achieve a Css, average of 2 mg/L in a patient with an ideal body weight of 60 kg, the loading dose would be 240 mg.

CBA (240 × 300,000 = 7.2 million IU), the suggested maximum loading dose. The first regular daily dose should be administered 12 h later.

Dosage adjustment requires to be done for patients with deranged creatinine.[13]

For only Polymyxin susceptible: Colistin 30,000 × 2 × weight. IU + Meropenem 2 g over 3 h × 8 hourly (for better pharmacokinetics and pharmacodynamics).

Polymyxin B: Dosing is based on actual body weight. Loading dose: 25,000 IU/kg as a 2 h IV infusion.

Maintenance dose: Then 12 h later start 15,000 IU/kg as a 1-hour IV infusion. Repeat q12h. There is no need to reduce the dose for impaired renal function.

Option 3: If the strain is sensitive to Fosfomycin then colistin plus Fosfomycin.

Colistin same dose as above plus Fosfomycin 4 g 8 to 6 hourly.

- *Fosfomycin*: It is a low molecular weight (138) phosphonic acid derivative available for over 20 years.
- The IV preparation is Fosfomycin disodium.
- *Unique mechanism of action*: Inhibition of the synthesis of cell wall peptidoglycan, a key constituent of both gram-positive and gram-negative bacteria. Considered bactericidal with time-dependent killing.
  - In vitro activity includes ESBL-producing and some CR Enterobacteriaceae:[14,15]

2. *E. Coli*: Treatment for ESBL *E. coli* and CR *E. coli*, would be on same grounds as *Klebsiella*, unlike CR *Klebsiella*, CR *E. coli* may or may not be susceptible to CZA plus CZA plus AZT. In vitro susceptibility has to be demonstrated.

3. *Pseudomonas*: It is a nonfermenter and has varied mechanisms of resistance unlike the Enterobacteriaceae group.

- *P. aeruginosa* has a wide variety of antibacterial resistance mechanisms which may occur in combination including:
  - Beta-lactamase mediated
    - AmpC (most common) due to production and/or overexpression of chromosomal AmpC which hydrolyses penicillins, monobactams, cephalosporins (with possible exception of cefepime), and not inhibited by tazobactam
    - Extended-spectrum beta-lactamases (less common), which hydrolyze antipseudomonal cephalosporins (e.g., Cefepime, Ceftazidime)
    - Production of serine carbapenemases is rare but metallo-beta-lactamases may be present
  - Mutation of drug target, e.g., fluoroquinoline resistance due to selection of gyrase mutants
  - Permeability mutants due to multidrug efflux pumps and/or loss of outer membrane porins.
- Susceptibility results available with no in vitro resistance detected
- Piperacillin-tazobactam 4.5 g IV loading dose over 30 minutes, then 4 hours later, start 4.5 g IV over 4 hours and then repeat q8h over 4 hours
- Ceftazidime 2 g IVq8h
- Cefepime 2 g IV q12h if BMI ≥ 30, 2 g IVq8h
- Meropenem 1–2 g IVq8h
- AZT 2 g IV q6h
- Consider use of higher dose of Meropenem infused over 3 hours every 8h for more serious infections or for strains with MICs near the breakpoint.
- ESBL
- Meropenem 1–2 g IVq8h
- Ceftolozane-tazobactam 3 g IV over 1 h q8h (not available in India)
- Piperacillin-tazobactam 4.5 g IV loading dose over 30 minutes, then, 4 hours later, start 4.5 g IV over 4 hours and then repeat q8h over 4 hours
- All the above to be combined with Gentamicin 3–5 mg/kg per day or Tobramycin 1.5–2.0 mg/kg/day.
- *Carbapenem-resistant*:
- Colistin plus a carbapenem—most commonly used is meropenem as treatment of *Klebsiella* given earlier.

- CZA 2.5 g IV over 3 hours q8h *or* [due to Verona Integron-Mediated Metallo-β-lactamase (VIM) production does not work in India]
- Meropenem-vaborbactam 4 g IV over 3 hours q8h *or* (so far not available in India)
- Imipenem-cilastatin-relebactam 1.25 g IV over 30 min q6h (CrCl>90 mL/min) (so far not available in India)

Resistance may be due to efflux or porin mutations specific to carbapenems; check susceptibility to antipseudomonal cephalosporins and piperacillin-tazobactam.[12,16]

4. *Acinetobacter*: Among all GNB, the greatest number and diverse resistance mechanisms are shown by *Acinetobacter* species.

- MDR is shown by nearly >50% of Acinetobacter baumannii isolates. In some regions, a significant percentage of isolates show extensive drug resistance and also pan-drug resistance.
- *Resistance mechanisms comprise, either alone or in combination*:
  - Production of aminoglycoside-modifying enzymes and ESBLs
  - Production of AmpC cephalosporinases (rarely)
  - Presence of efflux pumps
  - Production of metallo-, serine-, as well as OXA-carbapenemases
  - Alteration in drug target binding sites, such as DNA gyrase mutations and penicillin-binding protein sites
  - Mutant porins proteins with successive reduced outer membrane permeability
- In clinical practice, the emphasis is on phenotypic in vitro resistance patterns. It is impossible to determine which mechanism, or combination of mechanisms, is accountable for the laboratory's report of antibiotic resistance outside of a research environment.

5. *Susceptible strains*:

- Meropenem 2 g IV infused over 3 hours and repeat q8h (continuous infusion regimens in clinical trial) or
- Cefepime 2 g IV q8h or
- Ampicillin-sulbactam 9 g (6 g Amp/3 g Sulb) IV over 4 hours and repeat q8h.[17]

MDR strains: Ampicillin-sulbactam 9 g (6 g Amp/3 g Sulb) IV infused over 4 hours and repeat q8h + Meropenem 2 g IV infused over 3 hours and repeat q8h + Polymyxin B 2.5 mg/kg loading dose IV infused over 2 hours then, initiating 12 hours later, 1.5 mg/kg IV infused over 1 hr q12h OR Colistin.[18]

- *Cefiderocol*: Not available In India
- Cefiderocol is a parenteral siderophore cephalosporin FDA-approved for the treatment of adults with:
- The drug should be reserved for use in patients with limited or no alternative treatment options. It is inactive against gram-positive and anaerobic bacteria.
- Active in vitro versus broad range of fermentative and non-fermentative MDR-GNB.
- Cefiderocol functions as a siderophore, chelating ferric ions and taking advantage of the bacterial iron transport system for enhanced accumulation in the bacterial periplasmic space.[19] Adult dose
- 2 g (over 3 hours) IV q8h × 7–14 days.
- *B. cepacia:* This organism has gained importance with right sided endocarditis due to permacaths and prolonged dialysis catheters as the vehicle is water. Multiple mechanisms of antibiotic resistance, variably expressed, complicating recommendations for empiric therapy and resulting in limited treatment options. Optimal therapy unknown, susceptibility highly variable; antimicrobial therapy should be selected based on results of in vitro susceptibility testing.
- Minocycline 200 mg IV loading dose and then 100 mg IV/PO BID
- Meropenem 2 g IV q8h
- Ceftazidime 2 g IV q8h
- CZA 2.5 g 8 hourly (in vitro data indicate activity of CZA against MDR strains, including those resistant to Ceftazidime).
- *B. cepacia* is usually resistant to aminoglycosides and intrinsically resistant to Colistin and Polymyxin B.[20,21]

CULTURE NEGATIVE ENDOCARDITIS

Potential reasons for negative blood cultures:

1. Culture(s) obtained after initiation of empiric antimicrobial therapy
2. Blood cultures not incubated long enough to detect slow-growing bacteria, e.g., HACEK bacteria
3. Etiologic pathogen requires nonculture method(s) for detection:
   - Detection of microbial antigen and/or antibody
   - Molecular probes (RT-PCR) of serum and/or infected heart valve or other pertinent biopsy tissue
   - Histopathology with special stains
4. Noninfectious disease entities that mimic the clinical picture of endocarditis, e.g.,
   - Systemic lupus erythematosus that includes Libman–Sacks endocarditis
   - Advanced adenocarcinoma with marantic endocarditis[22]
5. Patients previously treated with antibiotics prior to obtaining blood cultures; these patients likely are infected with more typical organisms causing endocarditis, but suppressed by antibiotics:
   - Staphylococcus aureus (MSSA and MRSA)
   - Coagulase-negative staphylococci (prosthetic valve infection)
   - Viridans group streptococci (including nutritionally-deficient organisms)
   - Enterococci
   - HACEK bacteria
6. Patients infected with rare and fastidious organisms that do not grow well in routine blood culture media (often with associated epidemiological risk factors).
   Bartonella species, *Brucella* species, *Chlamydia* species, *C. burnetii (Q fever)*

- *Fungi*:
  - *Aspergillus* species
  - *Histoplasma* species
  - *Malassezia restricta*

- *Legionella* species
- Non-tuberculous mycobacteria, e.g., *M. chimera*
- *Tropheryma whipplei*

DIAGNOSTIC APPROACH
- *Clarify and expand the history*:
  - Timing of antibiotics and cultures
  - Detailed epidemiology: Risk factors and exposures
- Three sets of blood cultures incubated for 7 days
- *Other diagnostic tests as pertinent to epidemiology*:
  - Serology for *Coxiella, Bartonella, Tropheryma,* and *Brucella*
  - Airway secretions for PCR for *Legionella* and *Coxiella*
  - Other potential diagnostic methods that may be helpful
  - Submit resected valve tissue (or other pertinent tissue biopsies) for:
    - Histopathology
    - Tissue RT-PCR
  - Can do broad range PCR [16S rDNA (bacteria), 18S rDNA (fungi)] on serum and/or tissue
  - Successful diagnosis with metagenomic sequencing reported.[23]

PRIMARY REGIMENS
- Goal is specific therapy tailored for an identified pathogen. Empiric therapy is appropriate in individual patients pending results of blood cultures and other diagnostic tests
  - In patients with acute symptoms and an illness spanning a few days, an empiric combination of Vancomycin + Cefepime is reasonable
  - In patients with subacute symptoms and an illness spanning weeks, empiric therapy may not be necessary.
    - Should individual patient circumstances so dictate, an empiric combination of Vancomycin + Ampicillin-sulbactam is recommended.

Staphylococcus aureus[24]

This organism causing left as well right endocarditis is on rise due to pacemakers, permanent catheters, and intracardiac devices.

Important to note vancomycin inferior when it comes to treatment of MSSA compared to beta-lactams[25]
- *MSSA:*
  - Native valve: (Flucloxacillin or Cloxacillin) 2 g IV q4h × 4–6 weeks
  - Tricuspid valve, uncomplicated: Flucloxacillin or Cloxacillin × 2–4 weeks
  - Prosthetic valve: (Flucloxacillin or Cloxacillin) 2 g IV q4h ≥ 6 weeks + Rifampin 600–900 mg/day PO/IV in 2–3 divided doses ≥ 6 weeks + Gentamicin 1 mg/kg IV q8h × 2 weeks
  - Cefazolin 2 g IV q8h × 4–6 weeks
- *MRSA:*
  - Native valve: Vancomycin 15–20 mg/kg IVq8-12h to achieve preferred target AUC_{24} 400–600 µg/mL × hour (see vancomycin AUC dosing calculator); alternative is trough of 15–20 µg/mL) × 6 weeks
  - Prosthetic valve: Vancomycin 15–20 mg/kg IV q8-12h to achieve preferred target AUC_{24} 400–600 µg/mL × hour (use vancomycin AUC dosing calculator); alternative is trough of 15–20 µg/mL) ≥ 6 weeks + Rifampin 600–900 mg/day PO/IV in 2–3 divided doses ≥ 6 weeks + Gentamicin 1 mg/kg IV q8h × 2 weeks
  - Daptomycin 8–12 mg/kg q24h

ALTERNATIVE REGIMENS
- *MSSA*: Beta-lactam Intolerance
  - Vancomycin 15–20 mg/kg IV q8-12h to achieve preferred target AUC_{24} 400–600 µg/mL × hour (see vancomycin AUC dosing calculator); alternative is trough of 15–20 µg/mL) × 6 weeks (only in setting of major penicillin and cephalosporin allergy)
  - Daptomycin 8–12 mg/kg q24h

ANTIMICROBIAL STEWARDSHIP
- Targeting Vancomycin AUC preferred over trough concentration[26]
- *First-line choices*:
  - Cloxacillin (or other anti-staphylococcal penicillin) or Cefazolin for MSSA (comparable to antistaphylococcal penicillins)
  - Vancomycin or Daptomycin for MRSA[27]
- Daptomycin FDA-approved for right-sided endocarditis and bacteremia; case series suggests that high-dose daptomycin 8–12 mg/kg q24h is efficacious for left-sided endocarditis.[28]

MARANTIC ENDOCARDITIS

The "marantic endocarditis" or nonbacterial thrombotic endocarditis (NBTE) is defined as spectrum of lesions that range from microscopic aggregates of platelets to large vegetations that are present on previously undamaged heart valves (commonly aortic and mitral), when bloodstream bacterial infection is not present. This condition is rarely found and is generally related to hypercoagulable states or advanced malignancies (such as adenocarcinomas). The occurrence of NBTE is also reported to found among individuals with valvular pathology, connective tissue disorders, as well as acute inflammatory diseases, such as burns or septicemia. The vegetations are found superficially and the underlying valvular tissue is completely normal or demonstrates subtle histological evidence of abnormal collagen as well as elastic fibers.

The primary clinical manifestations related to NBTE are caused by systemic emboli instead of valvular dysfunction. About 50% of those having NBTE can have occurrence of systemic emboli that lead to the presenting symptom. The sudden neurological deficit (in the form of localized or diffuse) is considered to be the most common as well as the most destructive clinical presentation of NBTE. There is infrequent presence of cardiac murmurs, and therefore, indicated to be poor sign for NBTE. In the presence of cardiac murmurs, these are located at the left lower sternal border and present as nonspecific soft systolic murmurs. One of the signs for NBTE includes cutaneous manifestations as well as psychotic illness.

None of the pathognomonic signs as well as symptoms confirm the diagnosis of NBTE.

The diagnosis is frequently confused with culture-negative IE. A triad was outlined by Mckay and Wahler, which consisted of:

- A disease process related to NBTE
- Existence of heart murmur
- Presence of multiple systemic emboli

However, high clinical suspicion of NBTE is essential for diagnosis:

- Among those who received treatment for IE and no clinical progression is seen
- Among carcinoma patients in whom there is development of neurological deficit or acute ischemic cerebrovascular stroke, and
- Among those who present with cerebral embolism of unknown etiology.

One of the characteristic features of NBTE is recurrent emboli, which is found among nearly 50% of the patients. It is required to exclude an underlying occult malignancy at the time of evaluation of NBTE patients without clear etiology. The diagnosis of NBTE is far more difficult as compared to IE. The markers of the bloodstream are lacking. There are small, easily friable vegetations that more commonly embolize, and leave only small remnants to be recognized on the valve.

The treatment of NBTE aims at controlling the underlying disease, which are in majority of the cases neoplasia and sepsis. Another aim of management includes treating thromboembolism with or without associated DIC.[29,30]

Nontuberculous mycobacteria: IE due to NTM has been reported in immune compromised individuals with long standing in dwelling catheters. In 2010, Sidi and Sepkowitz reviewed 36 studies with 151 patients having proven RGM (rapidly-growing mycobacteria) bacteremia in cancer patients with long standing in swelling catheters. Therapy is further compromised because of difficulty in isolating the organisms. Sensitivity is required as each organism has variable susceptibility. Combination therapy is recommended and valve replacement is required for those patients unresponsive to initial line of management or presence of prosthetic valve. Usually a macrolide like Clarithromycin plus an Aminoglycoside like Amikacin and Linezolid is preferred.

Infections due to RGM are increasing worldwide, especially in immunocompromised hosts. However, data on the clinical features of patients with RGM bacteremia are limited. Data on the incidence of clinically significant NTM infections from India are scarce as these are frequently underdiagnosed due to either under recognition by clinicians because of the nonspecific nature of their clinical manifestations, and/or the inadequacy of laboratory services. *Mycobacterium abscessus* native tricuspid valve endocarditis in a patient, who had a PICC, has been reported **(Figs. 1A and B)**. Clinicians need to be aware of RGM as a cause of prolonged fever in patients who have chronic indwelling intravenous catheters.[31]

Candida endocarditis: *Candida albicans* or *Candida* non-albicans

- Caspofungin 150 mg/day or Micafungin 150 mg/day or Anidulafungin 200 mg/day

or

- Lipid-based Amphotericin B 3–5 mg/kg/day + Flucytosine 25 mg/kg QID
- Valve replacement strongly recommended whenever possible, particularly in those with prosthetic valve endocarditis.

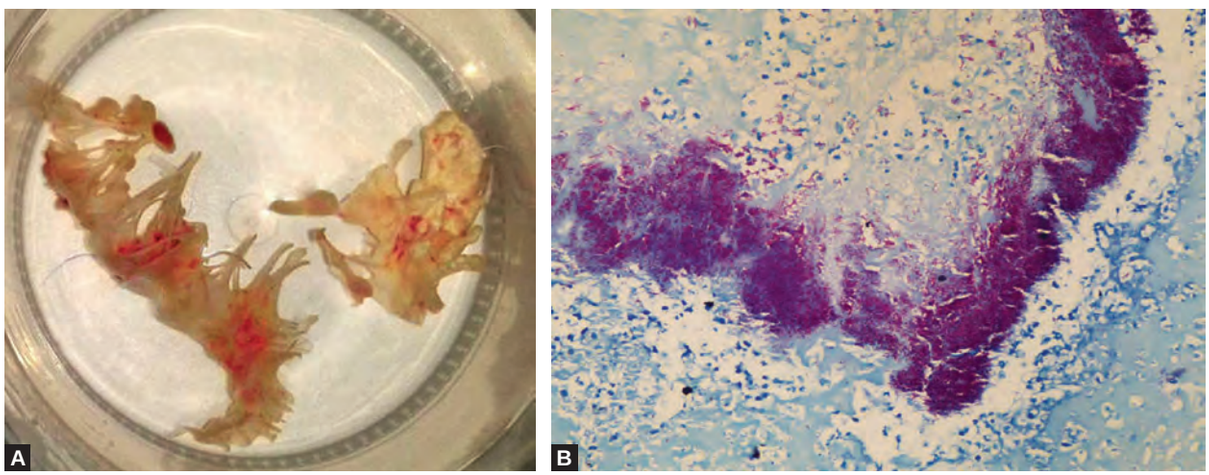
ALTERNATIVE REGIMEN

Fluconazole 400–800 mg PO (in stable patients with negative blood cultures and fluconazole susceptible organism) + (Lipid-based Amphotericin B 3–5 mg/kg/day or an echinocandin)

- One of the above primary or alternative regimens followed by Fluconazole 400–800 mg/day for 6 months.

ANTIMICROBIAL STEWARDSHIP

- *Duration of therapy*:
  - Treat for at least 6 weeks after valve replacement, longer in those with complications (e.g., perivalvular or myocardial abscess, extensive disease, delayed resolution of candidemia).



FIGS. 1A AND B: Tricuspid valve with Ziehl-Neelsen (Z-N) stain showing tricuspid valve full of acid-fast bacilli (AFB)

- Long-term, possibly life-long, suppression with fluconazole 400–800 mg/day for prosthetic valve endocarditis if no valve replacement[32]
- Multidrug-resistant *C. auris* has emerged as a cause of insidious hospital outbreaks and complicated infections. Prolonged hospitalizations, invasive devices, dialysis, long-term catheters, ports, malignancies, immune compromised states and multiple antibiotic usages are risk factors for the development of *C. auris* infections. Issues with management occur due to poor susceptibility of many antifungal to *C. auris*. Echinocandins, which usually exhibit good susceptibility against *C. auris*, have very poor penetration in the heart. Hence combination with amphotericin B with high dose of echinocandins is recommended. Even with this the outcome is poor and surgery is usually recommended.[33,34]

CONCLUSION

Due to difficulty in culturing rare organisms causing IE and lack of proper guidance, diagnosing and managing such cases remain a major challenge in clinical practice. Due to prolonged central catheters, Permacaths, Ports, Hickman's catheters, PICC lines, nosocomial endocarditis due to MDR Enterobacteriaceae, *Pseudomonas, Acinetobacter*, and nonfermenters like *B. cepacia* which have varied susceptibility and limited options for treatment. Infact there are no guidelines specific for MDR pathogens and except a few case reports and all are experimental treatments with high mortality.

Treatment is experimental as there are not adequate studies on penetration in the valves and vegetations of the reserve drugs.

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CHAPTER 17

Clinical Assessment of the Severity of Valvular Heart Disease and Pitfalls

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ABSTRACT

The burden of rheumatic and degenerative valvular diseases is high in Southeast Asian countries. Despite the technological advancements in imaging and easy availability of bedside modalities such as echocardiograms, a diligent physical examination of the patient is irreplaceable. It gives the first clue to the possible valvular lesion, its severity, and any hemodynamic compromise. All these factors have bearings in time referral and planning the management. The objective of this chapter is to discuss the systematic examination of valvular heart diseases and the assessment of their severity. The cardinal findings of each valvular lesion and differentials for murmurs in various areas have been discussed. Dynamic auscultation is also discussed to differentiate various valvular lesions.

INTRODUCTION

In the current era of technology and easy availability of hand-held ultrasound and echocardiograms, physical examination has taken the back seat. However, a detailed physical examination provides a clue to the presence of a valvular lesion and an assessment of its severity. In this chapter, we have discussed the clinical assessment of various valvular lesions. One has to progress methodically from general physical examination; evaluation of jugular venous pulse (JVP), carotid and radial pulse; inspection, palpation, percussion, and auscultation of the chest. One must not forget the percussion and auscultation of the lung fields.

AORTIC VALVE DISEASE

Aortic Stenosis

The common cause of aortic stenosis (AS) includes a degenerative calcific valve (65%), bicuspid aortic valve disease (35%), and rheumatic heart disease (RHD) (1.1%). Isolated AS is more common in males, having a ratio of 1.7:1.[1] The incidence of degenerative calcific AS peaks in the seventh decade, while bicuspid aortic valve and rheumatic valve are more common at a younger age. With an increasingly aging population, the incidence of AS would increase. In a systematic review by Stanger et al.,[2] the sensitivity and specificity of ultrasound in identifying AS ranged from 62 to 94% and 85 to 98%, respectively, and these ranges were similar to auscultation.[2]

The presence of reduced volume and slow up-stroking carotid pulse, ejection systolic murmur in right second intercostal space (ICS), and absent second heart sound (S2) could diagnose AS. The ejection systolic murmur radiates to the carotid arteries and the absence of it makes AS highly unlikely. A carotid pulse consists of a rapid upstroke and a smooth gradual downstroke which is interrupted briefly at the pulse peak. Patients with significant AS (i.e., >75% stenosis of the aortic valve) produce a slow rising "tardus" and low volume "parvus" carotid pulse.[3] This wave has a delayed systolic peak. However, the pulse pressure may increase in patients with increased vascular stiffness (e.g., elderly) and hyperkinetic states and does not effectively rule out AS.

In isolated AS, palpation reveals an accentuated precordial thrust which is located in the fifth ICS at the midclavicular line. In the left lateral decubitus position, a bifid apical pulse can be appreciated: The first component is contributed by the atrial contraction and the second by the left ventricle (LV) contraction. A palpable thrill corresponding to ejection systolic murmur is there in the second left ICS in significant AS.

The cardinal auscultation findings in AS are normal first heart sound (S1), soft single S2, and an aortic ejection click followed by an ejection systolic murmur, best heard at the base of the heart. The click is a high-pitched sound heard shortly

after S1 at the base. It is heard when the aortic root is dilated, in a bicuspid aortic valve and in a flexible stenotic valve. It is absent in severe AS when the valve is calcified and less pliable. However, the click is not always audible and is not a sensitive finding for severe AS. The typical murmur of AS is a high-pitched, crescendo–decrescendo, ejection systolic murmur. It is high-pitched and is heard best with the diaphragm of the stethoscope. It starts at a short interval after S1 and ends before S2. The murmur is heard best in the left second ICS and radiates to the carotids and both clavicles. Etchells et al.[4] showed that the absence of radiation of murmur to the right clavicle effectively rules out AS. It is sometimes heard in the third and the fourth left ICS along the sternal border. In 15% of the cases, murmur radiates to the apex due to high-frequency vibrations.[4] This is called the Gallavardin phenomenon. The intensity (grade 4 or more) and mid-to-late peaking of the murmur indicate the severity of the stenosis. The higher intensity indicates high turbulence and velocity across the valve. However, the intensity may be fallaciously low in cases with LV dysfunction and increased in high output states such as anemia, thyrotoxicosis, and fever. The late peaking happens because the blood takes longer to eject through a narrower orifice but it is difficult to assess clinically, especially when there is tachycardia or a low-grade murmur. As the LV ejection time increases in severe AS, aortic valve closure (A2) comes after pulmonic valve closure (P2) leading to a paradoxical split, which may be absent with LV dysfunction. In severe AS, as the valves become more immobile, A2 becomes softer and may become inaudible. A palpable fourth heart sound (S4) is caused by forceful contraction of atria into the hypertrophied and noncompliant ventricle. S4 indicates severe AS and is significant in young patients but may not be so in older patients as diastolic dysfunction is frequent in them. Apart from the pitfalls associated with signs of severe AS, one must be able to differentiate the murmur of AS from other murmurs heard at the base of the heart.

- *Hypertrophic cardiomyopathy*: An ejection systolic murmur is heard along the left sternal border. The murmur increases with exercise, squatting, Valsalva maneuver, administration of vasodilator, and positive inotropic drugs.
- *Supravalvular AS*: The ejection systolic murmur is not preceded by a click, and S2 is loud. The carotid murmurs are louder than in valvular AS.
- *Pulmonic stenosis* (*PS*): The murmur is very much similar to AS and is loudest in the pulmonary area. It does not radiate to carotids.
- *Atrial septal defect*: It may be associated with a murmur similar to PS, but the S2 is wide and fixed.
- Functional murmurs sound similar but are usually faint, and S2 is normal. Patients with hypertension and aortic sclerosis may have medium-pitched murmurs but with a loud or normal S2.

Aortic Regurgitation

In chronic aortic regurgitation (AR), the focus is on the examination of pulse and cardiac examination. In significant chronic AR, it is a large volume pulse with a sharp upstroke and rapid collapse, also called Corrigan's or water hammer pulse. Large-volume pulses can also be found in other conditions such as thyrotoxicosis and severe anemia. The other peripheral findings related to wide pulse pressure have a long list, but their sensitivity and specificity are not well established. Some of them are given in **Table 1**.

TABLE 1: Aortic regurgitation–peripheral signs.

Corrigan's sign[3]	Dancing carotid arteries
Müller's sign[3]	Systolic pulsations of the uvula
de Musset's sign[3]	Head bobbing with systolic pulse
Traube's sign[3]	Systolic and diastolic "pistol shot" sounds were heard while auscultating the femoral artery
Landolfi's sign[3]	Pupillary hippus
Becker's sign[3]	Retinal artery pulsations
Duroziez's sign[3]	Systolic and diastolic bruit heard with partial compression of femoral artery
Quincke's pulse[3]	Systolic pulsations in nail bed with light compression
Hill's sign[3]	The lower limb systolic blood pressure is higher than the upper limb systolic blood pressure by >20 mm Hg. A difference in blood pressures between lower and upper limbs of >60 mm Hg is highly suggestive of severe AR

(AR: aortic regurgitation)

The apical impulse is hyperdynamic, diffuse, and displaced laterally and inferiorly. With LV dysfunction, the S1 becomes softer due to an increase in the LV end-diastolic pressure, and third heart sound (S3) can be heard at the apex.

In auscultation of chronic AR, S1 is normal with single or accentuated S2. An early diastolic murmur and a faint mid-systolic murmur can be heard at the base. The early diastolic murmur has a sensitivity of 76% and specificity of 96% when present.[5] It is a high-pitched, blowing murmur, best heard with the diaphragm of the stethoscope. It is a decrescendo murmur better heard with the patient leaning forward in a sitting position. It starts after S2 and when the AR is significant can be holodiastolic. It is commonly audible along the left sternal border in the third and fourth interspaces in patients with valvular AR. It is usually transmitted to the cardiac apex. The duration and quality of the murmur correlate with the severity of the murmur:

- Mild AR has an early diastolic blowing quality murmur.
- Moderate-to-severe AR has a harsh holodiastolic murmur (>2/3rd of diastole).

The murmur may become soft or disappear in severe LV dysfunction. Hence, the absence of murmur does not rule out AR. The Austin Flint murmur is a low-pitched, rough, and rumbling diastolic murmur, best heard at the apex. The sensitivity varies from 25 to 100%.[6] A mid-systolic murmur is sometimes heard due to a large volume of blood being ejected out and in those with calcified aortic valves.

In acute AR, the above findings may not be there. The patient is usually sick and has tachycardia. Other features of acute heart failure predominate. The regurgitation murmur is a low-pitched early diastolic murmur, and the peripheral signs of chronic AR are absent.

Other basal diastolic murmurs which could be confused for AR are murmurs of pulmonary regurgitation and Dock's murmur.

- Pulmonary regurgitation murmur is indistinguishable, but there is no cardiomegaly on palpation. The peripheral signs of AR are absent in it.
- The Dock's murmur is a high-pitched early diastolic murmur caused by stenosis of the left anterior descending artery. Unlike the widespread murmur of AR, it is heard along the left sternal border in the second and third left space.

MITRAL VALVE DISEASE

Approximately 25% of RHD patients have isolated mitral stenosis (MS), and 40% have both MS and mitral regurgitation (MR). Thirty-eight percent of MS patients have involvement of other valves also. MS is more common in females and is mostly rheumatic in etiology (97.4%). The most common causes of isolated MR are rheumatic (41.1%) and mitral valve prolapse (MVP) (40.8%).[1]

Mitral Stenosis

The examination must include a note of JVP, peripheral pulse palpation, precordial examination, and auscultation. The general examination may show mitral facies, i.e., plethoric cheeks with bluish patches. The JVP is elevated with a prominent "*a*" wave in the presence of pulmonary hypertension (PH). These "*a*" waves are lost if atrial fibrillation (AF) is present, which develops in 40% of the patients with MS.[7] In the presence of AF, the pulse will be irregularly irregular. Precordial palpation will reveal a tapping apex. A diastolic thrill can be palpated at the apex, and right ventricular (RV) heave is appreciable in the presence of PH.

Cardiac auscultation should be done in supine, left lateral, and sitting positions. The auscultatory findings could be very subtle and should be performed in a quiet environment. The S1 is loud due to the wide closing excursion of the mitral leaflets and the rapidity of the rise of LV pressure. The intensity of S1 sound will decrease in severely thickened and calcified valves and will be variable in the presence of AF with louder S1 in shorter cycles. The S2 will be loud in the presence of PH. With a further increase in PH, the S2 split will become narrower and then single. The opening snap (OS) is a high-pitched early diastolic sound caused by the sudden tensing of mitral leaflets and subvalvular apparatus at the end of the diastole. The A2–OS interval varies inversely with the severity of MS. In the presence of AF, the A2–OS interval varies directly with the length of the previous RR interval. The OS must be differentiated from other diastolic sounds. Being a higher pitch sound, OS can be heard over a wider area over the precordium at the left sternal border and the base. The S3 is usually heard over the apex only. A loud P2 is typically localized to the pulmonary area unless there is severe PH when it can also be heard in the aortic area. The classical murmur of MS is a mid-diastolic murmur with presystolic accentuation, best heard at the apex in the left lateral decubitus position. The severity of the murmur depends on the duration of the murmur and not on the intensity of the murmur. Increasing the heart rate helps in detecting a faint murmur as the mean diastolic gradient is directly related to heart rate.

Pulmonary artery dilatation due to severe PH may produce a nonvalvular ejection click which paradoxically decreases with inspiration. A tricuspid regurgitation (TR) murmur can be heard along the left sternal border in the fourth ICS. A high-pitched decrescendo diastolic murmur is heard along the left sternal border in the second to third ICS. This is a Graham Steell murmur caused by functional pulmonary regurgitation in severe PH. The above two murmurs could be confused with those of MR and AR, which are a common association in RHD.

Other causes for a diastolic murmur are as follows:

- Flow murmur across a nonstenotic mitral valve in severe MR and large ventricular septal defect (VSD)
- A diastolic murmur may be heard in the left atrial myxoma and may cause a diastolic murmur with the tumor plop mimicking OS.
- Austin Flint murmur is a mid-diastolic murmur heard at the apex in AR. It is caused by an eccentric jet of AR on the anterior leaflet of the mitral valve causing reverberations.
- Cor triatriatum sinister is a congenital abnormality where the left atrium (LA) is divided into two chambers by a thick fibromuscular septum. A diastolic murmur can be heard, but loud S1 and OS are absent.

MITRAL REGURGITATION

The examination findings depend on the chronicity of the development of MR and its severity. Apical impulse is downward and outward with a brisk hyperdynamic nature. A late systolic thrust may be palpable in the parasternal region due to the expansion of the large LA during systole. This could mimic RV enlargement. The S1 is usually soft. The S2 is wide and variable because of earlier closure of the aortic valve as a result of shortened LV ejection time. The P2 is loud in the presence of PH. S3 is heard due to the increase in diastolic flow across the mitral orifice during the rapid filling phase.

In acute MR, the patient is sick and in pulmonary edema. A short early systolic murmur is heard. The regurgitation into the noncompliant LA leads to early equalization of the pressure of LA and LV. A left-sided S4 can be heard. PH can cause a loud P2. Increase in the pulmonary artery pressure in acute severe MR can prematurely close the pulmonary valve and cause paradoxical splitting of the S2.

In chronic severe MR, the S1 is soft. The holosystolic murmur of MR is blowing in nature, high-pitched, and best audible at the apex with radiation to the left axilla or base of the heart. It starts after a soft S1 and may continue beyond A2 because of the persistent pressure difference between LV and LA. The intensity of the murmur does not correlate with the severity of the murmur. Murmurs of mild MR are of shorter duration. It is early systolic in functional MR and late systolic in MVP or papillary muscle dysfunction.

The MR murmur should be differentiated from the systolic murmurs of AS, TR, and VSD.

- In AS, the intensity of murmur increases after a premature beat or in the beat after a long cycle length in AF. The intensity of the MR murmur does not change after a premature beat; it can decrease (papillary muscle dysfunction) or become shorter after a premature beat.
- The holosystolic murmur of a VSD is associated with a parasternal thrill and is loudest at the left sternal border.

TABLE 2: Dynamic auscultation findings in conditions with systolic murmur.

	MVP	Other cases of MR	Hypertrophic cardiomyopathy
Inspiration	Increased duration	Decrease	Decrease
Sudden standing	Earlier, longer, and louder	Decreases	Increases
Squatting	Later, softer may decrease	Increases	Decrease
Hand grip	Delayed and decreased duration	Increased	Decrease
Strain phase of Valsalva	Longer and louder	Decreased	Increases

(MR: mitral regurgitation; MVP: mitral valve prolapse)

- In TR, there is a prominent "*v*" wave and "*y*" descent in the JVP. The murmur of TR is best heard at the left sternal border and its intensity increases with inspiration.

Mitral Valve Prolapse

Mitral valve prolapse can occur due to a simple chordal rupture with prolapse of an isolated posterior leaflet, or there may be multisegment prolapse affecting one or both leaflets of the valve.[8] There is sudden tensing of the mitral valve apparatus as the leaflets prolapse into the LA during systole.[8] This results in a high-pitched mid-systolic click which is characteristic of MVP. Sometimes, multiple clicks can be heard at different times of systole. The clicks are followed by a mid or late systolic murmur and the duration of the murmur correlates with the severity of MR.[8]

Other situations where mid-systolic click can be heard are tricuspid valve prolapse and atrial septal aneurysm. Dynamic auscultation is very important in the diagnosis of MVP **(Table 2)**.

- A decrease in LV volume will cause the mitral valve leaflets to prolapse earlier in systole, leading to a long murmur, for example, decreased venous return, tachycardia, increased myocardial contractility, or reduced afterload[8]
- An increase in LV volume will cause a delay in the onset of the click and a shorter murmur.[8]

TRICUSPID VALVE

Tricuspid regurgitation is more common than stenosis. Functional TR is more common than organic valve lesion. The function regurgitation is secondary to PH due to left-sided lesions. The signs and symptoms due to tricuspid valve lesions are overshadowed by those due to left-sided lesions. Pedal edema and ascites are predominant features of isolated tricuspid valve disease.

In TR, the JVP is elevated, and a large "*c-v*" wave and a sharp "*y*" descent are seen. A venous thrill and murmur can be heard in the neck in case of severe TR. It presents a hyperdynamic parasternal lift and pulsatile liver. When TR is due to an organic tricuspid valve lesion, the murmur is limited to the first half of systole and is of low intensity. With an increase in the degree of TR, S3 appears. In TR, secondary to PH, the murmur is pansystolic and high-pitched, best heard at the left lower sternal border and associated with a loud P2. These right-side sounds become more prominent with inspiration. The augmentation of the murmur with inspiration is called Carvallo's sign. The murmur also increases with Müller's maneuver, exercise, leg raising, and hepatic compression.

Tricuspid stenosis (TS) is almost always rheumatic in origin and is mostly associated with MS. The signs of TS are more subtle compared to MS and require a high index of suspicion to detect TS. In sinus rhythm, the "*a*" wave is tall and presystolic hepatic pulsations are felt. The "*y*" descent is blunted. Despite engorged neck veins and systemic venous congestion, these patients have no orthopnea, and lung fields are clear. A diastolic thrill is palpable at the lower left sternal border and it may appear or become more prominent during inspiration. The auscultatory findings may get masked by the findings of associated MS. The tricuspid OS and diastolic murmur are augmented by maneuvers which increase blood flow through the tricuspid valve such as inspiration, Müller's maneuver, right lateral decubitus position, leg raising, isotonic exercise, and squatting. The tricuspid OS and diastolic murmur are best heard at the left lower sternal border. The murmur is softer, higher pitched, and shorter in duration than the murmur of MS.

PULMONARY VALVE

Congenital PS is the most common cause of PS. Its prevalence is 0.5 in 1,000 live births and is higher in Asians.[9] It can be a part of other congenital defects such as tetralogy of Fallot, Williams syndrome, and Noonan's syndrome. Rheumatic involvement is very rare and associated with other valve involvement.

In severe PS, the "*a*" wave of JVP is prominent and the RV heave is palpable. The ejection systolic murmur of PS is heard at the left base and increases with inspiration. With increasing severity of PS, the ejection click moves closer to S1 and the click disappears in severe PS. The murmur of PS is similar to that of AS, but is heard louder in the pulmonary area and extends beyond the S2. The S2 is widely split and does not radiate to the carotids.

Pulmonary regurgitation is mostly secondary to PH. It can also be seen in infective endocarditis (IE), associated with other congenital heart defects, as residual PR after treatment of congenital PS or tetralogy of Fallot, catheter trauma, and carcinoid. Hyperdynamic RV pulsation and pulsations in the pulmonary artery area can be palpated. The S2 is widely split and there is a mid-systolic ejection murmur due to augmented RV systolic volume. PH causes regurgitation due to dilation of the pulmonic annulus. This murmur is called the Graham Steell murmur and is a high-pitched blowing decrescendo murmur. It begins immediately after the P2 and is best heard in the left parasternal region in second to fourth ICS. The murmur of pulmonary regurgitation is low-pitched in the absence of PH. This murmur of PR is difficult to distinguish

from that of AR murmur by auscultation. Lack of peripheral signs of AR and increase in the intensity of murmur with inspiration suggests PR.

CONCLUSION

Despite the advancement of medical technology including handheld ultrasound and echocardiogram, the general physical and cardiac examination in particular are irreplaceable and is the central tool for cardiac disease management. Many clues about the severity and seriousness of the cardiac disease can be acquired by a simple clinical examination of a patient. It is an important tool for primary care physician for referral of appropriate patient to a higher center. Clinical cardiac examination though has certain pitfalls, its sensitivity and specificity are reasonable to continue it in clinical practice. The chapter has described in details the clinical examination of the lesions of all the four cardiac valves.

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CHAPTER 18

Sleep Apnea and Heart Disease: Management Strategies

Amal Kumar Khan, Amartya Khan, Indrani Mandal

ABSTRACT

Sleep apnea is characterized by repetitive episodes of apnea or hypopnea occurring during sleep leading to intermittent hypoxemia, autonomic fluctuation, and sleep fragmentation.

Different forms of cardiovascular diseases (CVD) have been associated with obstructive sleep apnea (OSA) and they are—resistant hypertension (HTN), heart failure (HF), stroke, atrial fibrillation (AF) and other arrhythmias, pulmonary hypertension (PH) and coronary artery disease (CAD).[1] OSA prevalence is as high as 40–80% in this population. In general population, OSA prevalence affects 34% of men and 17% of women.[2]

Despite their high prevalence in CVD and adverse cardiovascular outcomes OSA is often underdiagnosed and undertreated.

We have to keep in mind that despite their clear association between CVD and OSA, randomized trials have failed to demonstrate that the treatment of OSA improves hard cardiovascular endpoints.[3] This area is controversial.

We will try to describe the association between OSA and different forms of CVD and management strategies in a nutshell. The American Heart Association (AHA) scientific statement recommends screening for OSA in patient with HTN, PH, recurrent AF or in certain population of HF.[2] All patients with OSA should be considered for treatment with behavioral modification and weight loss. Continuous positive airway pressure (CPAP) should be offered with severe OSA whereas oral appliances to CPAP intolerant patients.

INTRODUCTION

The evaluation of sleep apnea should be done clinically documenting signs and symptoms mentioned in **Figure 1**, following this assessment they should undergo diagnostic testing with polysomnography (PSG)/home sleep apnea test (HSAT).

Treatment for obstructive sleep apnea (OSA) is reserved for those patients with an apnea-hypopnea index [(AHI), number of apnea-hypopnea observed per hour] of ≥5 measured during sleep study with either signs and symptoms of OSA or associated medical condition [e.g., heart failure (HF), resistant hypertension (HTN), pulmonary hypertension (PH), coronary artery disease (CAD), and atrial fibrillation (AF)/other forms of cardiovascular diseases (CVD)].[4]

An AHI ≥15 is often treated without signs and symptoms or associated medical conditions. Severity is determined using AHI with 5–14 considered mild, 15–30 as moderate, and >30 as severe disease. All patients with severe disease should be offered either continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) who failed to tolerate CPAP and in some cases of central sleep apnea (CSA).

Diagnostic evaluation needs HSAT using a portable device compared with PSG done in sleep laboratory. Diagnostic accuracy of HSAT is lower and variable. Despite this caveats HSAT remains viable alternative to PSG and is recommended in uncomplicated patients. The limited sensitivity or false negative results of HSAT warrens follow-up with PSG. Full-night PSG remains the preferred testing modality.

RISK FACTORS

Male sex, older age, obesity with craniofacial dimorphisms, and family history remain established risk factors.[5] OSA correlates with body mass index (BMI), increased waist circumference, and neck size. It has been seen that 10% weight gain was associated with a nearly 32% increase in AHI.[6] Craniofacial anatomic abnormalities are important risk factors

which can be quantified with Mallampati classification. Neck circumference is an independent predictor of OSA after BMI. Other less established factors are smoking and family history.

SIGNS AND SYMPTOMS OF OBSTRUCTIVE SLEEP APNEA (FIG. 1)[4]

See **Figure 1**.

CARDIOVASCULAR COMPLICATION OF OBSTRUCTIVE SLEEP APNEA (FIG. 2)

The following cardiovascular complications have been associated with OSA.

Obstructive sleep apnea has been implicated for worsening of these conditions and that may in turn worsen OSA. They are shown in **Figure 2**.

Hypertension and Resistant Hypertension

Both OSA and HTN are common conditions with multifactorial causes.

About 30–50% of hypertensive patients will have comorbid OSA.[4] Meta-analysis of CPAP therapy in hypertensive patients shows a reduction of 2–3 mm Hg BP.[7] In non-CPAP therapy like oral appliances BP reduction was similar to that noted with CPAP therapy. In a randomized proof of concept study of 60 patients renal denervation significantly decreased. In office and ambulatory BP after 3–6 months of the procedure with modest reduction in OSA severity.[8]

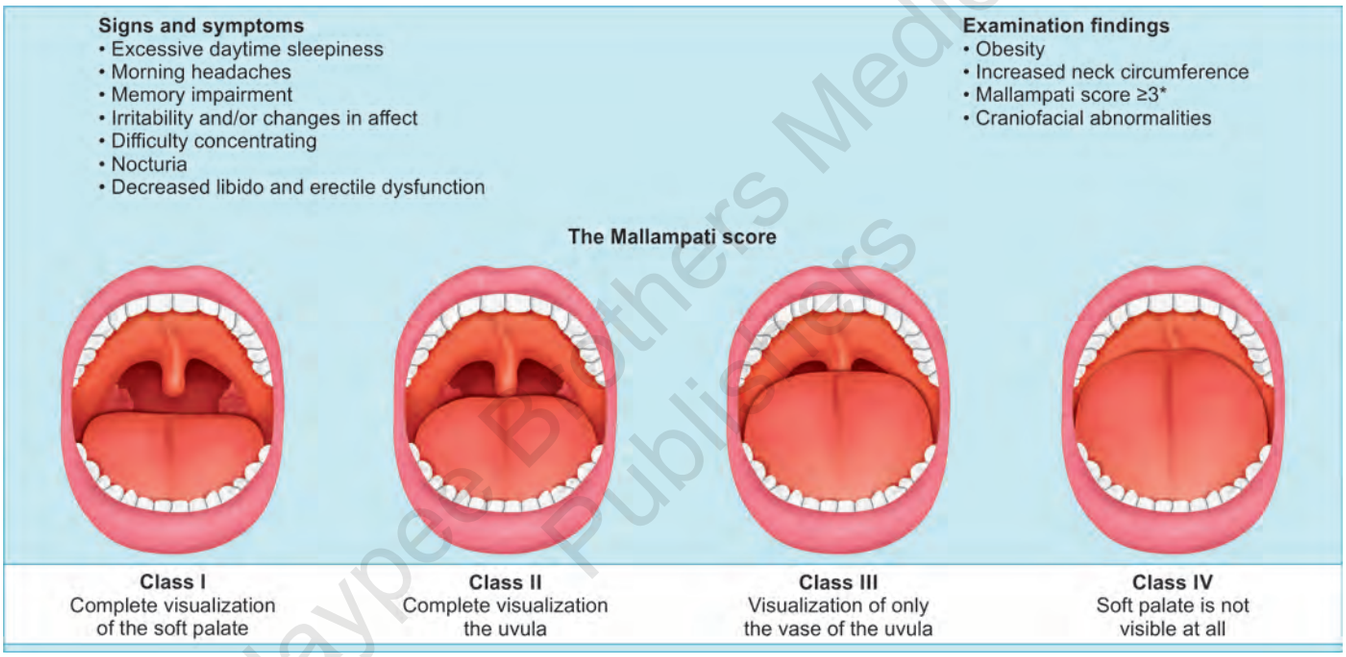


FIG. 1: Signs and symptoms of obstructive sleep apnea (OSA).

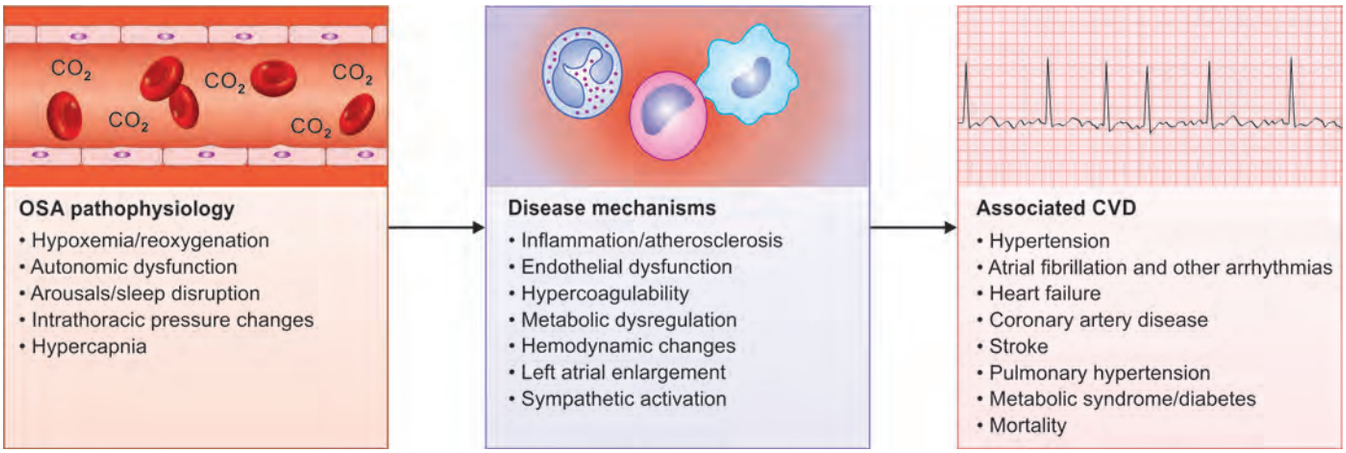


FIG. 2: Cardiovascular complication of OSA.
(CVD: cardiovascular disease; OSA: obstructive sleep apnea)

Atrial Fibrillation

Obstructive sleep apnea and AF are common conditions and prevalence of AF is 1–2% in general population.[9] In OSA, prevalence of AF is 5%.[10] OSA is an independent risk factor for AF but it has not been definitely proved that OSA causes AF.[10] Multiple mechanisms are involved to explain the association, they are nocturnal surge in sympathetic drive, hypertension, and structural remodeling of atria. Besides epidemiologic association between two conditions there are evidences to suggest a significant role of OSA in recurrent or treatment in refractory AF. Current literature suggests a possible benefit of treating OSA with CPAP with respect to AF burden and risk of recurrence during rhythm control.[11,12] Before catheter ablation for AF diagnostic testing by HSAT or PSG is suggested in patients with suspected sleep apnea.

Other arrhythmias that are associated with OSA are sudden cardiac death (SCD) and reported 22% prevalence of prolonged pauses, bradycardia in patients with moderate to severe OSA.[13] Severe OSA has been associated with higher risks of complex ventricular ectopy such as nonsustained ventricular tachycardia (NSVT), bigeminy, trigeminy, etc.

Increased risk of SCD has been reported with severe OSA with nocturnal oxygen desaturation of <78%.[14]

Heart Failure

Sleep apnea is highly prevalent in patients with HR indicating a prevalence of 50–70%. Here, CSA accounts for about two-thirds cases and OSA comprises about one-third.[15] A meta-analysis of 2,570 patients with heart failure with reduced ejection fraction (HFrEF) and moderate to severe sleep apnea CSA represents about >70% of cases.[16] In HF with OSA, the pathophysiological mechanisms are neurohormonal activation, increased oxidative stress, acute increase of preload and afterload, and exacerbation of systemic hypertension.

- Two ongoing trials ADVENT-HF (Effect of ADaptive servo VENTilation ASV on survival and hospital admissions in HF) and LOFT-HF (the impact of LOw-Flow of oxygen Therapy on hospital admissions and mortality in patients with HF and untreated sleep apnea) will likely inform the benefit of ASV and nocturnal oxygen supplementation, respectively for treatment of HF and CSA.[17]

A meta-analysis of patients with OSA reported that CPAP did not have significant effects on either left ventricular ejection fraction (LVEF) on hospitalization rates.[18] Therefore, 2017 American Heart Association/American College of Cardiology (AHA/ACC) guidelines on HF states CPAP as a possibly reasonable treatment strategies (class IIB) to improve sleep quality and daytime sleepiness in patients with CVD and OSA.[19]

Pulmonary Hypertension

Obstructive sleep apnea has a strategy association with PH and plays a causative role in pathophysiology. About 10–20% patients with moderate to severe OSA have coexistent PH.[20] Both hypoxemia and hypercapnea can trigger pulmonary arterial vasoconstriction leading to acute reversible elevation in pulmonary arterial pressure. PH resulting solely from OSA is mild. However, OSA can further exacerbate elevation in PAP and pulmonary vascular resistance (PVR) when superimposed with other underlying causes.

Observational studies have found consistent benefits in reducing PAP (5 mm Hg) and PVR among patients receiving CPAP therapy.[21]

Coronary Artery Disease

Obstructive sleep apnea independently increases the risk of coronary events. OSA increases oxidative stress and systemic inflammation which may contribute to acute myocardial infarction (AMI) events and coronary calcification. The SAVE (Sleep Apnea cardioVascular Endpoints) trial with 2,717 patients with moderate to severe OSA and either CAD or cerebrovascular diseases have failed to demonstrate a significant reduction of primary endpoints (a composite of CV death, MI, hospitalization for HF, stroke, PIA) among patients treated with CPAP in addition to usual care. OSA may be implicated with increased risk of MACE after PCI. Whether CPAP therapy decreases the risk of MI remains controversial.[22]

Cerebrovascular Disease

Obstructive sleep apnea is an independent risk factor for incident stroke and stroke recurrence. Recent meta-analysis demonstrated a prevalence of post-stroke OSA to as high as 71%.[23] The association with stroke has not been explained by HTN or traditional risk factors. The ongoing sleep for stroke management and recovery trial will likely inform the need for CPAP to improve stroke recovery and prevent recurrence.
Trials such as:

- SAVE (Sleep Apnea CV Endpoints)
- RICCADSA (CPAP treatment in CAD and sleep apnea)
- CERCAS (effect of CPAP on incidence of HTN and CV events in nonsleepy patients with OSA)

All have failed to show a high level of evidence to support benefits of CPAP for primary stroke prevention.[16,22]

Metabolic Syndromes and Type 2 Diabetes Mellitus

There is a greater likelihood of metabolic syndrome and type 2 diabetes mellitus because central adiposity is linked to the development of both OSA and metabolic syndrome and has similar pathophysiological features.[24]

Mortality

In epidemiological studies, OSA has been associated with reduced survival. A meta-analysis of 16 studies with 24,308 patients showed that severe OSA associated with increased all cause and cardiovascular mortality.[25] In an analysis from sleep heart health studies a PAP prescription was associated with 42% lower mortality among patients with severe OSA. Randomized controlled trials with longer follow-up and focused on high-risk patients with severe OSA are needed to clarify the clinical benefits of PAP therapy.[26]

MANAGEMENT STRATEGIES

Proposed algorithm to select patients for formal diagnostic sleep testing based on this cardiovascular condition **(Flowchart 1)**.
Diagnostic testing:

- Clinical tools, questionnaires
- Either PSG or HSAT in uncomplicated patients
- Those who have negative or inconclusive HSAT should undergo PSG.
- Polysomnography should be used rather than HSAT in complicated patients.

In spite of relationship and association of OSA with CVD in epidemiological studies, clinical trials that have evaluated the efficacy of CPAP treatment in primary and secondary cardiovascular prevention have not demonstrated a significant reduction in the incidence or recurrence of CV events. OSA may be a potentially modifiable risk factor for vascular disease.

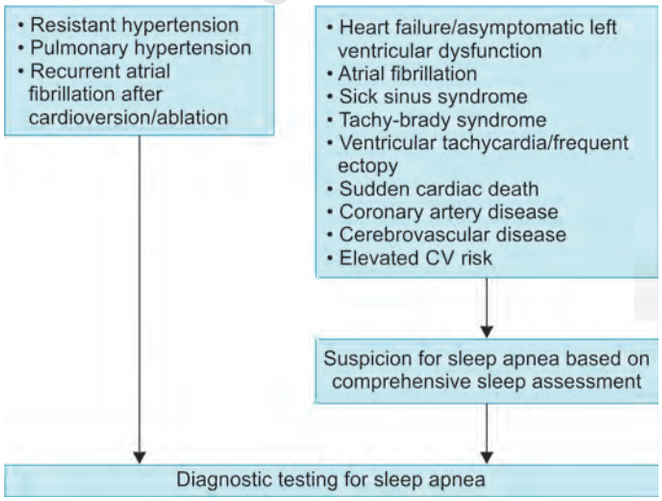
In ISAACC study (effect of OSA and its treatment with CPAP on the prevalence of CV events in patients with ACS), a randomized controlled trial showed that "among nonsleepy patients with ACS, the presence of OSA was not associated with an increased prevalence of CV events and treatment with CPAP did not significantly reduce the prevalence".[27,28]

TREATMENT (TABLE 1)

All patients with diagnosed OSA should be offered treatment. A multidisciplinary approach to the management of OSA should be used involving physician trained in sleep medicine, otolaryngology, head and neck surgery, cardiology, Maxillofacial surgery, and dentist **(Table 2)**.

CONCLUSION

Although OSA increases the risk of all-cause and cardiovascular mortality, this condition is often underrecognized and undertreated in cardiovascular practice. A strong association is present between OSA and numerous cardiovascular conditions. It is recommended to screen for OSA in patients with resistant/poorly controlled hypertension, PH, and recurrent AF after either cardioversion or ablation. In patients with New York Heart Association class II to IV HF and suspicion of sleep-disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable. Patients with nocturnally occurring angina, MI, arrhythmias, or appropriate shocks from implanted cardioverter-defibrillators may be especially likely to have comorbid sleep apnea. All patients with OSA should be considered for treatment, including behavioral modifications and weight loss as indicated. CPAP should be offered to patients



FLOWCHART 1: Diagnostic testing for sleep apnea.

TABLE 1: Behavioral therapy for obstructive sleep apnea (OSA).

Treatment	Patient selection
Weight loss	All overweight or obese patients should be encouraged to lose weight as adjunct to primary therapy
Positional therapy	• Can be used as either a secondary or adjunctive therapy in patients with significant reduction in nonsupine position as compared with supine • Can be considered as primary therapy in select cases when normalization of AHI in a nonsupine position has been demonstrated by polysomnography and adherence can be assured
Avoidance of alcohol or other substances	• Patients should be encouraged to minimize alcohol intake • Physicians should monitor for and avoid prescribing medications with potential to exacerbate sleep apnea, such as benzodiazepines, opiates, or other central nervous system depressants

TABLE 2: Treatment options for obstructive sleep apnea (OSA).

CPAP	On the basis of AHI ≥ 15 events per hour or AHI ≥ 5 with documented symptoms or comorbidities
APAP	Trials have not shown improved adherence
BiPAP	Patients intolerant to CPAP or who requires adequate ventilator supports
ASV	SERVE-HF showed increased mortality in those with LVEF < 45%
Oral appliances	Alternative to CPAP or who does not tolerate CPAP
Upper airway surgery	Multilevel surgery where multiple levels of obstruction such as nasal septoplasty, adenotonsillectomy, uvulopalatoplasty, maxillomandibular advancement
Neurostimulation	Adults with moderate to severe OSA, inability to use CPAP, lack of complete concentric collapse on DISE, most effective in those with a BMI of < 32 kg/m^2

(AHI: apnea-hypopnea index; CPAP: continuous positive airway pressure; DISE: drug-induced sleep-endoscopy; LVEF: left ventricular ejection fraction; SERVE-HF: adaptive Servo Ventilation in patients with Heart Failure; APAP: autotitrating positive airway pressure; BiPAP: bilevel positive airway pressure; ASV: adaptive servo ventilation)

with severe OSA, whereas oral appliances can be considered for patients with mild to moderate OSA or for CPAP-intolerant patients. Follow-up sleep testing should be performed to assess the effectiveness of treatment.

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CHAPTER 19

Left Ventricular Noncompaction

Satyavir Yadav, Rakesh Yadav

ABSTRACT

Isolated left ventricular noncompaction (LVNC) is a relatively rare genetic form of dilated cardiomyopathy. It is characterized by prominent ventricular trabeculations and deep inter-trabecular recesses, or sinusoids, in communication with the left ventricular cavity. The diagnosis is made by high index of clinical suspicion supplemented by echocardiography and cardiac magnetic resonance imaging (cMRI). Most of the patients present with heart failure, cardiac arrhythmia or stroke in young age. Prognosis is usually poor. Relative rarity of this condition has prevented large scale clinical trials for insight into management of this disease.

INTRODUCTION

This is a rare type of cardiomyopathy, first described as spongy myocardium long back by Grant in 1926.[1] But, still there is ambiguity on its classification. The American Heart Association classifies it as a genetic cardiomyopathy[2] while the European Society of Cardiology considers it as unclassified.[3] Genesis of left ventricular noncompaction cardiomyopathy (LVNC) is attributed mainly due to arrest in final stage of myocardial morphogenesis.[4-11] Although this theory does not explain several types of noncompaction, e.g., primary myocardial forms, forms associated with arrhythmias, and forms associated with congenital heart defects (association with Ebstein anomaly, septal defects, and hypoplastic left heart syndrome).[12-20] Early recognition of this entity is important because cases diagnosed in childhood have better prognosis.[21] It is associated with high rates of tachyarrhythmia, heart failure and thromboembolism, and poorer prognosis in adults.[22]

EMBRYOLOGY

During early phase of embryogenesis heart is a loose mesh of myocardial fibers, gradually it condenses and compaction of ventricular myocardium along with solidification of endocardial surfaces occurs leading to disappearance of large spaces in trabecular meshwork. Compaction of trabecular part occurs more completely in left side of heart that is why right ventricles have more trabeculations in mature heart. Arrest in normal process of endomyocardial morphogenesis leads to development of postnatal LVNC.[4-6,8-10] Gross pathological specimens show prominent trabeculations along with deep intratrabecular recesses, histologically endothelial lining is present all over the trough and recesses. There is no abnormality in coronary arterial circulation.[23] Extramural circulation is completely normal. Trabeculations may cause perfusion abnormality in intramural myocardial perfusion but there is no definitive role of endocardial ischemia.

EPIDEMIOLOGY

Lack of uniform diagnostic criteria is responsible for uncertainty in incidence and prevalence of LVNC. Few studies have shown variable prevalence in range from 0.05 to 0.26% during echocardiographic screening of all adult population.[24-26] Major limitation of this data is that it is solely based on retrospective databases from tertiary referral center which is prone to selection biases. These patients mostly present with heart failure, in this subset its prevalence has been 3–4%.[27,28] Nowadays prevalence is increasing mainly due to increased awareness, improvement in imaging modality, and guidelines recommended screening of family members.

TABLE 1: Major gene mutations associated with LVNC and their overlap with other cardiac disorders.

Disorders	TAZ-G4.5 mutation	DTNA mutation	Z-band mutation	FKBP12 mutation	LMNA mutations	NKX2.5, TBX5, and CSX mutations	ACTC, TNNT2, MYH7 mutation	SCN5A mutation	HCN4 mutation
Left ventricular noncompaction cardiomyopathy	x	x	x	x	x	x	x	x	x
Ventricular/Atrial septal defect		x		x		x			
Arrhythmogenic right ventricular cardiomyopathy				x					
Dilated cardiomyopathy	x		x	x	x		x		
Hypertrophic cardiomyopathy							x		
Other cardiomyopathies	x	x				x		x	
Other conduction abnormalities					x	x	x	x	x
Tetralogy of Fallot[3]						x			
Ebstein anomaly						x			
Brugada syndrome								x	
Romano–Ward syndrome								x	

Source: Adapted from Hussein A, Karimianpour A, Collier P, Krasuski RA. Isolated Noncompaction of the Left Ventricle in Adults. J Am Coll Cardiol. 2015;66(5):578-85.

GENETICS

Various studies have reported 13–50% familial occurrence in first-degree relatives therefore screening of first-degree relatives is recommended.[22,29-32] Almost all modes of transmission, e.g., autosomal dominant, autosomal recessive, X-linked, and mitochondrial inheritance have been reported.[12,33,34] Mutations of various genes and their overlap with other cardiac disorders have been summarized in **Table 1**.

Barth syndrome is an X-linked recessive disorder which is characterized by cardiomyopathy (predominantly LVNC) associated with skeletal myopathy, neutropenia, and short stature.[35] Autosomal dominant transmission is the most common mode in LVNC associated with congenital heart diseases (CHD).[12] Although genetic transmission of LVNC is heterogenous but all share a final common pathway. In most of the cases sarcomere genes are involved in primary pathway.

CLASSIFICATION

Though there is no uniform classification of LVNC, but there are various subtypes depending on associated clinical features, involvement of right side of heart, association with CHD.

Benign Left Ventricular Noncompaction Cardiomyopathy

Approximately 35% of all diagnosed cases of LVNC are of this subtype. Both systolic and diastolic functions are preserved and left ventricle size and thickness is normal. It is not associated with any clinically significant arrhythmia and has better prognosis.[36]

Left Ventricular Noncompaction Cardiomyopathy with Arrhythmia

Left ventricle size and wall thickness are normal in this subtype similarly like benign LVNC. But, this entity is associated with clinically significant arrhythmias. Despite advancement in cardiac imaging modality and surveillance methods, many of them are not identified at the time of diagnosis. These patients usually have worse prognosis in comparison with patients of similar rhythm disturbances who do not have LVNC.[15,36-43]

Dilated Left Ventricular Noncompaction Cardiomyopathy

This subtype is characterized by left ventricle dilation along with systolic dysfunction. In this subtype some patients may have undulating course, in which left ventricle becomes small with improvement in function before reversing to dilation. Prognosis is poor if this occurs in children and neonates while adults have similar prognosis compared to dilated cardiomyopathy without LVNC. Some of these patients have increased wall thickening along with left ventricle dilation and usually have worse prognosis such as burned out hypertrophic cardiomyopathy.[12,21,26,27,44-46]

Left Ventricular Noncompaction Cardiomyopathy with Congenital Heart Disease

It has been associated with almost every CHD. Right-sided lesion such as Ebstein's anomaly, pulmonic stenosis, pulmonary atresia, tricuspid atresia, and double outlet right ventricle are more frequently associated. It may contribute to myocardial dysfunction and arrhythmias. Perioperative risk is more in these patients.[17-20]

Restrictive Left Ventricular Noncompaction Cardiomyopathy

It is a rare subtype associated with biatrial enlargement with diastolic dysfunction. Prognosis is similar to other restrictive cardiomyopathy patients. Most common cause of death is sudden cardiac death (SCD) (mostly arrhythmic) rather than heart failure.[36]

DIAGNOSTIC MODALITIES

Diagnosis of LVNC depends mostly on noninvasive modalities such as transthoracic echocardiography and cardiac MRI.

- *Transthoracic echocardiography*: This is the most common modality used for diagnosis mainly due to widespread availability, lost cost, and easy interpretation. There is no uniform diagnostic criteria. The most accepted criteria is >2:1 ratio of the thickness of the noncompacted layer to that of the compacted layer at the end of diastole.[47] Ratios ranging between 2:1 and 3:1 have also been proposed. Punn and Silverman analyzed children with LVNC and concluded that ratio of compaction and noncompaction is not important rather density of trabeculation is crucial and strongly associated with LVEF and prognosis.[48] Advanced echocardiographic techniques such as strain, strain rates are being used more frequently nowadays but there is concern that it is causing over diagnosis of LVNC.
- *Cardiac MRI*: Similar to echocardiography, there is lack of uniform diagnostic criteria in MRI too. Thuny and colleagues compared echocardiography and MRI in 16 patients and concluded that extent and additional morphological characterstics of LVNC are defined better by MRI.[49] Few studies have shown that finding of delayed gadolinium enhancement and myocardial fibrosis on MRI could be good prognostic indicators.[50,51]
- *Cardiac CT*: Cardiac CT is a better modality for differentiation of global and regional wall motion abnormality which helps in excluding coronary artery disease as a cause of cardiomyopathy.[52]
- *Electrocardiography*: Most of the LVNC cases have abnormal ECG. Left ventricular hypertrophy, ST-segment abnormalities, left atrial enlargement, left axis deviation, T-wave inversion, and QTc prolongation are usually seen. Extreme QRS voltages may be seen in neonates and young children.[21,36,40,44,52,53]

CLINICAL PRESENTATION

Heart Failure

Most common mode of presentation is heart failure, it occurs in 53–73% patients of LVNC. Systolic dysfunction occurs in 58–76% patients.[13,22,24] Diastolic dysfunction is reported in 50% of adult patients with 36% having a restrictive filling pattern.[22] Apart from this arrhythmia, conduction disturbances and thromboembolism may also occur. Underlying etiopathogenesis of heart failure is unclear but both systolic and diastolic dysfunction occur. Hypoperfusion of subendocardium in absence of coronary artery disease is responsible for systolic dysfunction.

Arrhythmias and Sudden Cardiac Death

Twenty five percent of LVNC patients usually have supraventricular arrhythmia such as atrial fibrillation/flutter, paroxysmal supraventricular tachycardia or complete heart block.[22,29,44] Preexcitation occurs more commonly in children while atrial fibrillation is rare in pediatric population.[54] Ventricular arrhythmias occurs in range of 18–47% in adults[44] and 0–38% in children.[44,54] SCD has been reported in 18% of adults and 0–13% of children.[54]

Thromboembolism

It manifests as stroke, transitory ischemic attack, myocardial infarction, peripheral embolism or mesenteric infarction.[54] It occurs in 0–38% of children and 13–26% of adults.[22,54]

Treatment

Accurate phenotype diagnosis is required because surveillance strategies vary according to phenotype and affect outcomes. Screening of first-degree relatives is recommended.

ROLE OF GENETIC TESTING

Sarcomeric gene mutation is most commonly implicated. Genetic testing is now available in various institutions. After identifying pathogenic mutation, targeted genomic sequencing can be done in first-degree relatives which has important implications. Some of the family members may have the same mutation as the affected individual without any phenotype. The presence of a pathological mutation changes screening recommendations and genetic counseling should be provided about risk to future offspring.

DIFFERENTIAL DIAGNOSIS

Apical form of hypertrophic cardiomyopathy, endocardial fibroelastosis, eosinophilic myocarditis, arrhythmogenic right ventricular dysplasia, left ventricular thrombi, and cardiac metastases need to be excluded prior to diagnosis. Benign spongy myocardium pattern may be found in athletes, pregnant women, hypertensive heart disease, or aortic stenosis although further evaluation is needed if coarse trabeculations coexist.[33,55,56]

Differential diagnoses that must be excluded before diagnosing left ventricular hypertrabeculation (LVHT) include dilated cardiomyopathy, hypertrophic cardiomyopathy, apical type of hypertrophic cardiomyopathy, hypertensive heart disease, eosinophilic endomyocardial disease, aberrant bands or false tendons, focal type of hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, left ventricular thrombi, cardiac metastases, and endocardial fibroelastosis.[55]

TREATMENT

Conservative Management

Patients should be counseled to avoid strenuous physical exercises. Asymptomatic patients with normal left ventricular dimensions can take part in competitive sports however those with systolic dysfunction should avoid professional sports activities. Fetal diagnosis of LVNC is not an indication for termination of pregnancy.[57] Treatment is largely dictated by mode of presentation such as heart failure symptoms, arrhythmia or thromboembolic manifestations. Guidelines-based therapy includes angiotensin-converting enzyme inhibitors and β-blockers, and an aldosterone antagonist.[58,59] Loop diuretics therapy is reserved for patients with features of congestion or volume overload. Intravenous diuretics, inotropes or vasodilatory drugs are used for acute decompensated heart failure. The thromboembolic risks associated with LVNC are well known especially in adults[44,60] and if there is concomitant left ventricle or atrial dilation, therapy with antiplatelets or systemic anticoagulation should be given. No studies are available regarding the preference of novel anticoagulants over vitamin K antagonists; however, vitamin K antagonists are more preferred.[61] While in children these thromboembolic events are poorly characterized, thus antiplatelet therapy can be given in presence of atrial fibrillation, associated left ventricular systolic dysfunction, spontaneous echocardiographic contrast, severe left ventricular dilation, or dilated atria.

Invasive Management

Left ventricular noncompaction cardiomyopathy patients with ventricular tachycardia requires implantable cardioverter-defibrillators (ICD) implantation. Indications for implantation are same as in other cardiomyopathies. One study with 44 patients showed that 75% of ICD implantation was done for primary prevention.[62] In patients with normal systolic function along with late gadolinium-enhancement (LGE) should be given ICD therapy if there is coexistent family history of SCD, nonsustained ventricular tachycardia on 24 hours ECG, or previous syncope.[63] Electrophysiological study prior to ICD implantation is debatable as ablation of trabecular substrates successfully for ventricular arrhythmia has been reported. Cardiac resynchronization therapy might be beneficial in heart failure patients with prolonged intraventricular conduction. Heart transplantation should be considered for patients with refractory heart failure not responding to medical therapy. Caution should be taken because most of these patients have associated neuromuscular disease, as immunosuppression might be myotoxic and can exacerbate clinical or subclinical neuromuscular disorder (NMD). Previous studies have shown increased mortality however one recent study of 78 patients undergoing heart transplantation has shown mortality rate similar to idiopathic dilated cardiomyopathy.[64] Left ventricular assist device implantation should be considered if transplant is not immediately feasible or contraindicated. In patients with associated congenital heart defects, corrective surgery has beneficial effects in relieving heart failure, improving cardiac function, and decreasing heart size.[65,66]

PROGNOSIS

Prognosis and outcome are different in adults and children. 13% mortality rate (mostly in first year of diagnosis) has been reported in children.[29] After 10 years of diagnosis almost 90% children develop systolic dysfunction.[44] One study from Australia showed 23% incidence of SCD over 11.9 years in children.[67] Approximately two-thirds children develop cardiac dysfunction while one-third have arrhythmia.[58] The strongest predictor of mortality in children is presence of cardiac dysfunction. Repolarization abnormalities in ECG is also associated with increased mortality.

Prognosis in adult patients is better compared with children. Recent study by Stöllberger et al. showed 4–6% mortality over a follow-up of 4.5 years, >70% of patients had associated neuromuscular disease also.[68] Peters et al. showed 12.7% mortality over a period of 17 months in adult patients with systolic dysfunction.[69] Heart failure, atrial fibrillation, and diabetes mellitus have been associated with increased mortality. ICD therapy should be considered in patients of systolic dysfunction, nonsustained ventricular tachycardia and unexplained syncope.

CONCLUSION

Left ventricular noncompaction cardiomyopathy (LVNC) should be considered an important differential diagnosis in patients with heart failure at younger age. Though the condition can cause serious ventricular arrhythmia and SCD, role of ICD implantation is not clearly understood due to relative rarity of this disease. A meticulous work-up with echocardiography, cMRI and Holter may help to identify high risk groups.

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CHAPTER 20

Diagnosis and Management of Mid-cavitary Hypertrophic Obstructive Cardiomyopathy

Vaibhav Bandil, Suman Bhandari

ABSTRACT

Mid-cavitary hypertrophic obstructive cardiomyopathy (HOCM), first described by Falicov et al.[1] in 1976, is a rare type (1%) of HOCM.[2]

In this variant, there is significant midventricular hypertrophy associated with midventricular stenosis, which confers the aspect of a dumbbell shape to the left ventricle,[3] with the generation of a pressure gradient between the apical and basal chambers, as well as an absence of obstruction of outflow.[2]

Patients with mid-cavitary HOCM tend to be more symptomatic compared to patients with hypertrophic cardiomyopathy (HCM) with or without left ventricular outflow tract obstruction (LVOTO).

Also, they are associated with an increased risk of development of an apical aneurysm, apical clot, scarring, ventricular tachycardia, progression to heart failure and sudden cardiac death.

Diagnosis of mid-cavitary obstruction and its management is a challenge in the absence of a standardized treatment strategy.

DEFINITIONS

Hypertrophic cardiomyopathy (HCM) was defined as the echocardiographic appearance of left ventricular (LV) maximum wall thickness ≥15 mm in the absence of any other cause capable of producing such hypertrophy; or the presence of maximum wall thickness of 13 or 14 mm and positive family history for HCM and/or electrocardiographic changes compatible with HCM.[1-4]

Left ventricular outflow tract obstruction (LVOTO), caused by the anterior motion of mitral valve leaflets, was defined as present when the estimated peak instantaneous gradient on continuous Doppler application was ≥30 mm Hg.[3]

Mid-cavitary obstruction or midventricular obstruction (MVO) was defined as a midventricular gradient ≥30 mm Hg with a simultaneous appearance of midventricular muscular apposition, creating an hourglass shape of the LV on echocardiography or magnetic resonance imaging.[5]

CLINICAL COURSE

Mid-cavitary hypertrophic obstructive cardiomyopathy (HOCM) is a phenotype distinct from HOCM, associated with an unfavorable prognosis. Efthimiadis et al.,[6] in a study comparing clinical characteristics and natural history of patients with HCM, with and without MVO, observed that its presence is a strong and independent predictor of sudden death, as well as a determinant of progression to end-stage HOCM and heart failure-related death.

Patients with mid-cavitary obstruction have been far more symptomatic at first presentation, compared to HCM patients without obstruction or with LVOTO, with dyspnea being the dominating symptom. Additionally, a left ventricular apical aneurysm was identified in approximately one-fourth of HCM patients with mid-cavitary obstruction, a result confirmed by previous studies, also suggesting the existence of a close overlap between mid-cavitary obstruction and apical aneurysm in patients with HCM.[7,8]

The pathophysiology of apical aneurysm formation is fascinating. The mid-cavitary variant of HCM involves hypertrophy of the mid-ventricle, which can be exacerbated by hypertension. The hypertrophy creates two adjacent cavities on either side of the obstruction during systole. The proximal cavity develops a low-pressure zone and the distal cavity forms a high-pressure zone leading to necrosis due to chronic subendocardial ischemia. This subsequently leads to scarring, thinning, and apical aneurysm formation in the infarcted tissue.[9]

Apical aneurysm formation and the decrease in cardiac output are attributed to a higher risk of small vessel disease and increase the chances of sudden cardiac arrest or acute

myocardial infarction from ventricular arrhythmias and thrombus formation due to stasis of blood.[10,11]

Of note, noncontrast echocardiography did not correctly delineate this apical aneurysmal zone well. However, the addition of contrast imaging highlighted the apical dyssynergic zone very well. Unique Doppler patterns first described in mid-cavitary HCM by Nakamura et al. (paradoxical jet flow) were also noted.[12]

DIAGNOSIS

Electrocardiogram

Electrocardiogram with voltage criteria for left ventricular hypertrophy, secondary changes in ventricular repolarization, and deep inversion of T waves **(Fig. 1)**.

Two-dimensional Transthoracic Echocardiography

The diagnosis of HOCM was based on the 2020 American Heart Association/American College of Cardiology guideline and the 2014 European Society of Cardiology guideline, which mainly included unexplained septal hypertrophy with a thickness > 15 mm or a thickness of septal cardium > 13 mm with a family history of HCM.

The indication for LVOTO was an LVOT gradient ≥30 mm Hg at rest or with provocation.

Mid-cavitary obstruction was defined as a peak midventricular gradient ≥30 mm Hg with a simultaneous appearance of midventricular muscular apposition, causing an hourglass shape of the left ventricle on echocardiography **(Figs. 2A and B)**.

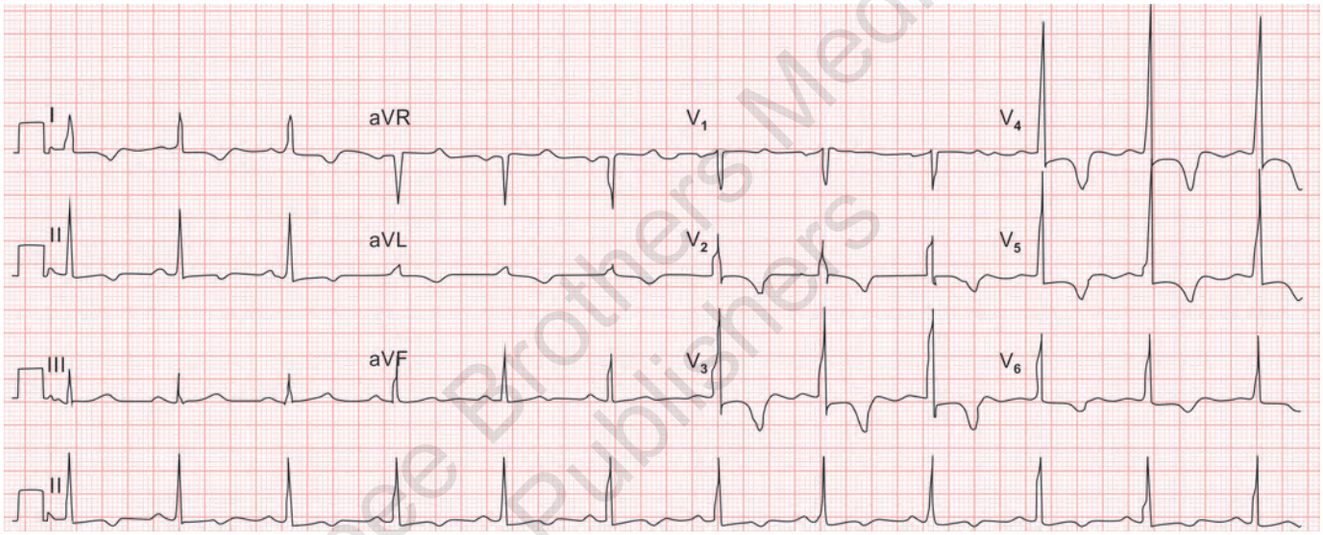
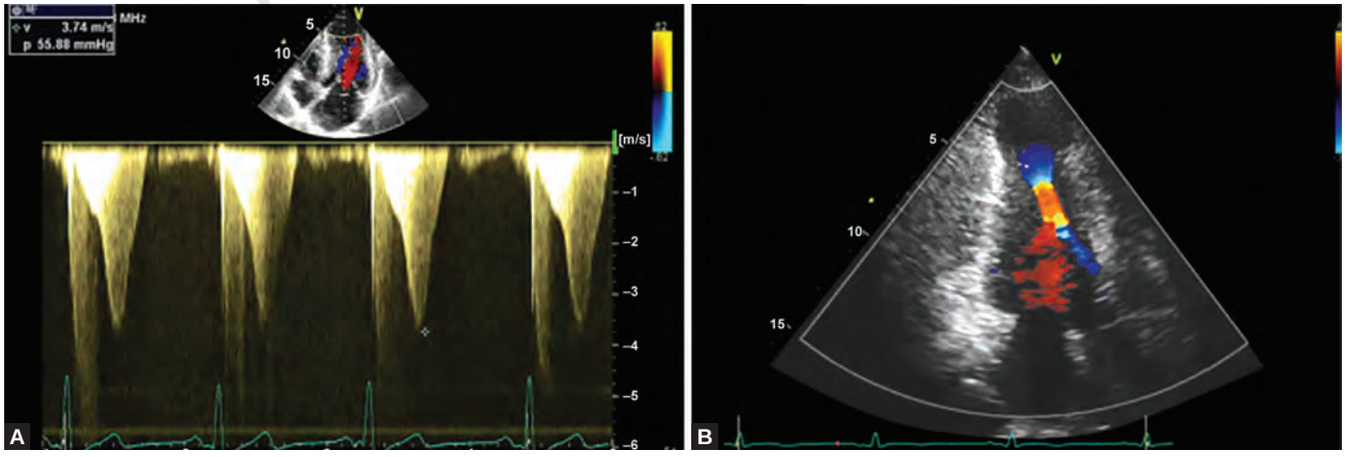


FIG. 1: Electrocardiogram with voltage criteria for left ventricular hypertrophy, secondary changes in ventricular repolarization, and deep inversion of T wave.



FIGS. 2A AND B: (A) A dagger-shaped waveform is obtained, showing a high midventricular gradient, and the estimated peak velocity of 3.74 m/s. (B) Two-dimensional transthoracic echocardiography from the left ventricular (LV) long-axis two-chamber view showing an hourglass shape of the left ventricle during systole.

Cardiac MRI

Cardiac MRI can show hypertrophy of the midventricular segments and can aid in the evaluation of cardiac volumes and cardiac function and associated myocardial fibrosis and scarring.[13] The following features might be present in midventricular HCM **(Figs. 3A and B)**:[5,13-17]

- *Cine imaging*:
  - Confined midventricular wall thickening
  - Dumbbell or hourglass shape of the left ventricle
  - Left ventricular apical aneurysm
  - Preserved or increased ejection fraction
- *Inversion-recovery gradient echo (IRGE)/Phase-sensitive inversion recovery*:
  - Late gadolinium enhancement in midventricular and apical segments
  - Indicating replacement fibrosis or myocardial scarring
  - Might show complications such as apical aneurysms or intracardiac thrombi

Left Ventriculography

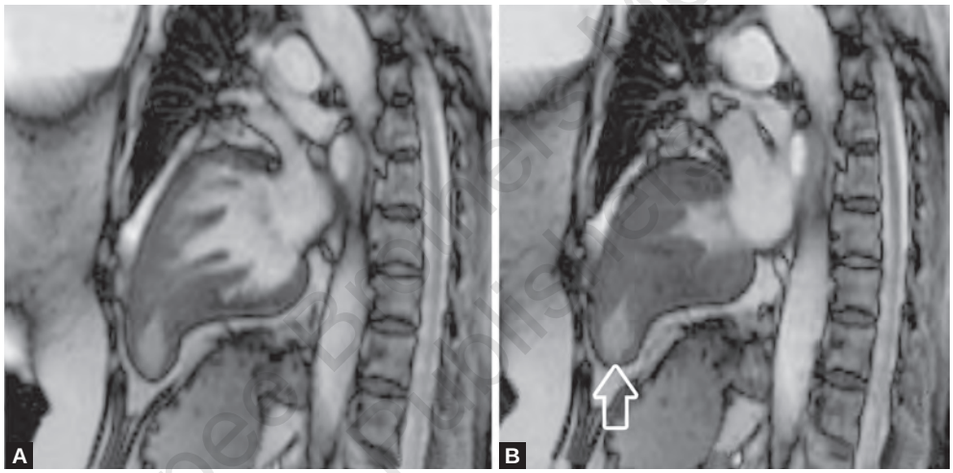
Left ventriculography showing severe midventricular hypertrophy, with almost complete mid-cavitary obstruction and apical dilation during diastole (A) and systole (B) **(Figs. 4A to C)**.

TREATMENT

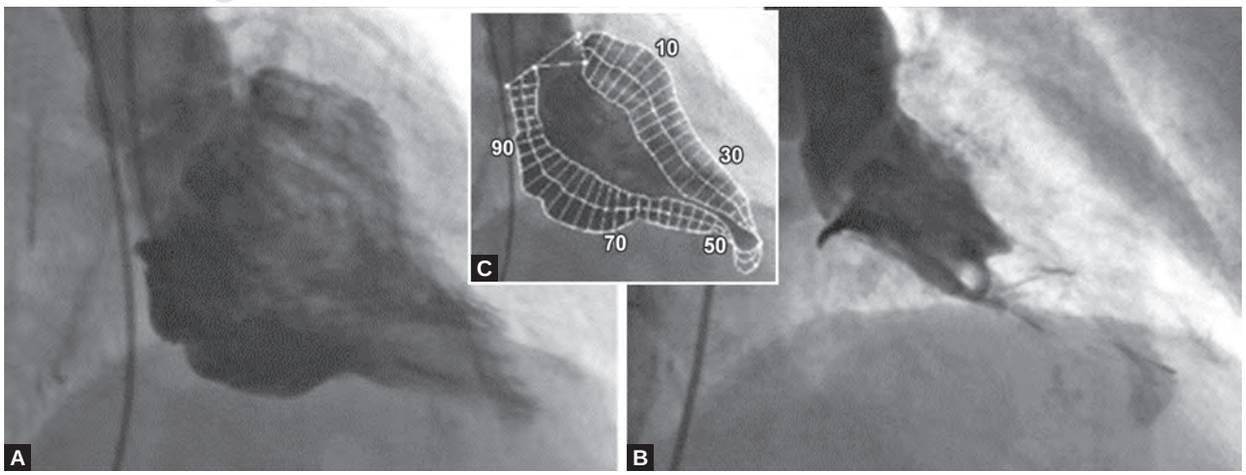
Treatment of mid-cavitary HCM is targeted at reducing the symptoms, such as the intraventricular gradient, and the risk of complications, such as heart failure and sudden cardiac death.

Beta-blockers and calcium blockers can contribute to the reduction of obstructive gradients with a negative inotropic effect, decreasing outflow obstruction and restoring cardiac output.[3]

While there is robust evidence and guidelines for surgical options such as septal myomectomy and alcohol ablation for the management of LVOTO not relieved by medications,



FIGS. 3A AND B: (A) Two-chamber magnetic resonance imaging view of the left ventricle (LV) during diastole with midventricular hypertrophy leading to the hourglass shape of the ventricle. (B) LV during systole. Absolute mid-cavity obliteration is evident along with the formation of an apical aneurysm (arrow).



FIGS. 4A TO C: Left ventriculography showing severe midventricular hypertrophy, with almost complete midventricular obstruction and apical dilation during diastole (A) and systole (B); these findings are best observed in figure 4C.

these treatment modalities have not been standardized for the treatment of mid-cavitary HOCM, though they can be offered.[3] There are some reports of successful transaortic septal myomectomy performed in these patients. However, the surgery is more challenging, encompasses more extensive myomectomy and requires alterations to the conventional surgical procedure used for LVOTO.[18,19] While alcohol septal ablation has been attempted in a limited number of cases,[19,20] it remains controversial due to the possibility of added damage and scar formation in an akinetic apex, from the ablation.[8]

For patients with mid-cavitary HCM and apical aneurysm, treatment options are controversial. Relief of obstruction at the mid- and basal ventricle follows standard recommendations as in the guidelines for HCM,[3,21] but this subset of patients is at a higher risk for ventricular arrhythmias and has been identified as one of the anatomic substrates in decision-making toward a primary prevention implantable cardioverter-defibrillator (ICD).

Anticoagulants are not normally given to patients with traditional HCM unless concomitant atrial fibrillation is noted; however, the mid-cavitary HCM with apical aneurysm variant may represent a higher risk variant due to apical stasis of the blood and high risk of thrombus formation and resulting embolization and warrant anticoagulation.[3]

CONCLUSION

Management of mid-ventricular HOCM is unclear, but failure to intervene can result in fatal ventricular arrhythmias and sudden death. β-blockers are the 1st choice of treatment in patients with HOCM, but the treatment for mid-ventricular HOCM has not yet been established. Dual-chamber pacing and percutaneous myocardial ablation have been proposed as nonsurgical treatments for mid-ventricular HOCM, but long-term benefits and the procedural safety of these options await further observations in large patient populations.

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CHAPTER 21

Environment and Cardiovascular Health

Vivek Gupta, Chinmay Gupta, Chaitanya Gupta

ABSTRACT

Despite many notable advances in treatment and management, cardiovascular disease (CVD) remains the most frequent cause of mortality in all human populations. It is generally believed that even though genetic defects underlie some infrequent forms of heart disease, most CVD is due to interactions between several gene variants and lifestyle factors. The modifiable nature of CVD is further supported by studies showing that even in the absence of large genetic changes, CVD risk in a population is affected by changes in the environment. In one of the largest nations in Asia, the data show that the age-adjusted CVD mortality rates increased by 50% for men and 27% for women due to environmental changes between 1984 and 1999. Hence, to understand the totality of human circumstance, we have to examine the social, personal, and natural domains of the human environment, which collectively make up the human environment.

INTRODUCTION

The Lancet Commission on pollution and health, formed on the basis of data from the Global Burden of Disease (GBD) study,[1] has estimated that air pollution (both indoor and ambient) is the single most important environmental factor presenting a risk to health and represents a greater disease burden than polluted water, soil contamination, and occupational exposures combined.[2]

The populations that are most vulnerable to air pollution live in cities in low- and middle-income countries and make up 55% of the global population. Air pollution is a heterogeneous mixture of particulate matter (PM) and gases.

Although a variety of gases (such as ozone gas) have been shown to have adverse effects on health, the largest body of evidence supports fine PM [≤2.5 μm in diameter (PM2.5)] as the most important environmental threat to global public health. Although PM2.5 has been implicated as a cause in numerous noncommunicable diseases (NCDs), more than half of all the deaths associated with these diseases are from cardiovascular causes.[1-6]

Nature of PM and gaseous co-pollutants guidance documents from Europe, the United States, and the World Health Organization (WHO) have extensively reviewed the size fractions and chemical constituents of the main gaseous air pollutants and their effect on health.[3-5] Whereas previous regulatory standards have principally focused on PM mass in several different fractions, including PM2.5 and coarse PM (2.5–10 μm), PM mass is well acknowledged to be an imperfect metric to understand effects on health. The reasons for assessing PM on the basis of size fractions are primarily related to the ease of quantitative estimation of the mass of each fraction and, conversely, the complexity of alternative measures to quantify pollutants in a mixture that varies by source as well as spatially and temporally.

No standards exist for specific particulate constituents, such as organic or elemental carbon, metals or the ultrafine size fractions within the nano-particulate range (PM0.1). Similarly, although there is strong evidence that road traffic-related air pollution and coal combustion have adverse effects on health, specific sources of pollution are not treated differently in major air-quality standards.[6,7]

For example, road traffic-related air pollution peaks during the late morning and evening rush hours and varies in composition even within short distances.[6,7]

PM2.5 is derived primarily from fossil fuel combustion, industrial processes, and power generation. PM2.5 consists of a mixture of primary particulates, such as elemental carbon; secondary particulates, including organic aerosols derived from volatile compounds; and sulfate and nitrate particles generated by conversion from primary sulfur and nitrogen oxide emissions.[8]

Ultrafine particles are mainly derived from primary combustion, typically short-lived, and influenced by the proximity to the source of emission.

Some nanoparticulates might even be able to disseminate into the systemic circulation after inhalation.[9] Although ultrafine PM can be highly toxic, the epidemiological data to implicate this fraction as an independent predictor of cardiovascular events are only now starting to emerge.

For example, in a prospective study involving 33,831 Dutch residents, exposure to ultrafine PM was associated with an increased risk of heart failure and myocardial infarction (MI).[10]

In the California Teachers Study,[11] organic carbon and sulfates were more strongly associated with cardiopulmonary mortality than other PM2.5 constituents, such as iron, potassium, silicon, and zinc.

A follow-up study revealed that among approximately 45,000 women enrolled, sulfate from fuel combustion and nitrates were associated with mortality from cardiovascular disease (CVD) and ischemic heart disease (IHD), with nitrates having the highest hazard ratio per interquartile range and best fit of the data.[12] In a 2014 systematic review that quantified the associations between particle components and mortality, sulfate, nitrate, and elemental and organic carbons were all linked with all-cause, cardiovascular, and respiratory mortality.[13] Finally, an analysis of 445,860 adults enrolled in the American Cancer Society Cancer Prevention Study II[14] showed that the risk of IHD mortality associated with PM2.5 derived from coal combustion was five times higher than the risk associated with overall PM2.5 mass, suggesting that strategies to limit IHD deaths associated with PM2.5 might be achieved through reductions in exposure to fossil fuel combustion, particularly coal-burning sources.

Use of car air conditioning, car air purifiers, and closing windows could also reduce cabin air pollution concentrations and has been associated with improved heart rate variability.[14] Landscape reform through the placement of highways away from residential areas, use of green belt barriers, and diversion of traffic to alternative routes or restricted hours of use have a large effect on reducing population exposures. Similarly, reducing exposure to sources such as power plants and ports is also important. Finally, exposure to indoor sources of pollutants should also be mitigated.

EPIDEMIOLOGY OF POLLUTION-INDUCED CARDIOVASCULAR DISEASE MORTALITY

The link between PM2.5 and cardiovascular mortality has been noted at both low and high levels of exposure. The association between PM2.5 and cardiovascular mortality has been described in a time series analysis that assessed the hourly, daily, and monthly variations in PM2.5 levels as contributors to cardiovascular death.[3]

A value of <35 μg/m^3 translates to a 0.3–1.0% increase in the relative risk of cardiovascular mortality per 10 μg/m^3 increase in PM2.5. At higher levels of daily exposure (such as in China, where daily PM2.5 levels are 39–177 μg/m^3), on the basis of data from a meta-analysis of seven studies (mostly time series and case-crossover studies), each 10 μg/m^3 increase in PM2.5 was associated with a 0.35% [95% confidence interval (CI) 0.06–0.65%] excess risk of cardiovascular death.[15]

Despite many notable advances in treatment and management, CVD remains the most frequent cause of mortality in all human populations. In the developed world, it kills more people than any other disease, and in low- and middle-income countries, its prevalence is on the rise. Deaths from IHD and stroke have increased worldwide. Even in the United States, where the rates of CVD mortality have been steadily decreasing from their peak in the 1960s, this rate of decline has substantially slowed down since the 1990s,[16] and by 2030, 40.5% of the population is projected to have some form of CVD.[17] While some of this increase may be due to an aging population, the near universal pervasiveness of CVD reflects our inability to prevent its escalating occurrence or to understand its fundamental nature.

The received view is that CVD is due to a set of chronic conditions that arise from a complex interplay between genetic predisposition and environmental influences that lead to progressive deterioration in the structure and the function of cardiovascular tissues. It is generally believed that even though genetic defects underlie some infrequent forms of heart disease, most CVD is due to interactions between several gene variants and lifestyle factors. Although the specific contribution of the genes and the environment remains poorly understood, it is thought that environmental factors and lifestyle play a more dominant role in CVD development. This belief is based on the results of many studies showing that, to a large extent, CVD could be prevented by maintaining a healthy lifestyle. For instance, data from the Nurses' Health Study[18] suggest that 82% of coronary events could be prevented by maintaining a healthy lifestyle. Similarly, it was found that 62% of all coronary events may have been avoided if men in the Health Professionals Follow-up Study had adhered to a low-risk lifestyle. Data combined from both these studies show that 47% of stroke in women and 35% in men could be attributed to the lack of adherence to low-risk lifestyle choices.[4] In a cohort of Swedish women, low-risk behavior was associated with a 92% decrease in risk of MI.[5] Taken together, these data suggest that, for the most part (50–90%), CVD is a modifiable and preventable condition.

The modifiable nature of CVD is further supported by studies showing that even in the absence of large genetic changes, CVD risk in a population is affected by changes in the environment. This is most strikingly demonstrated by data from China, which show that the age-adjusted CVD mortality rates in Beijing increased by 50% for men and 27% for women due to environmental changes between 1984 and 1999.[19] Changing environmental conditions have also been linked to a 75% decrease in CVD risk in Finland within 20 years,[20] and a 24% drop in coronary mortality in Poland in 9 years.[21] In England and Wales, the mortality rate for coronary heart disease (CHD) between 1981 and 2000 has decreased by 62% in men and 45% in women; and more than half of this decline was attributed to a reduction in environmental risk factors.[22] Additionally, a recent study of the decrease in CHD deaths from 1980 to 2000 in the United States suggested that approximately 44% of the decrease could be attributable to environmental changes.[23]

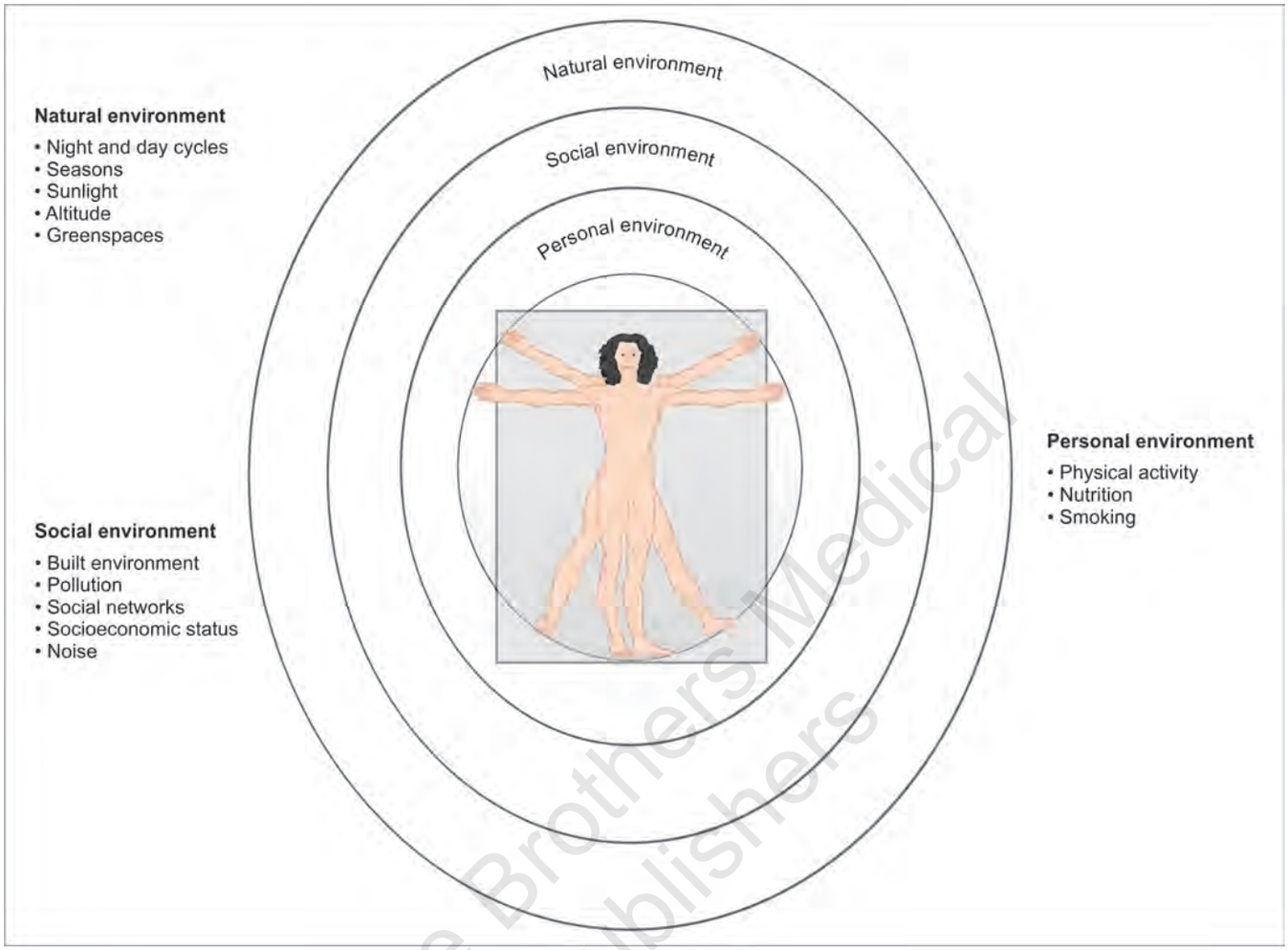

FIG. 1: The human environment. The human environment is categorized into natural, social, and personal domains. The natural domain of the environment is characterized both by natural ecology and geology and by the diurnal cycles, seasons, and greenspaces. The influence of the natural environment is moderated both by the physical attributes of the social environment and by social and networks and socioeconomic status of the individual within society. Features of social environments, such as pollution and occupation, also affect cardiovascular disease (CVD) risk. The social environment permits, promotes, facilitates, or constrains lifestyle choices such as physical activity, nutritional choices, and smoking that constitute important domains of the personal environment. Collective influences of these nested domains of the environment have been found to have a profound influence CVD risk, incidence, prevalence, and severity.

Hence, to understand the totality of human circumstance, we have to examine the social, personal, and natural domains of the human environment, which collectively make up the human environment **(Fig. 1)**. We have to apprehend how these domains interact, and we have to understand how they individually and collectively bear upon CVD risk.

The most primeval component of the human environment is the natural ecosystem. This includes the recurrent day/night cycle, the changing seasons, and the local features of geography; a rather invariant set of conditions that have been the primary determinants of human evolution to date, and which continue to exert a powerful influence on human physiology, psychology, and health. During early human evolution and history, other living things such as bacteria, viruses, predators, parasites, and pests were important health relevant components of the natural environment. However, with increasing civilization, these threats were progressively minimized. Now, the rates of parasitic and infectious diseases have plummeted and, even in developing countries, NCDs have emerged as major threats to human health. Moreover, with increasing acculturation, humans have created complex social environments. These environments have become the primary domains of human activity and they moderate both the salutogenic and the pathogenic influences of the natural environment on humans. Within such natural and social domains, however, humans, with their advanced rational and cognitive abilities, create personal environments, which they populate by their own individual choices. Being a proximal and malleable domain, the personal environment is a powerful determinant of human health. Nevertheless, as reviewed below, all—personal, social, and natural—domains of the human environment individually and collectively affect CVD risk.

According to the GBD study's report,[24-26] NCDs are the leading cause of mortality worldwide.[27] The four main NCDs are CVDs, cancers, respiratory diseases, and diabetes.[28]

Cardiovascular diseases remain the main cause of premature death and disability worldwide.[29] The number of CVD-related deaths is expected to rise to 23.3 million by the year 2030.[30] Furthermore, by 2030, medical burdens of CVD are predicted to increase by about 100%.[31]

The CVD risk factors were categorized into two groups of behavioral and metabolic risk factors. Behavioral risk factors include unhealthy diets (salty food, fat, and sugars), physical inactivity, addiction to alcohol and tobacco, high body mass index (BMI), and waist-to-hip ratio.

Metabolic risk factors include hyperglycemia, hyperlipidemia, inflammation, and raised blood pressure.[32-34] Moreover, socioeconomic discriminations, psychosocial stress, living in deprived conditions, and risky behaviors are associated with NCDs.[35] A systematic review revealed that in many countries, the low socioeconomic status (SES) factors were drinking alcohol, tobacco use, and insufficient consumption of fruits and vegetables.

The socioeconomic factors were inactivity and consuming excess fat, salt, and processed food.[36] The results of some studies showed that having high-quality social relationships was linked to decreased health risks (e.g., immune functioning, cardiovascular functioning, and cognitive decline), while experiencing low-quality social relationships increased the risks.[37-39]

Actually, risk factors for NCDs are multidimensional, comprising biological, social, behavioral, economic, and environmental factors.[40,41] Therefore, political, social, cultural, and economic issues need to be considered in the prevention and control of NCDs.[42]

Prevention programs such as the "25 by 25" campaign aim to reduce premature mortality from CVD by 25% by 2025.[43] In fact, they focus on reducing behavioral and metabolic influences on the risk of CVD, but the long-term success of such lifestyle-related decision-making is multifactorial.[44,45] However, the prevention of CVD risk factors is a high-ranking priority for all health policy planners.[46] Nevertheless, an understanding of the community and household determinants of major cardiovascular risk factors, which may vary by geographical region and cultural background, is needed to develop prevention strategies. For instance, context-dependent strategies must be evaluated to ensure their efficiency.[47] Furthermore, interventions are needed to decrease barriers to cardiovascular healthiness. These strategies must encompass family and community contexts, small groups, interactive methods, culturally sensitive materials, and valid data sources.[48]

DISCUSSION

Determinants that cause CVD can also affect traditional risk factors. A total of 45 determinants were identified in United States and Japan.[49] Findings from a meta-analysis suggest that workplace stress prevention could decrease the incidence of CVD.[50] Even so, prevention of workplace stress would have a much smaller impact than standard risk factors such as smoking. Inappropriate socioeconomic conditions during childhood are associated with the risk of ischemic stroke, regardless of identified risk factors and adult SES.[51] Evidence suggests that during pregnancy, the physiological state of a mother predisposes her newborn to adult diseases such as heart disease and stroke.[52] Strong and consistent evidence, however, indicates that parental, social, childhood, and early life influences and inequalities in health services often lead to an increased risk of CVD in people living in high-income countries with low socioeconomic backgrounds.[53] Childhood deprivation, marked by violence, neglect, and instability in the home, is a phenomenon that has a profound effect on individuals, communities, and society.[54] Adverse experiences in children may be related to high rates of anxiety and lack of sufficient care, contributing to increased risk of adverse coping mechanisms. Adverse experiences of childhood can influence emotional and psychological development and increase susceptibility to mental health issues such as major depression and post-traumatic stress disorder (PTSD), correlated with CVD risk factors. Early life adversity can also change biological performance in stress management pathways and lead to long-term adult stress responses.[55] In high-income countries, the high prevalence of several behavioral and psychosocial risk factors among people with low SES reveals an inverse association of SES with the risk of CVD.[56] In fact, poverty has been considered as one of the most important social determinants of heart disease worldwide.[57] The Marmot Review results highlight that people living in England's poorest neighborhoods will die 7 years earlier on average than people living in the richest neighborhoods. Also, the social gradient of health inequalities shows that the lower is the one's social and economic status, the poorer is the one's health.[58] Socioeconomic deprivation is a strong independent indicator of the risk for heart failure and its adverse effects.[59] The sociodemographic determinants of sudden cardiac deaths include lower SES, position in a social organization, social support, social exclusion and inequities, marital status, the role of employment, and stressful economic and social conditions. Three dimensions of social support have been distinguished: (1) emotional support offered by family members and other close people can improve self-esteem and strengthen the sense of identity; (2) support for evaluation, knowledge, advice, and guidance in difficult situations; and (3) concrete support for practical assistance.[60] All three dimensions are essential in order to maintain good cardiovascular health.

Chronic stress shifts the homeostatic balance with sustained sympathetic overdrive and decreased vagal tone in the autonomic nervous system. Regardless of the involvement or absence of depression, inflammation occurs in neurological, gastrointestinal, and cerebrovascular pathology. Endothelial dysfunction, a preamble to atherosclerosis and atherothrombosis, is closely associated with inflammation. Endothelial dysfunction was observed in depression, which may be a characteristic marker for this disorder.[61] Nonetheless, social support can predict improvements in CVD patients.[62] In contrast, the combination of social isolation and depression worsens the prognosis and accelerates the progression of CVD.[63,64]

In developing countries, urbanization has become a concern, as it affects the prevalence of risk factors for CVD.[65] Psychosocial and behavioral mechanisms mediate the effects

of the factors associated with urbanization on the risk of NCD mortality.[66] For the CVD, it was explained that there are macro-social forces such as urbanization that affect the prevalence of major risk factors (i.e., dietary quality and tobacco use), which in turn are distributed differently within social groups. Furthermore, stressors in urban environments (noise, social isolation, and anxiety) were linked with the development of cardiovascular risk factors (hypertension and atherosclerosis).[67] Due to urbanization, behavioral and environmental changes may increase the risk of CVD.[68] Individual geographical location also affects CVD development. Living in the countryside, surrounded by meadows, trees, flowers, and plains, is quite different from living in the city, where people suffer from traffic jams and noise pollution.[69] Moreover, according to the WHO, air pollution and traffic noise are the two major environmental pollutants that affect health. In 2010, the American Heart Association reported that cumulative evidence regarding air pollution was consistent with the causal relationship between exposure to PM2.5 and cardiovascular morbidity and mortality.[70] Similarly, low neighborhood SES can influence MI survival through inadequate leisure–time physical activity.

Therefore, an intermediate mechanism between neighborhood SES and post-MI outcome is revealed and it can provide opportunities for prevention.[71] In addition, living in a deprived area often impacts CVD survivors, placing them at a higher risk of frequent hospital admissions.[72] It may be more helpful to consider a chronic disease as an "eco-disease," with its environmental and behavioral contributors, and consider nutritionally dependent chronic diseases as "eco-nutritional diseases."[73] Furthermore, socioeconomic and psychosocial factors exert influence on health, and also the development, progression, and prevention of diseases.[74,75]

Scientific evidence suggests that low SES, social isolation, psychosocial stress, hostility, and depression have a negative effect on CVD. Recommendations for promoting behavioral changes and the management of psychosocial and lifestyle factors in clinical practice include strategies for promoting a healthy lifestyle, improving interactions between healthcare providers and patients, implementing multimodal interventions, and managing psychosocial risk.

Factors other than the major risk factors should be considered in health policies such as education, local governments, sports and recreational organizations, health services, mass media, and public departments.

CONCLUSION

Environmental factors play an important, though largely unrecognized, role in causation of CVD. The cardiovascular system is vulnerable to various environmental factors, like air pollution, noise pollution, general ambience and stress. Factors like sedentary life style, smoking, binge alcohol consumption, poor sleep and diabetes mellitus interact with other environmental factors and significantly increase cardiovascular risk. A policy to reduce most of these modifiable factors could substantially lower CVD risk and premature death.

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CHAPTER 22

Proteomics and Metabolomics

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ABSTRACT

In order to understand complex biological events related to a particular disease, it is important to understand properties of the constituent parts. Recent advances in molecular and cellular biology has enabled scientists to perform large-scale genetic studies at protein level and characterize post-translational modification. Similarly, a number of metabolites have been studied for various disease processes. Nuclear magnetic resonance (NMR) has capability to integrate both proteomics and metabolomics. Proteomics and metabolomics provide unbiased pathophysiological assessment of cardiovascular diseases like heart failure, atrial fibrillation, and ischemic heart disease.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in industrialized countries. Although the prevalence of CVD continues to significantly increase worldwide, a detailed understanding of the molecular mechanisms associated with the underlying causes of CVD is still lacking in some areas, particularly for nonischemic CVD. To rectify this, extensive efforts and resources have been placed into systems biology approaches, which attempt to further understand the underlying conditions of CVD to improve early detection and treatment of CVD.

Metabolites are the end products of cellular regulatory processes, and their levels can be regarded as the ultimate response of biological systems to genetic or environmental changes.[1] Metabolites are also highly dynamic in time and space and they carry on the various pathological processes, leading to the ultimate state of disease. Metabolomics allows for a global assessment of a cellular state within the context of the immediate environment, taking into account gene expression, genetic regulation, altered kinetic activity and regulation of enzymes, and changes in metabolic reactions.[2-4] Thus, metabolomics studies, compared with genomics or proteomics, reflect changes in phenotype and function of a tissue, or organism in the state of a particular disease.

The human metabolome can be defined as the complete collection of small molecule metabolites found in the human body.[5] These small molecules include peptides, lipids, amino acids, nucleic acids, carbohydrates, organic acids, vitamins, minerals, food additives, drugs, toxins, pollutants, and just about any other chemical (with a molecular weight <2,000 Da) that humans ingest, metabolize, catabolize, or come into contact with. The metabolome itself is not easily defined. This is because the human metabolome is not solely dictated by our genes. Our environment (what we eat, breathe, drink) and our microflora (the bacteria that live in our intestinal tract) contribute to the metabolome. Over the past 10 years, the number of metabolite entries in the Human Metabolome Database (HMDB, hmdb.ca) has expanded from 2,200 to >110,000 metabolites.[6-8] Presently, the number of measured metabolites refers to only a part of the estimated number of metabolites comprising the entire metabolome. The nuclear magnetic resonance (NMR) and mass spectrometry (MS) are considered to be commonly used platforms for metabolomics analyses. These techniques are effective in detection, identification, and quantification of metabolites through high-throughput, automated manner.

This review presents the existing state of metabolomics technologies, comprising evaluation of several metabolomics

platforms; the evolving usefulness of stable isotopes for metabolic flux researches; and, utilization of metabolomics for understanding mechanisms behind particular CVDs.

Metabolomic Approaches

Nontargeted and Targeted Metabolomics

There are many metabolomics approaches that can be used to investigate a biological question of interest. Nontargeted metabolomics is a broad analytical approach that aims at detection, identification, and quantification of as many metabolites as possible in a biological sample. In contrast, in targeted metabolomics, a selective group of metabolites—often clusters of chemically related analytes—are measured with tailored analytic approaches for absolute quantification. A major benefit of targeted techniques is increased sensitivity and selectivity.

NMR-based Metabolomics

Certain atomic nuclei, such as 1H, 13C, 15N, and 31P, comprise an inherent nuclear spin, and thus having magnetic field related to them. These magnetic properties are manipulated by NMR through an exciting nuclear spin by rapid alterations in an external magnetic field and subsequently recording electromagnetic radiation released due to nuclei relaxation.

The resonance frequency of the energy released, also called the chemical shift, is dependent on the strength of the magnetic field as well as the compound properties. Signal splitting can be displayed by NMR spectra due to spin coupling, because there is an effect of the microenvironment of adjacent nuclei on the resonance frequency of a given nucleus.

In comparison to MS, NMR consists of an advantage in the sense of being noninvasive and non-destructive technique, which permits performance of NMR studies in vivo among humans as well as animals and in situ in perfused tissue systems. Moreover, there is physical isolation of biological sample from the NMR instrument, which leads to improved performance compared to continuous operation. In addition, the diverse spectral libraries of NMR give structural information in detail for recognition, particularly on implementing multidimensional NMR. Eventually, NMR analysis on samples is conducted without the requirement for chemical derivatization, lowering analytic variability.

MASS SPECTROMETRY-BASED METABOLOMICS

Mass spectrometry works by ionizing analytes and then measuring the intensity of the ions produced that is recorded using mass-to-charge (m/z) ratios. The m/z ratio spectra and fragmentation information are useful in identifying metabolites.

Mass spectrometers consist of three major components:

1. The ionization source
2. The mass analyzer(s)
3. The ion detector

Front-end separation, such as GC or LC, is generally done before using a mass spectrometer. In mass spectroscopy, chromatographic separation improves selectivity and reduces potential ion suppression effects.

Gas Chromatography-mass Spectrometry

Gas chromatography (GC) requires volatile metabolites and gas-phase chemistry. GC involves drying of samples, heating at high temperature, and then exposing of metabolites to harsh solution conditions. In spite of this limitation, GC-MS is commonly used to profile organic/amino acids in tissues as well as bodily fluids.[9-11] Advances in GC-Q-TOF (GC-quad time-of-flight) and GC-Q-Orbitrap technologies have enabled GC-MS systems to perform high-resolution, nontargeted metabolomics studies. Combining GC separation with accurate mass determination and MS/MS spectral data can result in improvement of discovery-based metabolomics. However, the general drawbacks of GC-MS techniques, such as their unsuitability for labile compounds and limited metabolite coverage, remain applicable to more advanced systems.

Liquid Chromatography-mass Spectrometry

The wide range of metabolites can be separated by liquid chromatography (LC) as there are advancement in high-performance LC, ultrahigh performance LC technology, as well as different column chemistries. This renders LC to be ideal for high-throughput, comprehensive metabolomic analyses of bodily fluids as well as tissue **(Fig. 1)**.

Liquid chromatography-mass spectrometry (LC-MS) methods, unlike GC-MS, do not need volatile analytes and usually need very little sample preparation after extraction. One of the advantages of LC-MS techniques is that they produce less in-source fragmentation than electron impact-based GC/MS. As a result, there is preservation of metabolite's chemical backbone that helps in determining the molecular weight as well as atomic composition of an unknown metabolite.

STABLE ISOTOPE APPLICATIONS TO METABOLOMICS

Measuring changes in metabolite concentration does not permit any conclusions on metabolic rates or the direction of a flux to be made. Changes in metabolite levels can either result from differential production or the utilization of a given intermediate due to increased flux from synthesizing reactions, decreased flux toward consuming reactions, or alterations in transporter activities. Therefore, accurate determination of metabolic flux is necessary for understanding cellular physiology and the pathophysiology of diseases.

Tracer-based approaches provide an apparent straightforward way of quantitatively assessing dynamic changes in cardiac metabolism. Especially, stable-isotope tracers allow administering probes to a biological system (e.g., animal cells) in cost-efficient and safe way. Metabolic conversions of labeled nutrients or small molecules allow tracking the incorporation of isotopic labels (e.g., carbon, nitrogen or hydrogen) into downstream products and pathways. The detection of specific metabolic products then allows the analysis of total metabolite

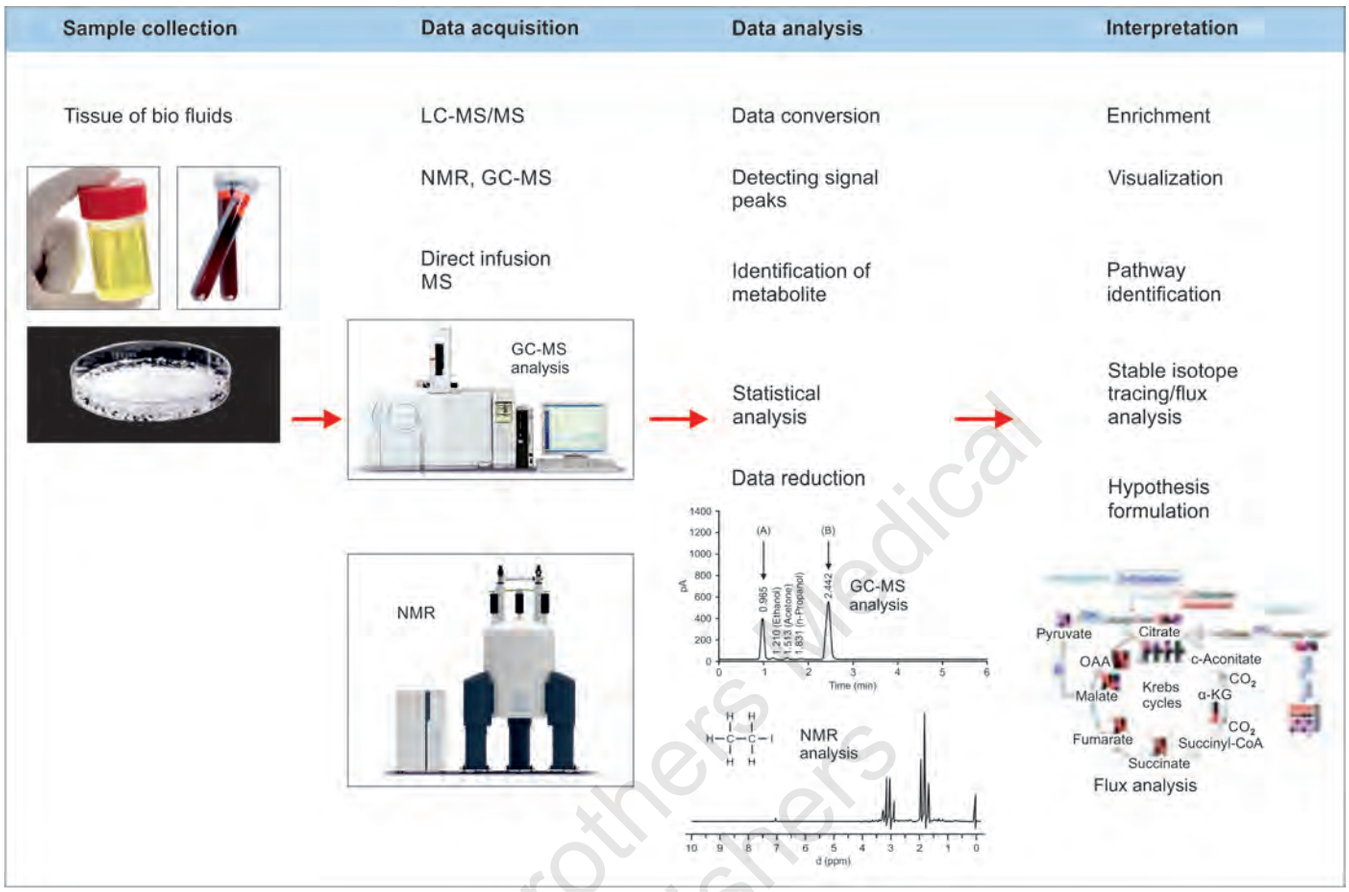

FIG. 1: Workflow of metabolomics.

changes alongside enzyme activities, flux rates, and overall contribution of specific pathways to the metabolic profile to be made. Tracer studies in isolated perfused murine hearts are commonly used to evaluate metabolic changes in model systems that resemble in vivo conditions as closely as possible.[12] Stable isotope probes (e.g., 2H, 13C, 15N) are used to assess multiple pathways simultaneously over longer experimental time periods. In studies related to cardiac metabolism they are administered to the model organism or patient using different delivery approaches including, infusions, injections, diets, or ex vivo perfusions. Heart tissue or biofluids are collected and metabolites are extracted based on downstream analytical methods. For example, tissue samples for total metabolite extraction are freeze-clamped in liquid nitrogen and the tissue is quenched during extraction, using organic solvents. To assess spatial metabolite abundances, tissue slides must be prepared. The incorporation of isotopic labels into metabolites is determined by using analytical techniques such as NMR or MS.

STATISTICAL APPROACHES AND DATA REDUCTION FOR "OMICS" APPROACHES

Although high-throughput metabolomics and proteomics approaches to biomarker discoveries bring many advantages, they also bring the danger of generating false-positive associations due to multiple testing and overfitting of data. Replication is imperative to minimize overfitting of data.[13] Newer statistical techniques, such as advanced resampling methods or control of the false discovery rate,[14] coupled with functional trend analysis, in which changes in constituents of common pathways are analyzed together, can aid in detecting subtle but important changes in multiple variables identified in "omics" approaches.[15-17] Several data reduction strategies can be used to construct multivariate metabolite biomarker profiles[18] including discriminant analysis,[19] partial least squares, principal components analysis,[20] and artificial neural networks.[21]

APPLICATIONS OF METABOLOMICS IN CARDIOVASCULAR DISEASE

The discovery of new biomarkers of CVD is a significant use of metabolomics. They also provide key insights into the pathophysiology of the diseased states by measuring the tissue and circulating concentrations of several metabolites, both in disease and normal states.

Heart Failure

The mammalian heart has a unique ability to switch between fuel sources to adapt to changing physiological or dietary conditions—so-called metabolic flexibility. In the condition

of normal fasting, the healthy heart generates the majority of its energy via mitochondrial fatty acid oxidation, and the remaining is provided by oxidation of glucose, lactate, and ketones.[22] Significant alterations in metabolite profiles, as measured by targeted quantitative LC-MS/MS, indicate that when pathological hypertrophy occurs, greater reliance is on glucose metabolism (enhanced glucose uptake as well as glycolysis) with reduction in fatty acid oxidation.

The shift from fatty acid oxidation to glucose use may promote cardiac hypertrophy and permit the heart to adapt to hemodynamic stresses earlier.[23] However, reliance on glucose for a long time possibly leads to a final state of ATP depletion as well as bioenergetics starvation when cardiac hypertrophy progresses to overt HF.[24,25]

Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) clinical trial[26] has shown that circulating levels of long-chain acylcarnitines were independently predictive of functional status and mortality in patients with chronic systolic HF. These findings suggest a potentially novel way to prognosticate and manage HF patients in clinical practice while providing an impetus for pharmacological targeting of the mitochondria for treatment of HF.

Myocardial Ischemia and Infarction

In patients with myocardial ischemia and infarction, sudden reduction in supply of oxygen and nutrients result in well-known changes in cardiac metabolism, specifically in oxidation of fatty acid as well as glucose.[27-29] In addition, during reperfusion, the sudden reintroduction of oxygen and nutrients results in the mitochondrial reactive oxygen species generation, which cause oxidative damage and finally cellular death.

Metabolomics has recently bring into light that tissue succinate levels regulate production of mitochondrial reactive oxygen species during reperfusion, which was previously considered to be a nonspecific response to the restoration of oxygen to ischemic tissues .[30]

In the study by Chouchani et al.,[30] 13C-substrate tracing was demonstrated in case of isolated ischemia-reperfusion hearts. Accumulation of succinate was found in every ischemic tissue. It was also found that succinate oxidation during reperfusion drives mitochondrial reactive oxygen species accumulation as well as injury. For decreasing ischemia-reperfusion injury, it is a good option to modulate succinate metabolism during reperfusion.

Amino acids serve as building blocks for protein synthesis as well as energy-providing substrates, although the relative importance of a bioenergetic contribution by amino acids in the heart remains unclear under both physiological or pathological conditions,[31] their functional relevance in the pathogenesis of heart failure is unknown. Recent studies have shown that the BCAA (branched chain amino acids, they include leucine, isoleucine, valine) catabolic pathway is the most significantly altered metabolic change in failing heart. In the BCAA catabolic pathway, BCAAs are first converted into branched-chain alpha-ketoacids (BCKAs) by branched-chain amino-transferase (BCAT) in a reversible reaction, followed by irreversible decarboxylation by branched-chain alpha-ketoacid dehydrogenase (BCKDH) complex, and eventually metabolized to acetyl-CoA or succinyl-CoA for oxidation in the tricarboxylic acid (TCA) cycle.

Tao Li et al.[32] showed that in normal hearts, BCAAs directly inhibit pyruvate dehydrogenase (PDH) activity. It has long been established that PDH activity is a key determinant for myocardial I/R injury. The production of UDP-GlcNAc by HBP (hexosamine biosynthesis pathway) governs the function of numerous proteins is also downregulated by BCAAs, resulting in high susceptibility to stress due to reactive oxygen species generated during reperfusion. Finally, several studies showed that pharmacological enhancement of BCAA catabolic activity significantly preserved cardiac function.

Cardiovascular Risk Prediction

Several applications of the metabolomics discussed previously demonstrate the use of the technology in revealing underlying metabolic mechanisms of CVDs. Metabolomics also play a significant role in identifying biomarkers for predicting risk of CVDs.[33-35]

As an example, among patients who underwent diagnostic coronary angiography, targeted quantitative LC-MS/MS-based metabolomics demonstrated independent predictive value of circulating BCAA metabolite factor for obstructive coronary artery disease.[36,37]

The role of the gut microbiome in finding the levels of circulating host metabolite is a rapidly evolving field of blood-based metabolomics in prediction of cardiovascular risk. Trimethylamine N-oxide (TMAO) is one such metabolite.

As per Wang Z et al.,[38] when unbiased LC-MS/MS metabolomics are used in patients with high-risk for CVD, novel markers of future cardiovascular events were recognized. The independent predictors of cardiovascular risk in a training and validation cohort were three metabolites of the dietary lipid phosphatidylcholine (present in red meat), which were TMAO, betaine, and choline. A successive study reported that when mice were fed with a diet supplemented with TMAO or choline, atherosclerosis was promoted.

CONCLUSION

Majority of the CVDs consist of disturbed cardiac metabolism. Specifically, metabolomics improved the knowledge of the molecular underpinnings of such conditions. Metabolomics, dissimilar to other omics technologies, gives a functional integration of upstream genetic, transcriptomic, and proteomic variation, and environmental exposures, thereby indicating molecular processes that are more proximal to disease states.

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CHAPTER 23

Epidemiology of Aortic Valve Disease in India

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ABSTRACT

Aortic valve disease is the second most prevalent valvular heart disease (VHD) in India while it is more common in the western population. Rheumatic etiology is yet common and contributes to one-third of valvular heart disease in India. The true prevalence of aortic valve disease in India is not known but as per western estimates it must be around 2–3% in the elderly subgroup. Indian population is still young so as it starts aging there will be a significant increase in incidence of degenerative aortic valve disease.

INTRODUCTION

Aortic valve disease is the most prevalent valvular heart disease (VHD) in those above 60 years of age.[1] The actual prevalence of it in the Indian population is not clearly known in absence of large scale multicenter studies. Aortic valve disease adds up significant morbidity and mortality in the elderly population with increased surgical risk being a hindrance for surgical aortic valve replacement.[2] Transcatheter aortic valve replacement (TAVR) has become a gold standard treatment for those with aortic stenosis (AS) and increased surgical risk with it becoming indication now also in those with low surgical risk and age >65 years of age.[3] However, till date TAVR is yet out of the reach of average Indian because of cost issues.

The epidemiology of aortic valve disease varies between the low income and high income countries with infective etiology (rheumatic heart disease) being more common in low income countries and degenerative etiology more common in high income countries. The prevalence of AS in western population with age >75 years of age has been 12.4% and those with severe AS being 3.4%.[4] The prevalence of AS keeps increasing with increasing age. The prevalence is 0.2% in 50–59 years age group, 1.3% in 60–69 years age group, 3.9% in 70–79 years age group and 9.8% in those with 80–89 years with incidence of new AS being 5 in 1,000 in those with mean age being >60 years of age.[5] The prevalence of aortic regurgitation (AR) has been reported to be 0.5% for moderate to severe AR in total US population as well as African American cohort.[6,7]

Currently, the Indian population stands at around 1.4 billion and this makes it second largest populous country in the world. Of this there is only 6.5% which are above 65 years of age and these are the ones with risk for degenerative aortic valve disease. Thus, estimated prevalence of severe AS would be around 0.9 million people that would require some form of intervention to improve the prognosis.

TRENDS OF VALVULAR HEART DISEASE IN INDIA

In Indian pretext, the most commonly involved single valve was the mitral valve with mitral stenosis being most common lesion.[8,9] Prevalence of aortic valve disease among VHD is 29% in rheumatic cohort where it is mostly associated with other valves while it is 35% in the overall cohort.[8] Isolated aortic stenosis (IAS) has been reported to be around 7.3% and it is third most common valve lesion.[8] Etiology behind IAS is degenerative calcification in 65%, bicuspid aortic valve (BAV) in 33% and rheumatic in 1.1%. Isolated aortic regurgitation (IAR) constitutes 5.8% with etiology most commonly being rheumatic followed by BAV, aortic root disease, and degenerative calcification.[8] In a single center study from North India, among all VHD predominant aortic valve disease constituted about 16%.[9] Of which there were 4.8% cases of IAS, 2% of IAR, and 9.4% with multivalvular involvement.[9] Mean age of presentation in the study for IAS and IAR was 44 and 35 years

TABLE 1: Patterns of aortic valve disease in various studies.

	Manjunath et al. 2014[8]		Sahu et al. 2020[9]		Lung et al. 2003[10]	
	IAS (7.3%)	IAR (5.8%)	IAS (4.8%)	IAR (2%)	IAS (33.9%)	IAR (10.4%)
Degenerative	65%	8.2%	58.1%	5.2%	81.9%	50.3%
Bicuspid valve	33.9%	15.7%	25%	42.7%	5.4%	15.2%
RHD	1.1%	47.8%	2.9%	36%	11.2%	15.2%
Congenital	–	15.7%	24.1%	2.7%	–	–
Aortic root	–	12.9%	–	10.7%	–	7.7%
IE	–	–	–	2.7%	–	7.5%

(IAR: isolated aortic regurgitation; IAS: isolated aortic stenosis; IE: infective endocarditis; RHD: rheumatic heart disease)

respectively with >60% being males.[9] IAS showed bimodal presentation in this study group with one peak in the age group of 0–10 years and other in the age group of 50–59 years.[9] Etiology behind IAS was degenerative calcification in 58%, BAV in 25%, and congenital AS in 24%. Rheumatic heart disease causing IAS was very rare only about 2%. In IAR, the most common reason was BAV in 42%, rheumatic heart disease in 36%, aortic root disease in 10%, and 2.5% each for infective endocarditis and subaortic membrane.[9]

In European population when we look at the most common single valve involvement it has been found to aortic valve with AS being the most common lesion around 33%.[10] The etiology responsible for IAS was degenerative calcification in 82%, rheumatic in 11% and congenital in 5%. Mean age of the population was 64 years thus a decade later when compared to the Indian population.[10] Similarly the proportion of AS has been reported to be 16.5% in US population and 55% in Swedish population.[6,11] IAR was reported to be around 10% with etiology being degenerative calcification in 50%, rheumatic heart disease in 15%, congenital in 15%, and aortic root disease/infective endocarditis each in 7%.[10] Proportion and etiological distribution of aortic valve disease in various studies has been shown in **Table 1**.

The true prevalence of aortic valve disease is not yet known but looking at global data it appears to be around 2% in those above the age of 65 years. Average Indian population is still young when compared to the western demographics. So with passing time as the population starts aging there will also be significant increase in patients with aortic valve disease. With country developing there is clear transition of etiology behind aortic valve disease changing from infective to degenerative. The most commonly affected single valve also changes from mitral to aortic as aortic is most commonly affected valve in degenerative etiology.

CONCLUSION

Though multivalvular involvement is common in RHD, finding of isolated aortic valvular disease is mostly non-rheumatic with bicuspid aortic valve and degenerative lesions taking the front seat. Also, some studies from India have reported acquired aortic valve disease at relatively younger age. There is definitely a serious lacuna of a large, multicentre population based study from India. Evolution of transcatheter valve therapies has created a new interest into the epidemiological studies of valvular heart diseases.

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CHAPTER 24

Dual Pathway Inhibition to Prevent Atherothrombotic Vascular Events: Current Status

Vibhav Sharma, Nitish Naik

ABSTRACT

Despite advances in secondary prevention strategies in patients with cardiovascular disease, the residual risk of recurrent atherothrombotic events remains high. Dual-antiplatelet therapy is the standard of care for secondary prevention in patients with acute coronary syndrome (ACS), whereas single antiplatelet therapy, usually with aspirin, is the standard of care for secondary prevention in stable patients with coronary artery disease (CAD), peripheral artery disease (PAD), or cerebrovascular disease. However, atherosclerotic plaque disruption in addition to triggering platelet activation also results in thrombin generation because of tissue factor exposure. Therefore, blocking both pathways by combining antiplatelet therapy with an anticoagulant, or dual pathway inhibition (DPI), has the potential to be more effective than inhibiting either pathway alone. The benefit of DPI has been demonstrated in many trials like ATLAS ACS 2-TIMI 51, COMPASS, and VOYAGER PAD trials, where the combination of rivaroxaban vascular dose (2.5 mg twice daily) plus aspirin significantly reduced the risk of atherothrombotic events compared with aspirin across a broad range of patients, including those with recent ACS, those with chronic CAD and/or PAD, and patients with PAD who have undergone peripheral revascularization. This manuscript provides the rationale for this regimen in more detail.

INTRODUCTION

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide. There is a residual thrombotic risk despite dual antiplatelet therapy (DAPT) in these patients. There is a 5–10% risk of recurrent ischemic events despite optimal treatment for secondary prevention.[1] The REACH (Reduction of Atherothrombosis for Continued Health) registry showed that patients with a prior history of ischemic events had a 18.3% incidence of a recurrent event during 4 years of follow-up with the greatest risk being in the initial 30 days following the event.[2] Aspirin has been shown to decrease major adverse cardiovascular events by 19% and cardiovascular death by 9% as compared to placebo.[3] Platelets have a central role in thrombotic complications and the role of antiplatelets in secondary prevention is well established, but thrombosis is not mediated by platelets entirely as we can recall from an understanding of basic sciences and there is definite evidence of involvement of the coagulation cascade in recurrent ischemic events **(Fig. 1)**. In a study of the novel oral anticoagulant ximelagatran,[4] a decline in D-dimer levels, a surrogate for in vivo coagulation activity, correlated directly with decreased risk of recurrent ischemic events. Similar findings were seen in the RE-DEEM (Dabigatran vs. Placebo in Patients with Acute Coronary Syndromes on Dual Antiplatelet Therapy) of dabigatran. Also studies of vitamin K antagonists (VKAs), in the era prior to DAPT, had shown benefit of anticoagulation, but showed increased bleeding risk. These observations led to the trials of anticoagulation for secondary prevention of CAD, though, the role of direct oral anticoagulants (DOACs) in the management of CAD in the absence of atrial fibrillation or any other indication for anticoagulation is not well established. In addition, there are concerns about the increased bleeding risk associated with the combined use of anticoagulation and antiplatelets. With this topic review, we intend to summarize the rationale behind the use of anticoagulation in addition to antiplatelet therapy in patient with stable CAD and those following an acute coronary syndrome (ACS), without concomitant atrial fibrillation or another indication for anticoagulation and the available evidence base.

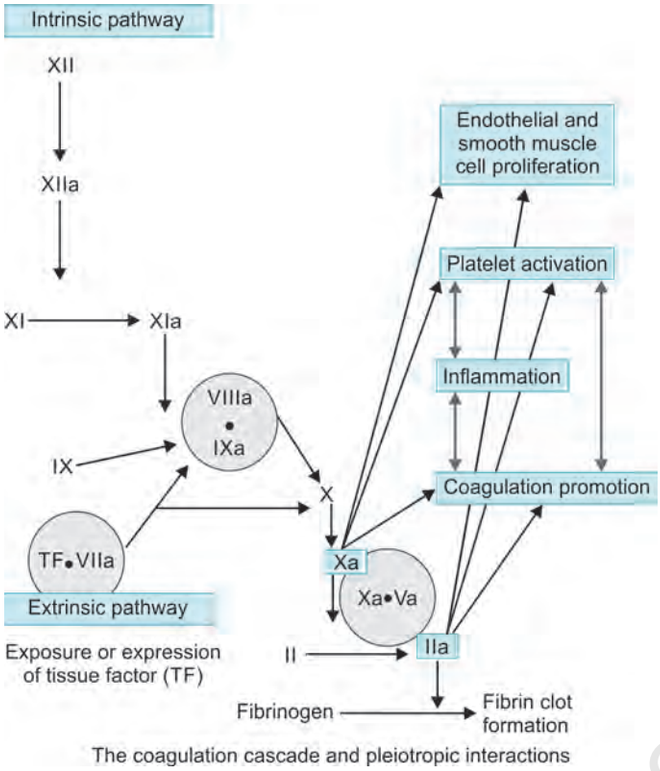

FIG. 1: Interaction between coagulation cascade, platelet activation, and inflammation.

PATHOPHYSIOLOGY OF ATHEROTHROMBOSIS AND THE RATIONALE BEHIND THE USE OF ANTICOAGULATION

Platelet activation, aggregation, and adhesion have a central role in the pathogenesis of atherosclerotic lesions, both atherogenesis and atherothrombosis. Inflammation, a hypercoagulable state, and enhanced platelet reactivity all contribute to plaque vulnerability. Vascular injury exposes subendothelial collagen and von-Willebrand factor leading to platelet adhesion and activation, followed by release of adenosine diphosphate (ADP) and thromboxane A2 which, in turn, amplify platelet activation and aggregation. Continuous ADP-P2Y12 receptor signaling sustains activation of Gp IIb-IIIa receptor signaling leading to stable platelet rich thrombus. Thrombin is mainly responsible for clot stabilization rather than clot formation. Also, thrombin is a potent platelet activator through PAR receptors. Perimyocardial infarction period is a hypercoagulable state with increased thrombin generation which persists for weeks to months following an ACS. Markers of thrombin generation have been shown to be higher in ACS patients and levels correlate with the probability of having a recurrent ischemic event. In a study that assessed the coagulation status of patients with unstable angina or myocardial infarction (MI) based on plasma levels of prothrombin fragment 1 + 2 (F1+2) and fibrinopeptide A (FPA), at baseline and after 6 months, found that those experiencing a recurrent ischemic event had a persistent hypercoagulable state.[5] An unstable yellow plaque with adherent thrombus may persist up to 30 days after an ACS as shown in an angioscopy based study of post-MI patients.[6] DOACs also have some anti-inflammatory effects as well. These mechanisms underlie the hypothesis that anticoagulation may have a role in secondary prevention of CAD.

Thrombolysis in myocardial infarction (TIMI) bleeding criteria: It will be useful to quickly review the TIMI bleeding criteria, as it is an important safety outcome in most of the trials discussed subsequently.

- *Major*: Intracranial hemorrhage
  - ≥5 g/dL decrease in hemoglobin (Hb) concentration
  - ≥15% absolute decrease in hematocrit
- *Minor*: Observed blood loss–
  - ≥3 g/dL decrease in Hb
  - ≥10% decrease in hematocrit

  No observed blood loss–
  - ≥4 g/dL decrease in Hb
  - ≥12% decrease in hematocrit
- *Minimal*: Any clinically overt sign of hemorrhage associated with <3 g/dL decrease in Hb or <9% decrease in hematocrit

REVIEW OF AVAILABLE DIRECT ORAL ANTICOAGULANTS: PHARMACOKINETICS AND PHARMACODYNAMICS

Relevant pharmacokinetic and pharmacodynamic properties of available DOACs are summarized in **Table 1**.

STABLE CORONARY ARTERY DISEASE

Vitamin K antagonists have been shown to decrease the risk of major adverse cardiovascular events (MACE) but significantly increase bleeding in secondary prevention of stable CAD.[7]

The COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies)[8] was a double-blind, double-dummy, randomized trial published in 2017 that assessed the efficacy of rivaroxaban as a single agent or combined with aspirin compared with aspirin alone for the secondary prevention of stable atherosclerotic vascular disease. The trial included 27,395 patients with CAD (73%) or peripheral artery disease (PAD) (9%), or both (18%). It included CAD patients with—(1) MI within 20 years, (2) Multivessel CAD with stable or unstable angina, (3) Patients who have undergone multivessel percutaneous coronary intervention (PCI) or CABG [4–14 days after coronary artery bypass graft (CABG)]. PAD patients included had—(1) history of revascularization, (2) history of amputation, claudication with ankle-brachial index (ABI) <0.90, stenosis >50%, (3) carotid revascularization or stenosis >50%. Those <65 years of age should have had disease of at least two vascular beds or ≥2 additional risk factors (1) smoking, (2) diabetes, (3) ischemic cerebrovascular accident (CVA) 1 month old (non-lacunar), (4) heart failure, (5) estimated glomerular filtration rate (eGFR) <60 mL/min. Notably, patients at high-bleeding risk were excluded. The study randomized participants into three arms: (1) Rivaroxaban

TABLE 1: Relevant pharmacokinetic and pharmacodynamic properties of available direct oral anticoagulants (DOACs).

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism	Anti-IIa	Anti-Xa	Anti-Xa	Anti-Xa
Bioavailability	3–7%	80–100%	50%	62%
Peak plasma concentration	• 1–2 hours • Delayed by food	• 2–4 hours • Shortened by food	3–4 hours	1–2 hours
Plasma t½	12–17 hours	5–13 hours	8–15 hours	10–14 hours
Dose	110 or 150 mg bd	• 2.5 mg bd • 15 mg od • 20 mg od	5 mg bd	60 mg od
Renal excretion	80%	33%	27%	50%
Renal adjustment	Avoid use if CrCl <30 mL/min or dialysis dependent	Avoid use if CrCl <30 mL/min or dialysis dependent	• 2.5 mg bd • Can be given even if dialysis dependent	• CrCl 15–50 mL/min—30 mg od • <15 mL/min—avoid
Hepatic adjustment	None	Avoid in moderate-to-severe impairment	Avoid in severe impairment	Avoid in moderate-to-severe impairment

2.5 mg bd + Aspirin 100 mg od, (2) Rivaroxaban 5 mg bd, (3) Aspirin 100 mg od who were followed for a mean duration of 23 months (the trial was stopped early due to efficacy in the very low dose rivaroxaban group). Stroke, cardiovascular death, and MI taken together comprised the primary outcome of the study and occurred in significantly fewer (24% lower) patients in rivaroxaban + aspirin group as compared to aspirin alone (4.1% vs. 5.4%; HR 0.76; 95% CI 0.66–0.86; $p < 0.001$), but the combination group also showed greater number of major bleeding (70% higher) events as compared to aspirin alone (3.1% vs. 1.9%; HR 1.70; 95% CI 1.40–2.05; $p < 0.001$). The benefit was mainly driven by a significant reduction in stroke overall (0.9% vs. 1.6%; $p < 0.001$) and CV death (1.7% vs. 2.2%, $p = 0.02$). There was no significant difference in the incidence of non-fatal MI in the three arms (1.9% vs. 2.0 vs. 2.2%). Of the major bleeding events, most were into the gastrointestinal (GI) tract with no significant difference in fatal bleeding, central nervous system (CNS) bleeding, or symptomatic bleeding into a critical organ. On the other hand, outcomes in patients given rivaroxaban alone were not better compared to aspirin alone but major bleeding was significantly higher in this group.

One salient feature of this trial was that they combined safety and efficacy outcomes and derived a common parameter called net clinical benefit (NCB), which was defined as a composite of cardiovascular death, stroke, MI, *fatal bleeding* (0.2 vs. 0.2 vs. 0.1%, no significant difference) or symptomatic bleeding into a critical organ which was again found to be significantly lower (20%) with rivaroxaban plus aspirin combination as compared to aspirin alone (4.7 vs. 5.9%; HR 0.80; 95% CI 0.70–0.91; $p < 0.001$). The results of the trial were consistent among both the subgroup of CAD and PAD and did not differ according to age, gender, race, ethnicity, renal function, body weight, and history of cardiovascular risk factors.

The trial had a 3 × 2 factorial design and also randomized participants to pantoprazole versus placebo and there was no significant difference seen in terms of upper GI events, though there may be a decrease in bleeding from gastroduodenal lesions.

Stable CAD group: Among the subgroup of CAD patients ($n = 24,842$), there was a significant 26% reduction in MACE (4.0% vs. 6.0%; HR 0.74; $p < 0.0001$) in group 1, again due to a significant reduction in stroke and death, without a significant reduction in MI. Group 2 showed a nonsignificant reduction in MACE. Bleeding events were similarly higher in both the groups that included rivaroxaban. The benefit with very low dose rivaroxaban did not vary with a history of MI, time since MI or a history of PCI.

Similar findings were also observed in two substudies of the trial: COMPASS-PAD[9] and COMPASS-lower extremity PAD[10] studies.

COMPASS-CABG substudy:[11] Rivaroxaban was studied in patients with CABG to prevent bypass graft failure. Rivaroxaban alone or in combination with aspirin was not shown to be beneficial as compared to aspirin alone in preventing early graft occlusion. The primary outcome of the study was graft failure at the end of 1 year as assessed by CT coronary angiogram and there was no significant difference between the three groups.

ACUTE CORONARY SYNDROME

Several older publications that studied the role of oral anticoagulation with a VKA in addition to aspirin alone or aspirin/clopidogrel combination in reducing recurrent ischemic showed benefit with added anticoagulation but at the cost of increased risk of bleeding.

2002: In a randomized controlled trial (RCT) involving 3,630 patients after an MI, including patients who underwent PCI or CABG, warfarin alone or in combination with aspirin, intended to target an international normalized ratio (INR) between 2.8 and 4.2, compared to aspirin alone was superior in reducing ischemic events but at the cost of increased bleeding.[12]

2002: The ASPECT-2 (Antithrombotics in the Secondary Prevention of Coronary Thrombosis-2) study—randomly assigned 999 patients to low-dose aspirin, high-intensity

oral anticoagulation, or combined low-dose aspirin and moderate intensity oral anticoagulation. Both arms containing anticoagulation were superior to low-dose aspirin alone in terms of efficacy.[13]

2005: A meta-analysis comprising 10 RCTs comparing ACS patients treated with aspirin plus warfarin (INR > 2) versus aspirin alone showed that the combination was superior to aspirin alone in decreasing MI, ischemic stroke, and revascularization although warfarin increased bleeding up to 2.5 times. PCI patients were not included.[14]

2006: Another meta-analysis comparing aspirin plus warfarin combination after an ACS showed that the combination was superior to aspirin alone in preventing major adverse events when INR was maintained in the range of 2–3 although it doubled the risk of major bleeding.[15]

2007: In a retrospective analysis of patients treated by PCI, warfarin plus aspirin combination was shown to be inadequate in preventing stent thrombosis and increased the risk of major bleeding.[16]

Although, these trials showed increased protection, at the cost of increased bleeding, this approach took a backfoot with the advent of DAPT. However, with the development of non-vitamin K antagonist oral anticoagulants (NOACs), there is renewed interest to explore this approach.

The first NOAC to be studied for this purpose was ximelagatran, a direct thrombin inhibitor, which was compared with placebo on a background of aspirin and showed a 24% reduction in the composite endpoint of death, MI, and recurrent ischemia, but significant increase in bleeding was seen.[17]

This was followed by the RE-DEEM trial that studied dabigatran on a background of DAPT, compared to placebo, among ACS patients, and showed a significant increase in minor and major bleeding, which increased up to four times in the high-dose group (150 mg bd).[18] Similar results were found in the RUBY-1 trial that tested darexaban, in ACS patients in a background of DAPT.[19]

The APPRAISE-2,[20] ATLAS ACS 2-TIMI-51,[21] and GEMINI ACS-1[22] are the latest trials that studied the role of DOACs in secondary prevention in the setting of ACS, the findings of which are summarized in **Table 2**.

The *APPRAISE-2* (Apixaban with antiplatelet therapy after acute coronary syndrome) trial was a double-blinded RCT that compared the efficacy of apixaban 5 mg bd to placebo in 7,392 patients who had a recent ACS within the previous 7 days and were at a higher risk of recurrent ischemic events (at least two risk factors). Majority of the participants had not undergone revascularization. The participants were followed up for a median of 241 days and primary efficacy outcome, which was defined as a composite of CV death, MI, or ischemic stroke occurred in 7.5% of participants compared to 7.9% in placebo (HR 0.95; 95% CI 0.80–1.11; $p = 0.51$) showing no benefit, whereas TIMI major bleeding including fatal bleeding and intracerebral hemorrhage (ICH) increased significantly (1.3% vs. 0.5%; HR 2.59; 95% CI 1.50–4.46; $p = 0.001$). This increase in bleeding was seen in patients taking both, the combination antiplatelet therapy as well as aspirin alone. An important drawback of the study is that it was terminated prematurely due to an increase in bleeding events, therefore reliable conclusions cannot be drawn from the study.

The *ATLAS ACS2-TIMI-51* (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction 51) trial was double-blind RCT, published in 2012, that studied the role of low-dose rivaroxaban in improving cardiovascular outcomes in patients with a recent ACS receiving standard DAPT. The study included 15,526 participants who were randomly assigned in a 1:1:1 manner to receive rivaroxaban 2.5 mg bd, rivaroxaban

TABLE 2: Direct oral anticoagulants (DOACs) in acute coronary syndrome (ACS).

	APPRAISE-2	ATLAS ACS 2-TIMI-51	GEMINI ACS-1
Study design	RCT	RCT	RCT
Number of participants (n)	7,392	15,526	3,037
Study population	• Recent ACS • Higher risk of recurrence	ACS patients on a background of DAPT	ACS
Study arms	Apixaban 5 mg bd vs. placebo	• Group 1: Rivaroxaban 2.5 mg bd • Group 2: Rivaroxaban 5 mg bd • Group 3: Placebo	• Group 1: Rivaroxaban 2.5 mg bd + P2Y12 inhibitor • Group 2: Aspirin 100 mg od + P2Y12 inhibitor
Primary outcome	• Composite of CV death, stroke or MI • 7.5 vs. 7.9% (HR 0.95; 95% CI 0.80–1.11)	• Composite of CV death, stroke, MI • Group 1 vs. group 3—9.1 vs. 10.7% (HR 0.84; 95% CI 0.72–0.97) • Group 2 vs. group 3—8.8 vs. 10.7% (HR 0.85; 95% CI 0.73–0.98)	• TIMI clinically significant bleeding • 5.0 vs. 5.0% (HR 1.09; 95% CI 0.80–1.50)
Major bleeding	1.3 vs. 0.5% (HR 2.59; 95% CI 1.50–4.46)	• Group 1 vs. group 3—1.8 vs. 0.6% (HR 3.46; 95% CI 2.08–5.77) • Group 1 vs. group 3—2.4% vs. 0.6% (HR 4.47; 95% CI 2.71–7.36)	

(APPRAISE-2: Apixaban for Prevention of Acute Ischemic Events 2; ATLAS ACS 2-TIMI-51: Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction 51; DAPT: dual antiplatelet therapy; GEMINI ACS-1: Safety of Rivaroxaban Versus Acetylsalicylic Acid in Addition to Either Clopidogrel or Ticagrelor Therapy in Participants With Acute Coronary Syndrome; RCT: randomized controlled trial)

5 mg bd or placebo on a background of standard DAPT. The basis for selection of these doses was that ATLAS ACS TIMI-46 trial[23] that was a phase 2 trial involving patients with a recent ACS and found that daily doses of rivaroxaban from 5 to 20 mg decreased the composite of death, MI, or stroke and there was a dose-dependent increase in bleeding such that the greatest benefit was obtained with the lower doses. In ATLAS ACS 2-TIMI 51 trial, the participants were followed for a mean duration of 13 months and a maximum of 31 months to look at the composite of cardiovascular death, MI, or stroke as the primary efficacy endpoint and TIMI major bleeding (not related to CABG) as the primary safety endpoint. The 2.5 mg dose of rivaroxaban significantly decreases the primary efficacy endpoint, 9.1% vs. 10.7% (HR 0.84; 95% CI 0.72–0.97; p = 0.02) as well as reduced CV death, 2.7% versus 4.1% (HR 0.66; 95% CI 0.51–0.86; p = 0.002), and all-cause death, 2.9% versus 4.5% (HR 0.68; 95% CI 0.53–0.87; p = 0.002). The 5 mg dose also significantly reduced the primary efficacy endpoint, 8.8% versus 10.7% (HR 0.85; 95% CI 0.73–0.98; p = 0.03), but did not significantly decrease CV or all-cause death. Both the doses significantly increased the rates of TIMI major bleeding and ICH but rates of fatal bleeding did not increase significantly as compared to placebo (0.3% vs. 0.2%, p = 0.66), and as expected, both TIMI major bleeding (1.8% vs. 2.4%, p = 0.12) as well as fatal bleeding (0.1% vs. 0.4%, p = 0.04) were significantly lower with the 2.5 mg dose when compared head-to-head. To conclude, the trial showed a 34% relative risk reduction and 1.4% absolute reduction in cardiovascular mortality and a 32% relative risk reduction and 1.6% absolute risk reduction in terms of all-cause death along with a significant reduction in stent thrombosis (2.2% vs. 2.9%, p = 0.02) and a nonsignificant reduction in MI. One reason for a difference between the results of APPRAISE-2 and ATLAS ACS 2-TIMI-51 trials might be due to the exclusion of patients with a history of stroke or transient ischemic attack (TIA) in the latter, this is a subgroup where higher degrees of antithrombosis have not shown any added benefit.

Clinically, significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (*GEMINI-ACS-1*): This was a double-blinded RCT, published in 2017, assessed the safety of rivaroxaban 2.5 mg bd compared to aspirin 100 mg od on a background of P2Y12 inhibition (clopidogrel: 44% or ticagrelor: 56%, based on physician discretion) among 3,037 ACS patients (mostly treated with PCI), randomized in a 1:1 manner within 10 days of the index presentation. The primary endpoint was non-CABG TIMI clinically significant bleeding up to day 390 and occurred in 5% of the participants in both the groups. The difference was not significant (HR 1.09; 95% CI 0.80–1.50; p = 0.58). There was a low frequency of TIMI major bleeding, fatal bleeding, and ICH in both the groups (all <1%). The results did not vary between ticagrelor (6–7%) and clopidogrel (~3%) subgroups, although ticagrelor group, in general had higher rates of bleeding. The composite outcome of CV death, MI, stroke or definite stent thrombosis did not differ between the groups (5% vs. 5%; HR 1.06; 95% CI 0.77–1.46; p = 0.73). Trial essentially replaced the DAPT regimen for a DOAC-SAPT regimen and found that both the approaches were equally safe, though it was not powered to assess the efficacy of the novel approach, and further large-scale trials are needed.

So, to summarize the findings of above trials, what we have learnt so far is that, apixaban did not show any ischemic benefit but did increase the risk of bleeding. Low-dose rivaroxaban did show some ischemic benefit but again, in combination with DAPT, increased the risk of bleeding. Finally, low-dose rivaroxaban when given with single antiplatelet agent P2Y12 inhibitor without aspirin had similar bleeding risk as compared to standard DAPT; however, the efficacy of this combination remains to be determined.

CONCLUSION

To conclude, the role of NOACs in secondary prevention of CAD is emerging and has a strong pathophysiological basis. As far as stable CAD is concerned, very low-dose rivaroxaban in combination with aspirin showed a definite benefit in terms of reducing ischemic endpoints and mortality but at the cost of significantly increased major bleeding, and may be used at discretion only in those patients with higher risk of recurrent ischemic events and those with recurrent ischemic events despite standard antiplatelet therapy. The combination of rivaroxaban 2.5 mg twice daily with low-dose aspirin has been approved for secondary prevention of CAD/PAD by the United States Food and Drug Administration (US-FDA) in 2018. As far as ACS is concerned, apixaban did not show any benefit. Very low dose and low-dose rivaroxaban did show benefit but significantly increased bleeding risk. Further studies are needed to assess the efficacy of very low-dose rivaroxaban as a replacement to aspirin on a background of P2Y12 inhibitor, since this combination was shown to have similar bleeding rates as compared to standard DAPT.

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CHAPTER 25

Renal Denervation Therapy, Is it the Way Forward?

Sameer Gupta, Purshotam Lal, Prashant T Upasani

ABSTRACT

Sympathetic denervation for treating hypertension (HTN) has been an area of active research for many years. An early study of catheter-based renal denervation (RDN) using a radiofrequency (RF) ablation technique showed that it was successful in lowering blood pressure (BP). However, a later randomized, controlled trial (SYMPLICITY HTN-3) did not demonstrate improved office and 24-hour ambulatory BP compared with sham treatment. Further studies in animals and humans demonstrated the potential importance of more distal and branch sites for RF ablation, and a second-generation multielectrode system was developed. Multiple other ablation systems using catheter-based ultrasound (RADIANCE-HTN SOLO) applied in just the main renal arteries significantly lowered daytime ambulatory and office BP compared with sham treatment. Another technique using injections of alcohol into the renal artery adventitia (Peregrine system) has shown promise. These studies have reinvigorated the interest in RDN as a potential treatment for HTN and are an area of active research.

INTRODUCTION

Cardiovascular disease remains the most common cause of global mortality. Many cardiovascular diseases are caused by hypertension (HTN), which is why there are medications to lower blood pressure (BP) levels of patients. However, there exists an underlying cause for the sustained high pressures that refuse to go away despite compliance with treatment. Multiple organ systems in the body can also be damaged from increased BP despite the use of antihypertensive drugs and lifestyle modifications and many patients continue to have elevated BP levels after several months of consecutive treatment.

In 2017, the American College of Cardiology and the American Heart Association (ACC/AHA) released new HTN guidelines redefining HTN to be any BP of 130 over 80 mm Hg. This was a change from the previous classification set forth by Joint National Committee (JNC) 7 guidelines at a systolic blood pressure (SBP) of >140 mm Hg or diastolic blood pressure (DBP) of >90 mm Hg, which is now the threshold for stage II HTN as per the ACC/AHA guidelines.[1]

This greatly increased the number of people who are considered to have high BP in America—from 31.9% of adults (72.2 million people) to 45.6% of adults (103.3 million people), as well as a decrease in the rate of medication-controlled HTN—from 53.4 to 39%, respectively.

Resistant HTN is now defined as BP persistently above target despite treatment with three different classes of antihypertensive medication at maximum doses, with at least one diuretic; alternatively, it can also refer to BP that is successfully controlled using at least four medications. Studies have estimated the prevalence of resistant HTN in adults to range between 12 and 18%.[2,3] These patients have a higher risk of cardiovascular events (death, myocardial infarction, heart failure, stroke, and chronic kidney disease) when compared to those with controlled HTN.

Side effects of increasing medications to control BP compounded by noncompliance have led to a review of research into its pathophysiology and treatment. This has given rise to alternate forms of treatment.

ROLE OF SYMPATHETIC NERVOUS SYSTEM IN HYPERTENSION

An exploration into the role of the sympathetic nervous system (SNS) in HTN has revealed that catecholamines are higher in hypertensive and borderline hypertensive subjects than in those without HTN.[4,5] The urinary excretion of catecholamines is higher in hypertensive patients as well, which suggests the higher activity of the SNS. The renal circulation[6]

and cardiac[6-8] and skeletal muscle[5,8] have also shown higher levels of sympathetic nerve activity. A direct relationship has been noted between BP and sympathetic activity.[9]

The SNS plays an important role in BP regulation **(Fig. 1)**. One evident piece of evidence supporting this claim is the effect seen following surgical sympathectomy (surgical removal of certain neural receptors within certain parts of the body). While not compared with no therapy or medical therapy in a controlled or randomized fashion, many studies show substantial improvement in BP reduction[10,11] as well as in making cardiopulmonary benefits more evident alongside lower frequency rates for headaches, chest pains, and cerebrovascular events.[12]

Of the several studies comparing surgical patients to a medically treated control group, the ones that suggested a reduction in mortality compared to an uncontrolled group of medically treated patients were counterbalanced by the evidence that showed unfortunate side effects such as significant operative morbidity and mortality, leading to what was confirmed as unnecessary since most newer antihypertensive medications were being developed. Although this procedure was first performed in 1950, many experts did not support the re-entry of sympathectomy due to certain setbacks associated with this procedure that proved that the older therapies for HTN—such as antihypertensive medication and lifestyle changes—were much more effective.

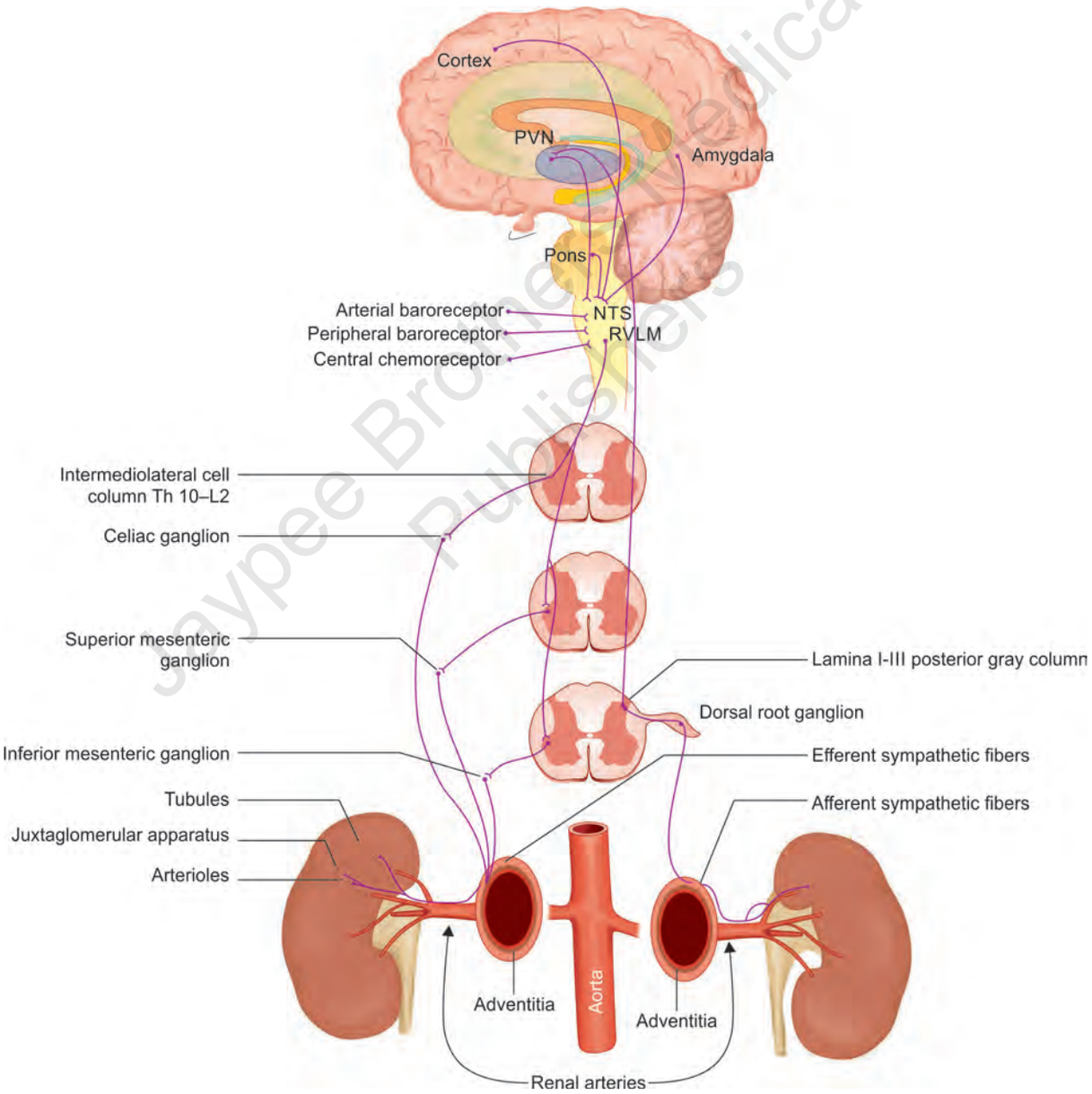

FIG. 1: Sympathetic nervous system.
(NTS: solitary track nucleus; PVN: paraventricular nucleus; RVLM: rostral ventrolateral medulla)
Source: Bertog SC, Sobotka PA, Sievert H. Renal denervation for hypertension. JACC Cardiovasc Interv. 2012;5:249-58.

The renal SNS is critical in the process of BP control **(Figs. 1 and 2)**. Overactivity of the SNS has been demonstrated in patients with severe kidney disease who are on dialysis, but after bilateral nephrectomy, sympathetic overactivity normalizes.[13] Even if they no longer have the uremic toxins after transplantation, the sympathetic overactivity persists if nephrectomy has not taken place after transplantation,[14] leading to the notion that the kidneys play a role in the sympathetic overactivity.

Removal of a diseased kidney (e.g., congenital hypoplasia) in patients with HTN can lead to BP normalization.[15-17] The same findings were noted when bilateral nephrectomy was performed in patients with end-stage renal disease who underwent kidney transplant surgery.[18,19]

Although overactivity of the renin–angiotensin system is common in patients with end-stage renal disease contributing to HTN, there is enough evidence that sympathetic nervous signals contribute to HTN at least as much as renin release. For example, β-blockers are only effective in kidney transplant patients if the native kidneys have not been removed.[20]

The renin–angiotensin system has a modest effect on muscle sympathetic nervous activity and BP control in patients with end-stage kidney disease. Although administration of the central sympatholytic agent, clonidine,[21] has a substantial BP-lowering effect, it is not clear what triggers the increased activity of renal afferent sympathetic nerves. However, one could argue that renal ischemia may be the cause or at least the contributor. To this end, patients with renal artery stenosis caused by ischemia have shown an improvement in muscle sympathetic activity after angioplasty of the renal artery.[22] Similarly, BP has also normalized in patients after unilateral nephrectomy where there was renal artery stenosis.[23]

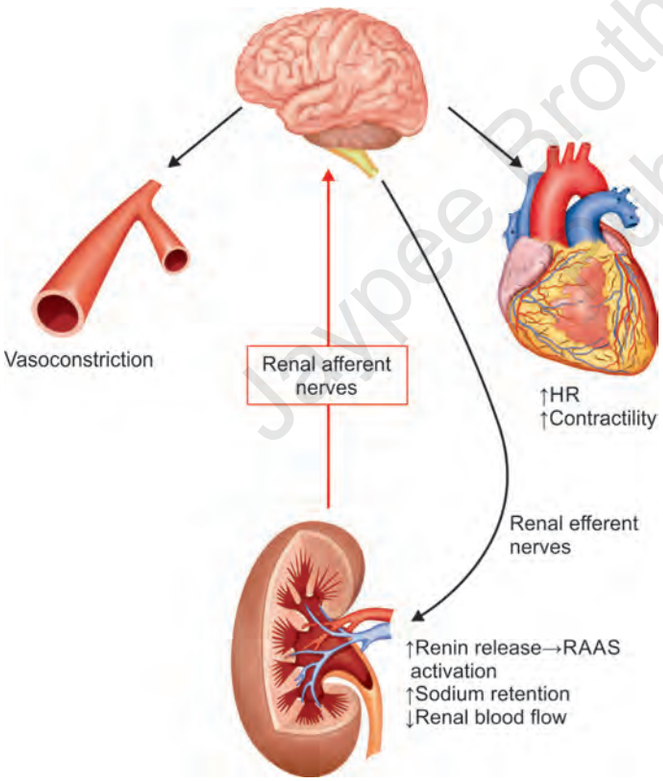

FIG. 2: Efferent and afferent pathways that may be interrupted by renal denervation. The *black arrows* indicate the efferent pathways, whereas the *red arrow* indicates the afferent pathway.

(HR: heart rate; RAAS: renin–angiotensin–aldosterone system)

Source: Weber MA, Mahfoud F, Schmieder RE, Kandzari DE, Tsioufis KP, Townsend RR, et al. Renal denervation for treating hypertension: current scientific and clinical evidence. JACC Cardiovasc Interv. 2019;12(12):1095-105.

ANATOMY AND PHYSIOLOGY OF THE RENAL SYMPATHETIC NERVOUS SYSTEM

The renal SNS has two different pathways for working with BP **(Figs. 1 and 2)**. The renal SNS sends a lot of efferent, noradrenergic sympathetic fibers to supply the kidneys and then returns signals from the kidneys to the central nervous system via afferent fibers.

The SNS is a part of our peripheral nervous system. It helps to regulate the internal environment of the body. Nerves are responsible for carrying signals within the body. The peripheral nervous system in mammals is divided into the somatic nervous system and the autonomic nervous system. The autonomic nerves (not controlled consciously) have motor fibers that control heart rate, digestion, breathing, urination, pupil diameter, and perspiration. They also have a sensory function: senses such as temperature, sweating, and fight-or-flight reactions. The neurons carry information to the different organs of the body. Fibers from neurons in the intermediolateral column (T10–T12, L1–L2) extend via splanchnic nerves to postganglionic neurons located in prevertebral ganglia. Postganglionic neurons reach the kidney via the adventitia of the renal arteries. Efferent sympathetic fibers supply every aspect of the kidney, including the renal tubular cells,[24] juxtaglomerular apparatus,[25] and vasculature.[26,27] Stimulation of efferent fibers causes activation of the adluminal basolateral Na^+/K^+ adenosine triphosphatases,[28] thereby promoting sodium and water retention, renin secretion via the juxtaglomerular apparatus,[29] and vasoconstriction of renal arterioles.

Renin secretion is influenced by the SNS, which releases noradrenaline. Noradrenaline increases BP by affecting the kidney and triggering an increase in salt and water retention. The release of renin also triggers the production of angiotensin II, thereby further increasing sodium and water retention. There appears to be a graded response dependent on the intensity of the sympathetic signal, in that low-frequency stimulation increases renin secretion, followed by an increase in tubular sodium reabsorption and renal vascular tone at higher frequencies.[30]

In addition, and often underappreciated, the kidney receives signals from the nervous system via afferent sympathetic fibers **(Fig. 1)**. These cell bodies are located in the dorsal root ganglia. These signals are further relayed to autonomic centers in the central nervous system as well as to the contralateral kidney.[31] The afferent fiber endings are found in all parts of the kidney, with the richest network being present in the renal pelvis. Signals are transmitted by two families of receptors. Mechanosensitive receptors relay information regarding hydrostatic pressure in the kidney, as well as arterial and venous pressure. Chemosensitive receptors pick up on changes in the chemical milieu of the

kidneys, such as due to ischemia.[32] Afferent sympathetic dorsal root neurons then transmit signals to the central nervous system, influencing overall sympathetic tone.

Thus, SNS plays a key role in regulating BP and also affects the kidney's ability in regulating BP. This in turn is also important in maintaining balance with regard to sodium and water. During this process, afferent fibers communicate with the contralateral kidney, which helps maintain proper levels of sodium and water via unilateral disturbances to that system. When examining the role of your SNS in the genesis of HTN, it is important to understand that it is not activated in an all-on or off fashion. Instead, the sympathetic activity can be increased only in certain organs (e.g., the kidney or heart) and thus have a direct impact on BP control in the absence of substantial activation of sympathetic fibers in other organs.

CLINICAL RESULTS OF RENAL DENERVATION IN HUMANS

Our better understanding of the interplay between the kidney and SNS has enabled researchers to gauge the importance of sympathetic nerves for controlling BP and how HTN develops. In addition, success with animal models and patients who have undergone nephrectomies, as well as the favorable location of the sympathetic fibers and their sensitivity to radiofrequency (RF), has led to the creation of an effective procedure involving catheter-based RF ablation, which ablates sympathetic nerves.

EXPERIENCE FROM THE FIRST-GENERATION RADIOFREQUENCY ABLATION SYSTEM

Because anatomical studies have shown that there is a close proximity of renal nerves to the renal arteries, a catheter-based RF ablation was introduced as a potential method of interrupting renal nerves and lowering BP. The first-generation RF ablation system **(Fig. 3)** (Symplicity Flex; Medtronic, Minneapolis, MN, USA) utilizes a single unipolar electrode on a flexible (4F) catheter to perform RF ablation. The procedure consists of rotating and withdrawing the catheter in the renal arteries, creating multiple lesions in a helical manner. Approximately four to six lesions were created in each renal artery **(Fig. 4)**.

Early observational studies demonstrated the safety and efficacy of the ablation system.[33,34] This led to the multicenter, randomized controlled trial (RCT)—SYMPLICITY HTN-2 trial.[35] This included patients who had an office SBP ≥160 mm Hg despite the prescription of ≥3 antihypertensive drugs, including a diuretic. Patients with hemodynamically significant renal artery stenosis, previous renal artery intervention, estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2, type 1 diabetes mellitus, secondary HTN, or unsuitable renal anatomy (defined as <4 mm diameter, <20 mm length, or >1 main renal artery) were excluded. Patients were randomized (1:1) to renal denervation (RDN) plus medical therapy or medical therapy alone. The mean office BP at 6 months fell by 32/12 mm Hg ($p < 0.001$) in the RDN group ($n = 52$) but increased by 1/0 mm Hg in the control group ($n = 54$; $p > 0.70$). The between-group difference in 24-hour ambulatory SBP was also significant **(Fig. 5)**.

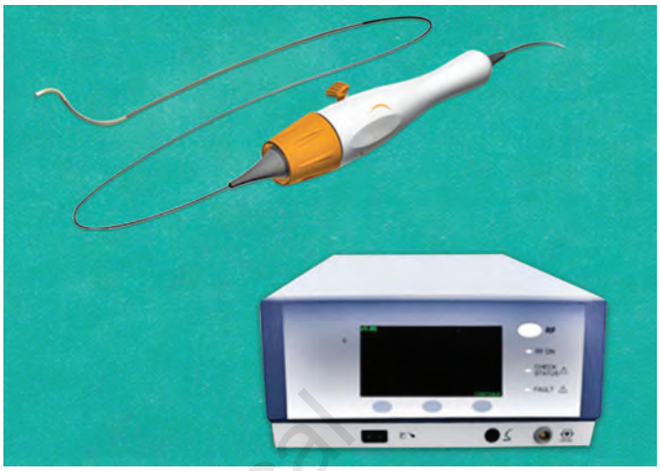

FIG. 3: Symplicity Flex ablation catheter, the steerable radiofrequency catheter is shown and the console that provides feedback to the operator regarding impedance and radiofrequency energy delivery as well as duration of energy application.

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Source: Bertog SC, Sobotka PA, Sievert H. Renal denervation for hypertension. JACC Cardiovasc Interv. 2012;5:249-58.

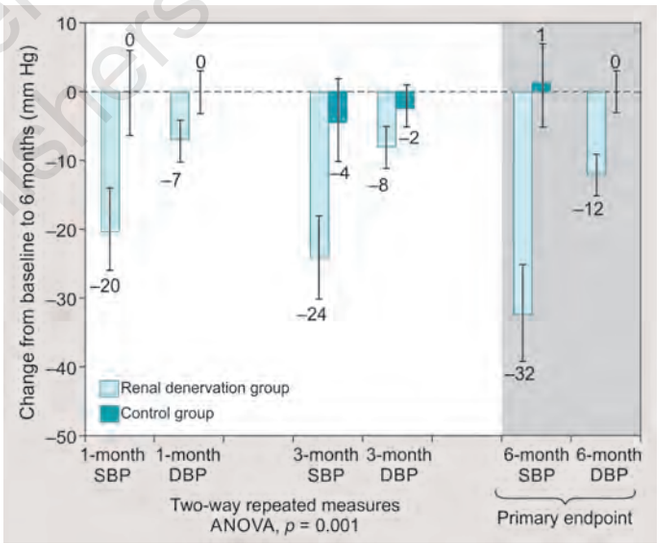


FIG. 5: SYMPLICITY HTN-2 results. Paired changes in office-based measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 1, 3, and 6 months for renal denervation and control groups.

(ANOVA: analysis of variance)

Source: SYMPLICITY HTN-2 Investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (the SYMPLICITY HTN-2 trial): a randomised controlled trial. Lancet. 2010;376:1903-9.

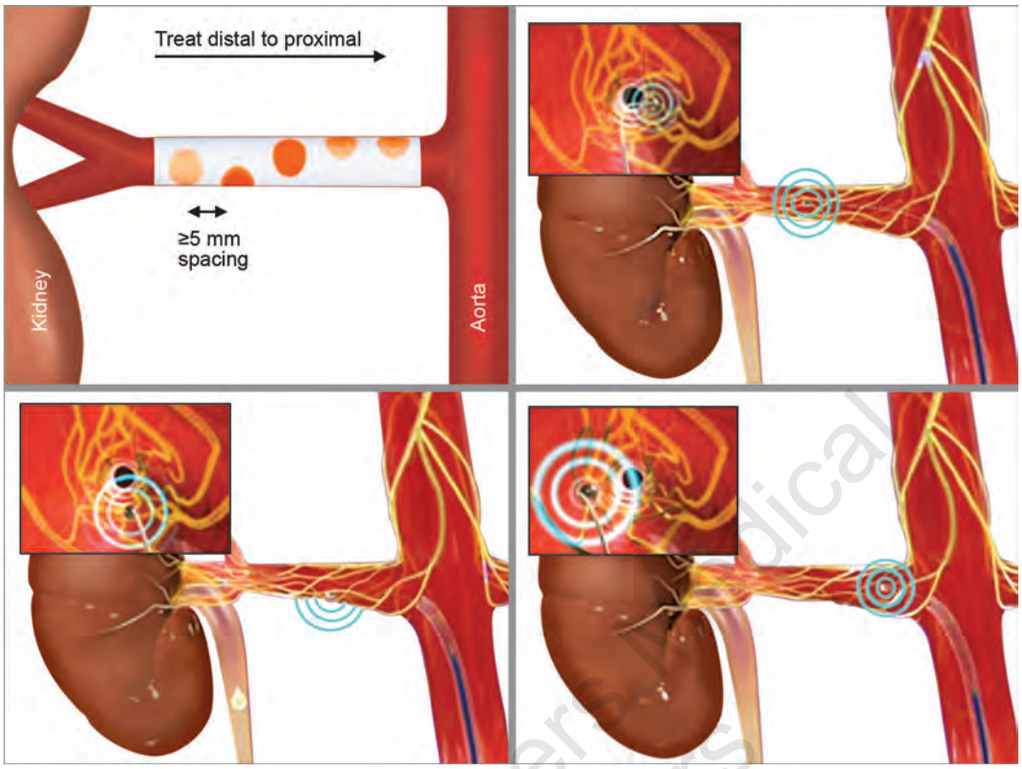


FIG. 4: Radiofrequency catheter positioning in the renal artery. Radiofrequency catheter positioning in the renal artery aiming at circumferential application of radiofrequency spaced apart by approximately 5 mm.

Reprinted with permission from Medtronic Ardian, Mountain View, CA, USA.

Sources: Bertog SC, Sobotka PA, Sievert H. Renal denervation for hypertension. JACC Cardiovasc Interv. 2012;5:249-58 and SYMPLICITY HTN-2 Investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (the SYMPLICITY HTN-2 trial): a randomised controlled trial. Lancet. 2010;376:1903-9.

The SYMPLICITY HTN-3[36] was an additional multicenter, single-blind RCT incorporating a sham treatment group and was conducted in patients with an office SBP >160 mm Hg despite the prescription of ≥3 antihypertensive medications, including a diuretic. A mean 24-hour ambulatory SBP >135 mm Hg was required to exclude patients with white coat HTN. A significant difference compared to SYMPLICITY HTN-2 was the presence of a sham procedure and patients being unaware if they received the treatment or not.[37] In this study, patients were randomly assigned to RDN versus sham procedure (renal angiography) in a 2:1 manner. After 6 months of follow-up, the mean decrease in office SBP from baseline (primary endpoint) was 14.1 mm Hg in the RDN group ($n = 364$) and 11.7 mm Hg in the control group ($n = 171$). Though both the changes were significant ($p < 0.001$), the between-group difference (2.39 mm Hg) was not significant **(Fig. 6)**. The between-group difference in the change in 24-hour ambulatory BP was not significant as well.

In essence, SYMPLICITY HTN-3 was conducted to confirm the results of the SYMPLICITY HTN-2. However, comparing the results of both trials, it was noted that though the baseline BPs in the two trials were similar, there was a clear difference in BP reduction between the RDN group and the control group in the two trials. At 6 months, for instance, in SYMPLICITY HTN-2, the average SBP reduction in the RDN group was 11 mm Hg, whereas it only decreased by 6.8 mm Hg in people participating in SYMPLICITY HTN-3.[38] There was a larger than expected decrease in SBP in the control groups of the two trials—3 mm Hg in SYMPLICITY HTN-2 versus 4.8 mm Hg in SYMPLICITY HTN-3.[38]

Several explanations have been proposed to account for the lack of a between-group difference in BP changes in the SYMPLICITY HTN-3 trial. 39% of patients reported one or more changes to their antihypertensive medications during the study period, which might explain the change in mean BP values over time.[39] The ablation catheters used in this study were nonergonomic and required high levels of operator experience for a complete circumferential ablation pattern that was supposed to be applied to main renal artery branches, so only 6% of patients received complete circumferential ablation according to protocol.[39]

The SYMPLICITY HTN-3 trial also included patients with isolated systolic HTN, and these patients appeared to have a reduced BP response to RDN.[40] Furthermore, African–Americans may have affected the overall outcome, as there was an unexpectedly large BP reduction in African–Americans in the sham group.[41]

Histological studies in human cadavers provided further evidence that more distal RF ablation might be an effective option for interrupting unintended nerve damage.[42,43]

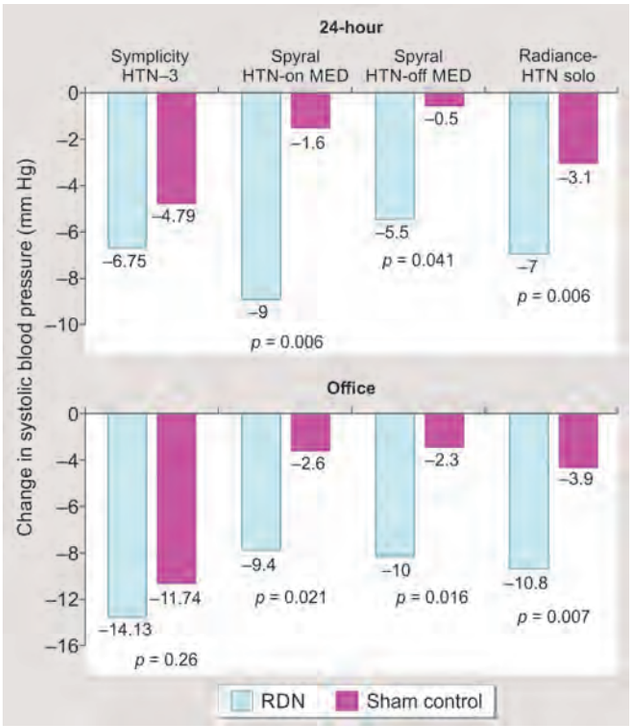


FIG. 6: Mean changes in systolic blood pressure from baseline for 24-hour ambulatory and office blood pressure in four prospective, randomized, sham-controlled trials of renal denervation (RDN). All of the trials except for SYMPLICITY HTN-3 showed significant reductions in mean 24-hour ambulatory and office systolic blood pressure in the RDN group compared with the sham control group at follow-up.

Source: Weber MA, Mahfoud F, Schmieder RE, Kandzari DE, Tsioufis KP, Townsend RR, et al. Renal denervation for treating hypertension: current scientific and clinical evidence. JACC Cardiovasc Interv. 2019;12(12):1095-105.

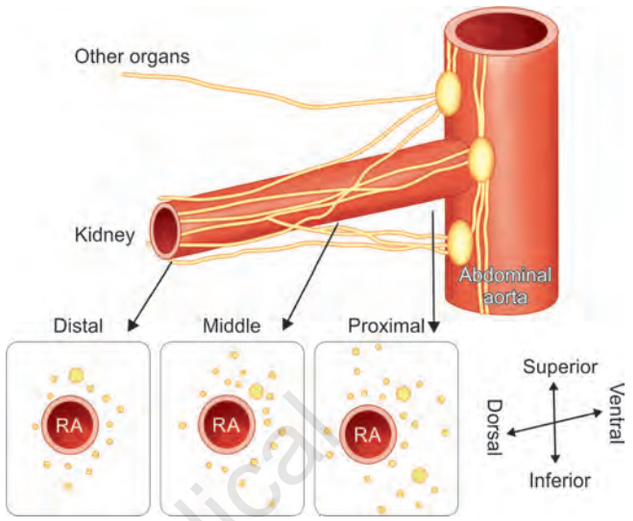


FIG. 7: Renal artery (RA) nerve density in different segments of renal arteries. Although there were fewer nerves surrounding the RA in the distal segment compared with the proximal and middle segments, and the mean distance from the RA lumen to nerve location was least in the distal segment.

Source: Weber MA, Mahfoud F, Schmieder RE, Kandzari DE, Tsioufis KP, Townsend RR, et al. Renal denervation for treating hypertension: current scientific and clinical evidence. JACC Cardiovasc Interv. 2019;12(12):1095-105.

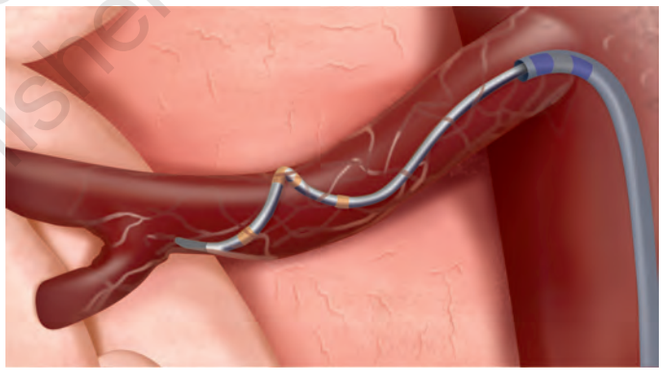


FIG. 8: Symplicity spyral catheter. Radiofrequency energy is delivered simultaneously at four sites for 60 seconds.

Source: Weber MA, Mahfoud F, Schmieder RE, Kandzari DE, Tsioufis KP, Townsend RR, et al. Renal denervation for treating hypertension: current scientific and clinical evidence. JACC Cardiovasc Interv. 2019;12(12):1095-105.

A study of 20 autopsy cases found 10,329 nerves surrounding the main renal artery. The mean individual number of nerves in the proximal and middle segments was similar to what was observed, with slightly fewer on average in the more distant parts. However, the distance of the nerves from the arterial lumen was closest in the distal segments **(Fig. 7)**.[44]

SECOND-GENERATION ABLATION SYSTEMS

The SYMPLICITY HTN-3 was conducted with a first-generation RDN system and the study failed to demonstrate a reduced BP compared to medical therapy. A second-generation RF catheter for RDN (Symplicity Spyral, Medtronic) that involves a flexible four-electrode array mounted on a 4 Fr system **(Fig. 8)** allows simultaneous lesions in a helical pattern. Two studies[45-47] were performed that involved this new technology to prove how effective it would be with regard to lowering BP and preventing strokes—SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED. These multicenter, single-blind, sham-controlled trials enrolled patients with combined systolic/diastolic HTN. All operators had previous RDN experience and a standardized approach was used to target all accessible renal arterial vessels, including branch vessels and accessory arteries with a diameter of 3–8 mm. Ambulatory BP was used as the primary endpoint because ambulatory BP provides a more accurate estimate of true BP. Patients were randomized (1:1) to RDN or sham treatment in both trials. Key exclusion criteria in both trials included >50% renal artery stenosis, eGFR <45 mL/min/1.73 m^2, and renal artery anatomy that was not suitable for ablation. There were approximately 9 main renal artery ablations and 13 branch artery ablations per kidney in each trial.

Enrollment in the HTN-OFF MED[45] trial required mild-to-moderate HTN (office SBP of ≥150 and ≤180 mm Hg, and DBP ≥90 mm Hg) in the absence of medications, and a mean 24-hour ambulatory SBP between 140 and 170 mm Hg. Analysis of the results in the first 80 patients showed that both

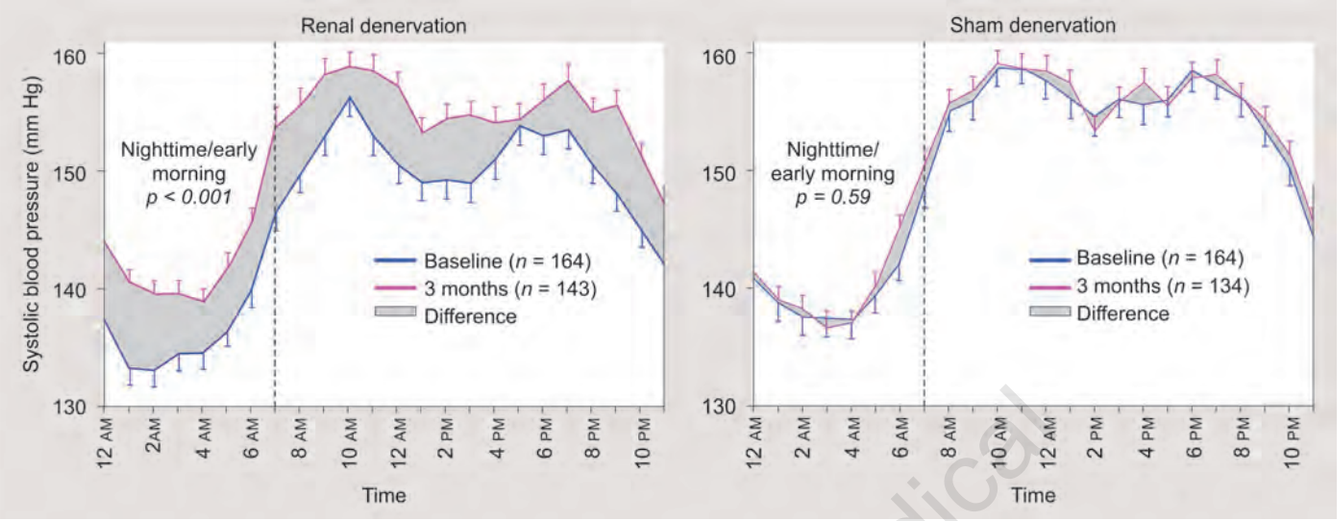


FIG. 9: Changes in systolic blood pressure (SBP) with renal denervation (RDN) therapy over 24 hours. Twenty-four-hour ambulatory SBP at baseline and 3 months for RDN and sham control groups in the SPYRAL OFF MED Pivotal Trial. Error bars indicate one standard error.

Source: Kandzari DE, Townsend RR, Bakris G, Basile J, Bloch MJ, Cohen DL, et al. Renal denervation in hypertension patients: proceedings from an expert consensus roundtable cosponsored by SCAI and NKF. Catheter Cardiovasc Interv. 2021;98(3):416-26.

24-hour ambulatory BP decreased significantly from baseline to 3 months in the RDN group but not in the control group. The between-group differences favored RDN for 24-hour ambulatory BP by 5.0/4.4 mm Hg, and this difference was significant. There were no major side effects in either of the groups during follow-up **(Fig. 5)**.

Enrollment in the SPYRAL HTN-ON MED[46] trial required office SBP >150 and <180 mm Hg, office DBP >90 mm Hg, and 24-hour ambulatory SBP >140 and <170 mm Hg in patients who were on one to three antihypertensive medications (thiazide-type diuretic, calcium-channel blocker, angiotensin II converting enzyme inhibitor, angiotensin II receptor blocker, or β-blocker). Medication adherence was evaluated by urine or serum assays both before and after RDN or sham treatment. This study enrolled a total of 80 subjects (RDN, n = 381; sham, n = 42) and the results showed that subjects with 24-hour ambulatory BPs in the RDN group experienced significant decreases at 6 months compared to sham control (7.4/4.1 mm Hg), and the difference was significant. The decrease in BP was noted in both the daytime and the nighttime hours. Though the medication adherence was 60% throughout the course of the study, there was no significant difference between the two groups at 3 or 6 months. There were no major adverse events in either group during follow-up **(Fig. 5)**.

The largest randomized evaluation of RDN in the absence of antihypertensive medications, the SPYRAL HTN-OFF MED Pivotal trial, confirms the effectiveness of this method to reduce BP and provides further reassurance related to safety specific to this technology and technique. Consistent with prior studies, the persistent reduction ("always on" effect) **(Fig. 9)** in BP achieved with RDN over a 24-hour period distinguishes this therapy from limitations associated with medications, including varied pharmacokinetic profiles and dosing regimens as well as drug adherence.

Overall, these studies have demonstrated significant BP reductions following RDN using two different treatment methods, in both the presence and absence of antihypertensive drug therapy.

OTHER RENAL DENERVATION ABLATION SYSTEMS

Other RF ablation systems have been evaluated and approved for use in Europe [EnligHTN (St Jude Medical, St Paul, MN, USA), Vessix (Boston Scientific, Marlborough, MA, USA), OneShot (Covidien, Dublin, OH, USA), and Iberis (Terumo, Ann Arbor, MI, USA) systems][48-52] but given the results of SYMPLICITY HTN-3, further studies for many of these catheters were abandoned.

Another technique currently under study is the use of a catheter inserted into the renal artery followed by injection of ethanol into periarterial adventitial space via three needles that extend perpendicularly from the intraarterial catheter[53,54] (Peregrine system infusion catheter, Ablative Solutions, San Jose, CA, USA) **(Fig. 10)**. This device is under investigation in a randomized, double-blind, sham-controlled trial in patients with HTN who are not taking medications.

Renal nerve ablation using catheter-based ultrasound has also been shown to be feasible[55] and is currently under investigation. A recent multicenter, single-blind, sham-controlled trial[56] (RADIANCE-HTN SOLO) evaluated catheter-based ultrasound in patients not receiving medications. The ultrasound is emitted circumferentially via a piezoelectric crystal on the end of the catheter that is centered in the renal artery by transient inflation of a water-cooled balloon **(Fig. 11)**. The patients had combined systolic/diastolic HTN, with a daytime ambulatory BP of >135/85 and

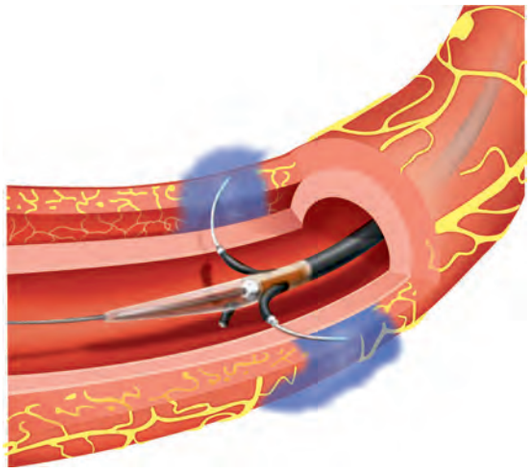


FIG. 10: The Peregrine system infusion catheter. The tips of three injection needles are inserted through the renal artery in a circumferential pattern and penetrate the adventitia to a depth of about 3.5 mm relative to the intimal surface. The *blue color* represents the circumferential spread of alcohol within the adventitial layer.

Source: Weber MA, Mahfoud F, Schmieder RE, Kandzari DE, Tsioufis KP, Townsend RR, et al. Renal denervation for treating hypertension: current scientific and clinical evidence. JACC Cardiovasc Interv. 2019;12(12):1095-105.

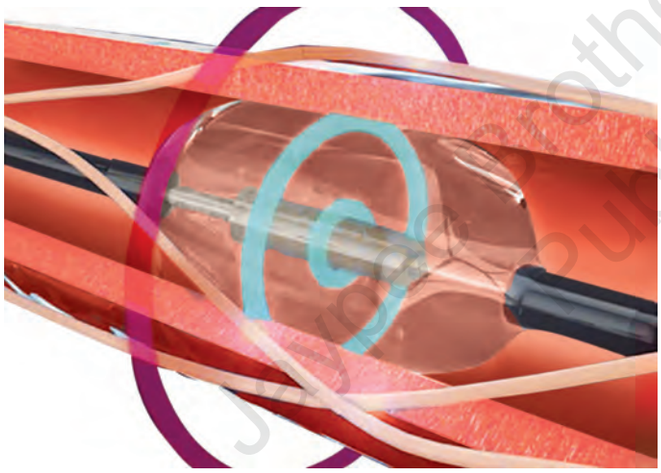


FIG. 11: The Paradise ultrasound catheter. The *purple circle* indicates the heat generated from the ultrasound energy in the tissue delivering energy within the artery. The *blue circle* indicates active cooling from circulating water within the artery to protect the artery from heat.

Source: Weber MA, Mahfoud F, Schmieder RE, Kandzari DE, Tsioufis KP, Townsend RR, et al. Renal denervation for treating hypertension: current scientific and clinical evidence. JACC Cardiovasc Interv. 2019;12(12):1095-105.

<170/105 mm Hg. Key exclusion criteria were an eGFR <40 mL/min/1.73 m^2, secondary HTN, a history of cardiovascular or cerebrovascular events, a main renal artery <4 or >8 mm, or renal artery stenosis ≥30%. Patients were randomized (1:1) to RDN with the ultrasound system or sham treatment. The decrease in daytime ambulatory SBP (primary endpoint) from baseline to 2 months was greater in the RDN group (8.5 mm Hg, $n = 74$) than in the sham group (2.2 mm Hg, $n = 72$).

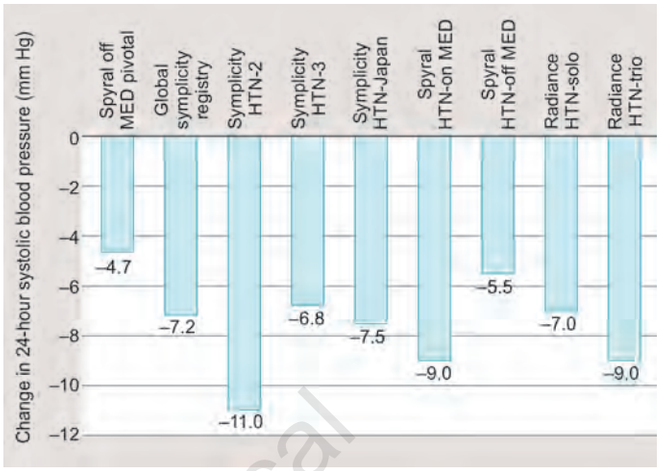


FIG. 12: Changes in 24-hour systolic blood pressure (SBP) with renal denervation (RDN) therapy in contemporary clinical trials.

Source: Kandzari DE, Townsend RR, Bakris G, Basile J, Bloch MJ, Cohen DL, et al. Renal denervation in hypertension patients: proceedings from an expert consensus roundtable cosponsored by SCAI and NKF. Catheter Cardiovasc Interv. 2021;98(3):416-26.

The between-group difference adjusted for baseline BP favored RDN for daytime ambulatory SBP by 6.3 mm Hg, and this difference was significant. There were no major adverse events in either group **(Figs. 6 and 12)**.

The RADIANCE-HTN TRIO,[57] a randomized, international, multicenter, single-blind, sham-controlled trial, was performed at 28 tertiary centers in the USA and 25 in Europe, and included patients aged 18–75 years with an office BP of at least 140/90 mm Hg despite three or more antihypertensive medications, including a diuretic. After 4 weeks of standardized therapy, patients with a daytime ambulatory BP of at least 135/85 mm Hg were randomly assigned (1:1) ultrasound RDN or a sham procedure. RDN reduced daytime ambulatory SBP more than the sham procedure (–8.0 vs. –3.0 mm Hg; median between-group difference –4.5 mm Hg). There were no differences in safety outcomes between the two groups **(Fig. 13)**.

The trial demonstrated a significant reduction in the daytime, nighttime, and ambulatory 24-hour BP in patients resistant to triple combination therapy with second-generation endovascular ultrasound RDN compared to a sham procedure. The difference between the groups was independent of adherence to antihypertensive medications and its magnitude was consistent with the results of meta-analyses of second-generation sham-controlled trials.

The efficacy of these two different modalities: ultrasound (Paradise ultrasound catheter) versus ablation (Symplicity Spyral catheter)—was studied head-to-head in the RADIOSOUND-HTN trial.[58] This was a randomized, single-blind trial in patients with uncontrolled HTN (office SBP >160 mm Hg or DBP >90 mm Hg despite ≥3 classes of antihypertensive drugs including a diuretic) **(Figs. 14A and B)**. The 120 enrolled patients were randomized (1:1:1) to RF ablation of the main artery, side branches, and accessory renal arteries, or ultrasound-based RDN of the renal artery. At 3 months, BP reduction was noted more in the ultrasound

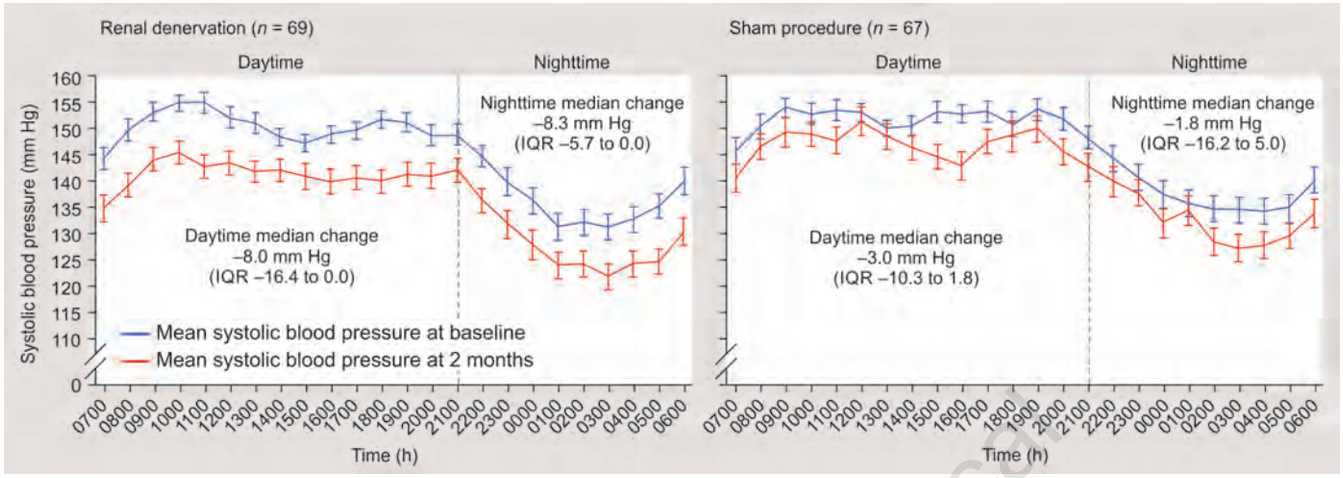


FIG. 13: Twenty four-hour ambulatory profiles of systolic blood pressure at baseline and 2 months in the renal denervation group and the sham group in the intention-to-treat population.

(IQR: interquartile range)

Source: Azizi M, Sanghvi K, Saxena M, Gosse P, Reilly JP, Levy T, et al. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. Lancet. 2021;397(10293):2476-86.

group compared to RF ablation of the main renal artery; however, there was not much difference between RF ablation of the main renal artery plus side branches compared with ultrasound-based ablation. However, the major limitations were the lack of a sham-controlled group and the lack of objective drug adherence testing.

Ahmad et al.[59] conducted a meta-analysis of all blinded placebo-controlled randomized trials of catheter-based renal sympathetic denervation for HTN. A total of seven trials totaling 1,368 patients were included. Denervation was noted to significantly reduce ambulatory SBP (mean difference –3.61 mm Hg), ambulatory DBP (–1.85 mm Hg), office SBP (–5.86 mm Hg), and office DBP (–3.63 mm Hg). Concomitant use of antihypertensives was not noted to have a significant outcome on the effect of denervation or on any of the endpoints. It was felt that denervation could be a useful strategy at various points for patients who are unwilling to add antihypertensive therapies[59] or patients who are having difficulty with medication adherence. This modest benefit should not be looked at as a "cure for all" approach, and long-term randomized control data are needed to confirm the sustainability of this treatment option.

REINNERVATION AFTER RENAL DENERVATION

In normal rats, although norepinephrine (NE) did not return to normal after surgical RDN,[60] both functional and anatomical reinnervation of renal nerves has been reported within 12 weeks.[61] In normal sheep, on the other hand, both anatomical and functional evidence of afferent and efferent reinnervation was shown at 11 months after RDN (Symplicity Flex catheter), with nearly complete recovery of NE levels.[62]

In humans, there are no data to support anatomical or functional renervation in patients who have undergone RDN. The BP-lowering effects have been noted to be sustained for up to 3 years in various studies, underscoring either no functional renervation or inconsequential renervation.[63-65]

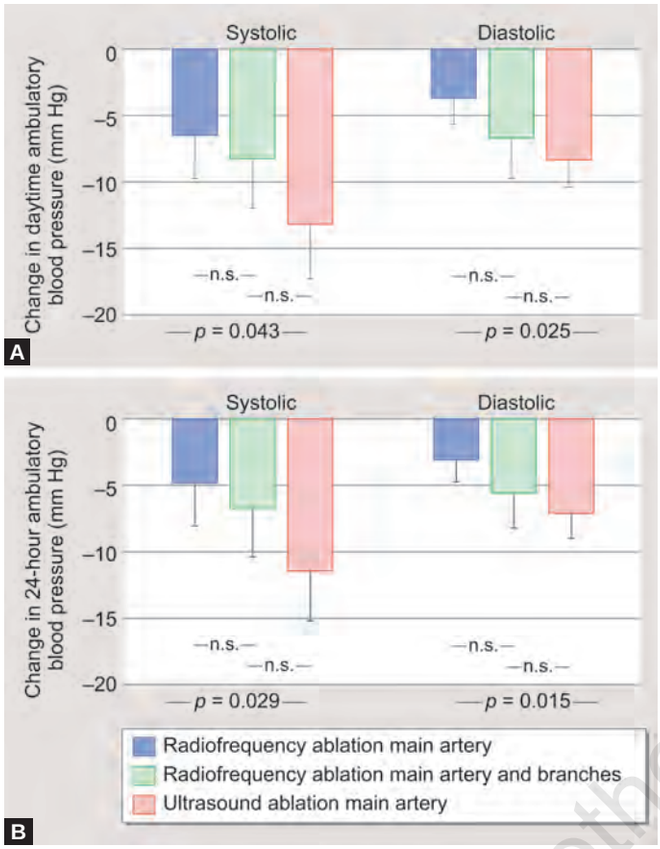
Renal denervation has been noted to have a depressor response in patients who are treated with the therapy for resistant HTN.[66-68] A renoprotective trend has also been noted in patients with chronic kidney disease and associated HTN. When compounded with heart failure, multiorgan damage and progression are felt to be exacerbated.[69] RDN of the renal afferent nerve could inhibit the regulation of the central sympathetic system and provide beneficial sympathoinhibition to heart failure.

BENEFITS BEYOND BLOOD PRESSURE CONTROL

Watanabe et al.[70] demonstrated that salt-sensitive hypertensive rats in the hypertrophic stage that underwent RDN led to improved survival, reduced left ventricular hypertrophy, improved left ventricular function, left ventricular myocyte hypertrophy, and increased tyrosine hydroxylase and beta-1 adrenergic receptors in the left ventricular myocardium. It also led to reduced renal damage and dysfunction. There were no alterations in the renal sodium excretion, daily sodium/water balance, cardiac output, and vascular resistance. A beneficial effect was also felt on hypertensive organ damage. It was concluded that RDN holds therapeutic potential in patients with heart failure and progressive renal damage, independent of BP-lowering responses. This along with other potential nonhypertensive-related benefits has been shown with limitations in some studies as detailed below.

Congestive Heart Failure

The SNS is responsible for causing pathological remodeling of cardiac structures, which is a primary component of the pathogenesis of heart failure. Increased sympathetic signaling



FIGS. 14A AND B: RADIOSOUND-HTN trial: Change in systolic and diastolic ambulatory blood pressure from baseline to 3 months. (A) Change in daytime ambulatory blood pressure [global p = 0.038 and 0.025, respectively, by analysis of variance (ANOVA)]. (B) Change in 24-hour ambulatory blood pressure (global p = 0.027 and 0.018, respectively, by ANOVA). Data are presented as means and 95% confidence intervals (CIs). p-values presented in the figure are from pairwise testing and are adjusted by using Bonferroni correction. n.s. indicates that the p-value is not significant.

Source: Fengler K, Rommel K, Blazek S, Besler C, Hartung P, von Roeder M, et al. A three-arm randomized trial of different renal denervation devices and techniques in patients with resistant hypertension (RADIOSOUND-HTN). Circulation. 2019;139:590-600.

exacerbates various pathological conditions that result in the impairment of cardiac integrity.[71] NE spillover has been associated with combined endpoints of all-cause mortality and heart transplantation in patients with heart failure. This points to the relationship between increased spillover and death from heart failure. Because β-blockers regulate sympathetic signaling, they are used in treating heart failure disorders as a means of significantly reducing sympathetic overactivity and cardiovascular complications.[72]

The REACH-Pilot study[73] showed improvements in symptoms and exercise capacity in patients with chronic systolic heart failure 6 months after RDN. In their research, Brandt et al.[74] demonstrated that RDN decreased left ventricular mass index, improved diastolic function, reduced interventricular septum thickness, decreased end-systolic volume, and improved ejection fraction.

Atrial Fibrillation

The ERADICATE-AF trial[75] was developed to determine whether adding RDN to pulmonary vein isolation would increase the chance of freedom from atrial fibrillation for patients afflicted with paroxysmal atrial fibrillation and HTN. The study's results demonstrated that the addition of RDN to catheter ablation significantly increased the likelihood of freedom from atrial fibrillation at 12 months when compared with catheter ablation alone. This has been further noted in other meta-analyses and studies[76] with similar results.

Glucose Metabolism

Research suggests that chronic compensatory sympathetic and neurohormonal activation are contributors to many types of cardiovascular diseases. Patients with resistant HTN have been found to have reduced fasting glucose, insulin, and c-peptide levels as well as mean 2-hour glucose levels during an oral glucose tolerance test after RDN.[77] Similar results were not found in the DREAMS study,[78] but this has been attributed to the small sample size and lack of proper control in the trial. Large-scale trials will be needed to show further benefits of this therapy for insulin resistance and diabetes.

Obstructive Sleep Apnea

Renal denervation decreases obstructive sleep apnea severity index[79] (apnea/hypopnea index, 39.4 vs. 31.2 events per hour) in patients treated with RDN for HTN. The decrease in the apnea–hypopnea index was also noted at 6 months after RDN in other studies as well.[80]

Other Comorbidities

The attenuation of sympathetic outflow and the renin–angiotensin–aldosterone signaling by RDN has demonstrated improvement in pulmonary vascular remodeling and pulmonary HTN, gestational HTN, anxiety, depression, and self-assessed physical and mental status.[81] As trials and studies continue, there may be more benefits of this procedure that we will learn about.

WHAT DOES ALL THIS MEAN?

Renal denervation continues to be an area of active research and study across the world and it is still considered a novel procedure with many unanswered questions. Not all patients may benefit from the procedure, so identifying the predictors and follow-up outcomes is an area of investigation. The effectiveness of this procedure in real-world conditions is a question that still needs to be answered. However, as we learn more about RDN procedures, the outcomes for patients with different types of HTN will expand exponentially in number over time.

While RDN continues to be an area of active research, carotid sinus procedures to alter the sympathetic tone are also being studied. There is optimism in the medical community that soon we will be able to offer patients more than medications as an adjunct therapy in the treatment of HTN.

In the GLOBAL SYMPLICITY Registry,[38,65] a similar magnitude of BP reduction was observed following RDN among patients with varying cardiovascular risk and comorbidities. This can be attributed to no single recognized method for classifying HTN severity or for determining optimal BP target value in this condition. Further direction in indications for treatment will be addressed in real-world registries inclusive of HTN patients representative of clinical practice and with dedicated long-term follow-up. Apart from confirmatory studies of safety and effectiveness, additional studies will further inform patient selection and optimize patient outcomes.

Across studies of varied designs and methods, consistent and clinically meaningful reductions in BP have been achieved with RDN. With this momentum, additional studies are being conducted to position RDN as part of standard therapy for HTN, which continues to be the world's leading cause of death and disability. Finding predictors of treatment effect is an evolving area of focus because to inform patient selection and expectations, certain factors need to be proven such as the ability to lower BP amidst unpredictable patient behavior (who tend to not always stick to a strict diet) and coexisting health conditions that may influence BP despite making sure their diets are right.

Altogether, the results of contemporary RDN studies not only reaffirm the biological proof of principle for this novel treatment but also offer insight into its complementary benefit in uncontrolled HTN despite prescribed medications.

CONCLUSION

The journey of renal denervation therapy can be summarized as a hype, a flop and then a possible resurgence. The success rate is operator dependent. RDN has been shown to have additional benefits other than blood pressure lowering, like improvement in sleep apnea, glucose metabolism, heart failure and possible role in atrial fibrillation management. Still there remain many hiccups before it is recommended as standard practice in resistant hypertension. Given a large heterogeneity of resistant hypertension cases and the highly variable success rate, RDN is still in search of a magic bullet.

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CHAPTER 26

Diagnosis and Management of Acute Pulmonary Embolism

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ABSTRACT

Acute pulmonary embolism (PE) can be a life-threatening event, if missed clinically. It should be clinically suspected in high risk individuals presenting with sudden dyspnea and/or chest pain. This catastrophic event can largely be prevented by use of oral anticoagulants. A rapid response to correctly diagnosing the severity of PE and tailoring therapy is essential to save the patient.

INTRODUCTION

Venous thromboembolism (VTE), clinically presenting as deep vein thrombosis (DVT) or pulmonary embolism (PE), is globally the third most frequent acute cardiovascular syndrome behind myocardial infarction and stroke.[1] In epidemiological studies, annual incidence rates for PE range from 39 to 115 per 100,000 population; for DVT, incidence rates range from 53 to 162 per 100,000 population.[2,3] Cross-sectional data show that the incidence of VTE is almost eight times higher in individuals aged ≥80 years than in the fifth decade of life.[2] In parallel, longitudinal studies have revealed a rising tendency in annual PE incidence rates[4-7] over time. Together with the substantial hospital-associated, preventable, and indirect annual expenditures for VTE, these data demonstrate the importance of PE and DVT in aging populations in Europe and other areas of the world. They further suggest that VTE will increasingly pose a burden on health systems worldwide in the years to come.

Pulmonary embolism may cause ≤300,000 deaths per year in the United States, ranking high among the causes of cardiovascular mortality.[2] In six European countries with a total population of 454.4 million, >370,000 deaths were related to VTE in 2004, as estimated on the basis of an epidemiological model.[8] Of these patients, 34% died suddenly or within a few hours of the acute event before therapy could be initiated or take effect. Of the other patients, death resulting from acute PE was diagnosed postmortem in 59% and only 7% of patients who died early were correctly diagnosed with PE before death.[8]

Time trend analyses in European, Asian, and North American populations suggest that case-fatality rates of acute PE may be decreasing.[4-7] Increased use of more effective therapies and interventions, and possibly better adherence to guidelines, has most likely exerted a significant positive effect on the prognosis of PE in recent years. However, there is also a tendency toward overdiagnosis of (subsegmental or even nonexistent) PE in the modern era, and this might in turn lead to a false drop in case-fatality rates by inflating the denominator, i.e., the total number of PE cases.

RISK FACTORS FOR PULMONARY EMBOLISM

There is an extensive collection of predisposing environmental and genetic factors for VTE; a list of predisposing risk factors are given in **Box 1**. VTE is considered to be a consequence of the interaction between patient-related—usually permanent risk factors—and setting-related—usually temporary risk factors.

Major trauma, surgery, lower-limb fractures, joint replacements, and spinal cord injury are strong provoking factors for VTE.[9] Cancer is a well-recognized predisposing factor for VTE. The risk of VTE varies with different types of cancer;[10] pancreatic cancer, hematological malignancies, lung cancer, gastric cancer, and brain cancer carry the highest risk.

Estrogen-containing oral contraceptive agents are associated with an elevated VTE risk, and contraceptive use is the most frequent VTE risk factor in women of reproductive age.[11] More specifically, combined oral contraceptives (containing both an estrogen and a progestogen) are associated

BOX 1 Predisposing factors for venous thromboembolism (VTE).[14]

- *Strong risk factors (OR >10)*: Fracture of lower limb, hospitalization for heart failure or atrial fibrillation/flutter (within previous 3 months), hip or knee replacement, major trauma, myocardial infarction (within previous 3 months), previous VTE, spinal cord injury
- *Moderate risk factors (OR 2–9)*: Arthroscopic knee surgery, autoimmune diseases, blood transfusion, central venous lines, intravenous catheters and leads, chemotherapy, congestive heart failure or respiratory failure, erythropoiesis-stimulating agents, hormone replacement therapy (depends on formulation), in vitro fertilization, oral contraceptive therapy, postpartum period, infection (specifically pneumonia, urinary tract infection, and HIV), inflammatory bowel disease, cancer (highest risk in metastatic disease), paralytic stroke, superficial vein thrombosis, thrombophilia
- *Weak risk factors (OR < 2)*: Bed rest >3 days, diabetes mellitus, arterial hypertension, immobility due to sitting (e.g., prolonged car or air travel), increasing age, laparoscopic surgery (e.g., cholecystectomy), obesity, pregnancy, varicose veins

(HIV: human immunodeficiency virus; OR: odds ratio)

TABLE 1: Classification of acute pulmonary embolism (PE).

Category	Presentation	Therapy
Massive PE	Systolic BP <90 mm Hg or poor tissue perfusion or multiorgan failure plus extensive thrombosis, such as "saddle" PE or right or left main pulmonary artery thrombus	Anticoagulation (usually with high-dose intravenous UFH), plus advanced therapy: Systemic thrombolysis, pharmacomechanical catheter-directed therapy, surgical embolectomy, and/or IVC filter
Submassive PE, high risk	Hemodynamically stable but moderate or severe RV dysfunction or enlargement, coupled with biomarker elevation indicative of RV microinfarction and/or RV pressure overload	Anticoagulation until decision regarding implementation of advanced therapy. For systemic thrombolysis, reducing the rate of cardiovascular collapse and death must be balanced against the increased rate of hemorrhagic stroke
Submassive PE, low risk	Hemodynamically stable with RV dysfunction or biomarker elevation, but not both	Anticoagulation followed by "wait and watch." Implement advanced therapy if clinical deterioration
Small-to-moderate PE	Normal hemodynamics and normal RV size and function	Anticoagulation and consider brief hospital stay or entirely home therapy

(BP: blood pressure; IVC: inferior vena cava; RV: right ventricle; UFH: unfractionated heparin)

with an approximately two- to six-fold increase in VTE risk over baseline.[12] In general, the absolute VTE risk remains low in the majority of the >100 million combined oral contraceptive users worldwide; however, VTE risk factors, including severe inherited thrombophilia, increase this risk. Third-generation combined oral contraceptives, containing progestogens such as desogestrel or gestodene, are associated with a higher VTE risk than the second-generation combined oral contraceptives, which contain progestogens such as levonorgestrel or norgestrel.

In postmenopausal women who receive hormone replacement therapy, the risk of VTE varies widely depending on the formulation used. Infection is a common trigger for VTE.[9] Blood transfusion and erythropoiesis-stimulating agents are also associated with an increased risk of VTE.[9] In children, PE is usually associated with DVT and is rarely unprovoked. Serious chronic medical conditions and central venous lines are considered likely triggers of PE.[13]

CLASSIFICATION OF PULMONARY EMBOLISM

Classification of acute PE can assist with prognosis and management **(Table 1)**. Massive PE accounts for 5–10% of cases. Submassive PE is more common, occurring in approximately 20–25% of patients. Low-risk PE constitutes the majority of PE cases, approximately 65–70%.

Massive Pulmonary Embolism

Patients with massive PE can develop cardiogenic shock and multisystem organ failure. Renal insufficiency, hepatic dysfunction, and altered mentation occur commonly. Massive PE has a high mortality rate. Thrombosis is widespread, affecting at least half of the pulmonary arterial vasculature. Clot is typically present bilaterally, sometimes as a "saddle" PE in the main pulmonary artery. Dyspnea is usually the most prominent symptom, chest pain is unusual, transient cyanosis is common, and systemic hypotension requiring pressor support occurs frequently. Excessive fluid boluses may worsen right-sided heart failure, rendering therapy more difficult. These patients may require heroic efforts to enable survival, such as extracorporeal membrane oxygenation (ECMO).

Submassive Pulmonary Embolism

Submassive PE patients present with normal systemic arterial pressure. Patients with submassive PE, high risk, present with right ventricle (RV) hypokinesia and elevated cardio biomarkers such as troponin, pro-B-type natriuretic peptide (proBNP), or B-type natriuretic peptide (BNP). Patients with submassive PE, low risk, present with either right ventricular dysfunction or elevated cardiac biomarkers, but not both. Usually, one-third or more of the pulmonary artery vasculature is obstructed in submassive PE patients. Acute onset of moderate pulmonary artery hypertension and RV enlargement occurs commonly.

Low-risk Pulmonary Embolism

Patients with low-risk PE exhibit no markers of an adverse prognosis. They present with normal systemic arterial pressure, no cardiac biomarker release, and normal RV function. They often have an anatomically small PE and appear clinically stable. Adequate anticoagulation usually leads to an excellent clinical outcome.

Pulmonary Infarction

Pulmonary infarction is characterized by pleuritic chest pain that may be unremitting or may wax and wane. Hemoptysis is common. The embolus typically lodges in the peripheral pulmonary arterial tree, near the pleura. Tissue infarction usually occurs 3–7 days after embolism. Symptoms and signs often include fever, leukocytosis, elevated erythrocyte sedimentation rate, and radiologic evidence of infarction.

Paradoxical Embolism

Paradoxical embolism may manifest with a sudden stroke, which may be misdiagnosed as "cryptogenic." The cause is a DVT that embolizes to the arterial system, usually through a patent foramen ovale. The DVT can be small and break away completely from a tiny leg vein, leaving no residual evidence of thrombosis that can be imaged on venous ultrasound examination.

Nonthrombotic Pulmonary Embolism

Sources of embolism other than thrombus are uncommon. They include fat, tumor, air, and amniotic fluid. Fat embolism most often occurs after blunt trauma complicated by long bone fractures. Air embolism can occur during placement or removal of a central venous catheter. Amniotic fluid embolism may be catastrophic and is characterized by respiratory failure, cardiogenic shock, and disseminated intravascular coagulation. Intravenous drug abusers sometimes self-inject hair, talc, and cotton as contaminants of the drug of abuse; these patients are also susceptible to septic PE, which can cause endocarditis of the tricuspid or pulmonic valve.

DIAGNOSIS

The increased awareness of venous thromboembolic disease and the ever-increasing availability of noninvasive imaging tests, mainly computed tomography pulmonary angiography (CTPA), have generated a tendency for clinicians to suspect and initiate a diagnostic workup for PE more frequently than in the past. This changing attitude is illustrated by the rates of PE confirmation among patients undergoing diagnostic workup: These were as low as 5% in recent North American diagnostic studies, in sharp contrast to the approximately 50% prevalence reported back in the early 1980s.[14] Therefore, it is critical that when evaluating noninvasive diagnostic strategies for PE in the modern era, it is ensured that they are capable of safely excluding PE in contemporary patient populations with a rather low pretest probability of the disease. Conversely, a positive test should have an adequate specificity to set the indication for anticoagulant treatment.

The clinical signs and symptoms of acute PE are nonspecific. In most cases, PE is suspected in a patient with dyspnea, chest pain, presyncope or syncope, or hemoptysis.[15] Hemodynamic instability is a rare but important form of clinical presentation, as it indicates central or extensive PE with severely reduced hemodynamic reserve. Syncope may occur and is associated with a higher prevalence of hemodynamic instability and RV dysfunction. Conversely, and according to the results of a recent study, acute PE may be a frequent finding in patients presenting with syncope (17%), even in the presence of an alternative explanation.[16]

In some cases, PE may be asymptomatic or discovered incidentally during diagnostic workup for another disease. Dyspnea may be acute and severe in central PE; in small peripheral PE, it is often mild and may be transient. In patients with pre-existing heart failure or pulmonary disease, worsening dyspnea may be the only symptom indicative of PE. Chest pain is a frequent symptom of PE and is usually caused by pleural irritation due to distal emboli causing pulmonary infarction. In central PE, chest pain may have a typical angina character, possibly reflecting RV ischemia, and requires differential diagnosis from an acute coronary syndrome or aortic dissection. In addition to symptoms, knowledge of the predisposing factors for VTE is important in determining the clinical probability of the disease, which increases with the number of predisposing factors present; however, in 40% of patients with PE, no predisposing factors are found. Hypoxemia is frequent, but ≤40% of patients have normal arterial oxygen saturation (SaO_2) and 20% have a normal alveolar-arterial oxygen gradient.[17] Hypocapnia is also often present.

Chest X-ray may be useful for excluding other causes of dyspnea or chest pain.[18] Focal oligemia (Westermark sign) indicates massive central embolic occlusion. A peripheral wedge-shaped density above the diaphragm (Hampton hump) usually indicates pulmonary infarction.

Electrocardiographic changes indicative of RV strain, such as inversion of T waves in leads V_1–V_4, a QR pattern in V_1, a S1Q3T3 pattern, and incomplete or complete right bundle branch block, are usually found in more severe cases of PE; in milder cases, the only abnormality may be sinus tachycardia, present in 40% of patients. Finally, atrial arrhythmias, most frequently atrial fibrillation, may be associated with acute PE.

ASSESSMENT OF CLINICAL (PRETEST) PROBABILITY

The combination of symptoms and clinical findings with the presence of predisposing factors for VTE allows the classification of patients with suspected PE into distinct categories of clinical or pretest probability, which correspond to an increasing actual prevalence of confirmed PE. The value of empirical clinical judgment has been confirmed in several large series. Clinical judgment usually includes common tests such as chest X-rays and electrocardiograms for differential diagnosis. However, as clinical judgment lacks standardization, several explicit clinical prediction rules have been developed.[19,20] Of these, the most frequently used prediction rules are the revised Geneva rule **(Table 2)** and the Wells rule **(Table 3)**.[21] Regardless of the

TABLE 2: The revised Geneva clinical prediction rule for pulmonary embolism (PE).

Items	Clinical decision rule points	
	Original version	Simplified version
Previous PE or DVT	3	1
Heart rate		
75–94 bpm	3	1
≥95 bpm	5	2
Surgery or fracture within the past month	2	1
Hemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation and unilateral edema	4	1
Age >65 years	1	1
Clinical probability		
Three-level score		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥11	≥5
Two-level score		
PE unlikely	0–5	0–2
PE likely	≥6	≥3

(DVT: deep vein thrombosis)

TABLE 3: Classic wells criteria for assessing clinical likelihood of pulmonary embolism (PE).

Criterion	Scoring
DVT symptoms or signs	3
An alternative diagnosis is less likely than PE	3
Heart rate >100 bpm	1.5
Immobilization or surgery within 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1
Cancer treated within 6 months of metastatic	1

(DVT: deep vein thrombosis)

score used, the proportion of patients with confirmed PE can be expected to be approximately 10% in the low-probability category, 30% in the moderate-probability category, and 65% in the high-probability category.[22]

The pulmonary embolism rule-out criteria (PERC) were developed for emergency department patients with the purpose of selecting, on clinical grounds, patients whose likelihood of having PE is so low that diagnostic workup should not even be initiated.[23] They comprise eight clinical variables significantly associated with an absence of PE: (1) Age <50 years, (2) pulse <100 bpm, (3) SaO_2 >94%, (4) no unilateral leg swelling, (5) no hemoptysis, (6) no recent trauma or surgery, (7) no history of VTE, and (8) no oral hormone use. The results of a prospective validation study,[24] and those of a randomized non-inferiority management study,[25] suggested safe exclusion of PE in patients with low clinical probability who, in addition, met all criteria of the PERC rule. However, the low overall prevalence of PE in these studies[24,25] does not support the generalizability of the results.

D-DIMER TESTING

D-dimer levels are elevated in plasma in the presence of acute thrombosis because of simultaneous activation of coagulation and fibrinolysis. The negative predictive value of D-dimer testing is high, and a normal D-dimer level renders acute PE or DVT unlikely. On the other hand, the positive predictive value of elevated D-dimer levels is low and D-dimer testing is not useful for confirmation of PE. D-dimer is elevated in other conditions like cancers, infections, inflammations, and pregnancy. The quantitative enzyme-linked immunosorbent assay (ELISA) or ELISA-derived assays have a diagnostic sensitivity of ≥95% and can be used to exclude PE in patients with either low or intermediate pretest probability. In the emergency department, a negative ELISA D-dimer can, in combination with clinical probability, exclude the disease without further testing in approximately 30% of patients with suspected PE. Outcome studies have shown that the 3-month thromboembolic risk was <1% in patients with low or intermediate clinical probability who were left untreated on the basis of a negative test result.[26]

COMPUTED TOMOGRAPHY PULMONARY ANGIOGRAPHY

Multidetector CTPA is the method of choice for imaging the pulmonary vasculature in patients with suspected PE. It allows adequate visualization of the pulmonary arteries down to the subsegmental level.[27] The Prospective Investigation On Pulmonary Embolism Diagnosis (PIOPED) II study observed a sensitivity of 83% and a specificity of 96% for (mainly four-detector) CTPA in PE diagnosis.[28] PIOPED II also highlighted the influence of pretest clinical probability on the predictive value of multidetector CTPA. In patients with a low or intermediate clinical probability of PE, a negative CTPA had a high negative predictive value for PE (96 and 89%, respectively), but its negative predictive value was only 60% if the pretest probability was high. Conversely, the positive predictive value of a positive CTPA was high (92–96%) in patients with an intermediate or high clinical probability, but much lower (58%) in patients with a low pretest likelihood of PE.[28] Therefore, clinicians should consider further testing in case of discordance between clinical judgment and the CTPA result. Several studies have provided evidence in favor of CTPA as a stand-alone imaging test for excluding PE. Taken together, the available data suggest that a negative CTPA result is an adequate criterion for the exclusion of PE in patients with low or intermediate clinical probability of PE. On the other hand, it remains controversial whether patients with a negative CTPA and a high clinical probability should be further investigated **(Table 4)**.

TABLE 4: Imaging tests for diagnosis of pulmonary embolism (PE).

Strengths		Weaknesses/Limitations	Radiation issues
CTPA	• Readily available around the clock in most centers • Excellent accuracy • Strong validation in prospective management outcome studies • Low rate of inconclusive results (3–5%) • May provide alternative diagnosis if PE excluded • Short acquisition time	• Radiation exposure • *Exposure to iodine contrast*: ○ Limited use in iodine allergy and hyperthyroidism ○ Risks in pregnant and breastfeeding women ○ Contraindicated in severe renal failure • Tendency to overuse because of easy accessibility • Clinical relevance of CTPA diagnosis of subsegmental PE unknown	• Radiation effective dose 3–10 mSv • Significant radiation exposure to young female breast tissue
Planar V/Q scan	• Almost no contraindications • Relatively inexpensive • Strong validation in prospective management outcome studies	• Not readily available in all centers • Interobserver variability in interpretation • Results reported as likelihood ratios • Inconclusive in 50% of cases • Cannot provide alternative diagnosis if PE excluded	Lower radiation than CTPA, effective dose ~2 mSv
V/Q SPECT	• Almost no contraindications • Lowest rate of nondiagnostic tests (<3%) • High accuracy according to available data • Binary interpretation ("PE" vs. "no PE")	• Variability of techniques • Variability of diagnostic criteria • Cannot provide alternative diagnosis if PE excluded • No validation in prospective management outcome studies	Lower radiation than CTPA, effective dose ~2 mSv
Pulmonary angiography	Historical gold standard	• Invasive procedure • Not readily available in all centers	Highest radiation, effective dose 10–20 mSv

(CTPA: computed tomography pulmonary angiography; SPECT: single-photon emission computerized tomography; V/Q: ventilation/perfusion)

LUNG SCINTIGRAPHY

The planar ventilation/perfusion [V/Q (lung scintigraphy)] scan is an established diagnostic test for suspected PE. The purpose of the ventilation scan is to increase specificity. In acute PE, ventilation is expected to be normal in hypoperfused segments (mismatched). Being a lower radiation and contrast medium sparing procedure, the V/Q scan may preferentially be applied in outpatients with a low clinical probability and a normal chest X-ray, in young (particularly female) patients, in pregnant women, in patients with history of contrast medium-induced anaphylaxis, and in patients with severe renal failure. Planar lung scan results have been revised.[29] To facilitate communication with clinicians, a three-tier classification is preferable: Normal scan (excluding PE), high-probability scan (considered diagnostic of PE in most patients), and nondiagnostic scan.[30] Performing only a perfusion scan might be acceptable in patients with a normal chest X-ray; any perfusion defect in this situation would be considered a mismatch.

PULMONARY ANGIOGRAPHY

For several decades, pulmonary angiography has been the "gold standard" for the diagnosis or exclusion of acute PE, but it is now rarely performed as less-invasive CTPA offers similar diagnostic accuracy.[31] The diagnosis of acute PE is based on direct evidence of a thrombus in two projections, either as a filling defect or as amputation of a pulmonary arterial branch. Thrombi as small as 1–2 mm within the subsegmental arteries can be visualized by digital subtraction angiography, but there is substantial interobserver variability at this level.

MAGNETIC RESONANCE ANGIOGRAPHY

Magnetic resonance angiography (MRA) has been evaluated for several years regarding suspected PE. However, the results of a large-scale study[32] show that this technique, although promising, is not yet ready for clinical practice due to its low sensitivity, the high proportion of inconclusive MRA scans, and its low availability in most emergency settings. The hypothesis that a negative MRA, combined with the absence of proximal DVT on compression ultrasonography (CUS), may safely rule out clinically significant PE is questionable.

ECHOCARDIOGRAPHY

Acute PE may lead to RV pressure overload and dysfunction, which can be detected by echocardiography. Given the peculiar geometry of the RV, there is no individual echocardiographic parameter that provides fast and reliable information on RV size or function. This is why echocardiographic criteria for the diagnosis of PE have differed between studies. Because of the reported negative predictive value of 40–50%, a negative result cannot exclude PE.[32] On the other hand, signs of RV overload or dysfunction may also be found in the absence of acute PE and may be due to concomitant cardiac or respiratory disease. RV

dilation is found in ≥25% of patients with PE on transthoracic echocardiography (TTE) and is useful for risk stratification of the disease.[33] More specific echocardiographic findings were reported to retain a high positive predictive value for PE even in the presence of pre-existing cardiorespiratory disease. Thus, the combination of a pulmonary ejection acceleration time (measured in the RV outflow tract) <60 ms with a peak systolic tricuspid valve gradient <60 mm Hg ("60/60" sign), or with depressed contractility of the RV free wall compared to the "echocardiographic" RV apex (McConnell sign), is suggestive of PE.[34] However, these findings are present in only 12% and 20% of unselected PE patients, respectively.[33] Decreased tricuspid annular plane systolic excursion (TAPSE) may also be present in PE patients. Echocardiographic parameters of RV function derived from Doppler tissue imaging and wall strain assessment may also be affected by the presence of acute PE. Mobile right-heart thrombi are detected by TTE or transesophageal echocardiography (TEE), or by computed tomography (CT) angiography, in <4% of unselected patients with PE.[35] Their prevalence may reach 18% among PE patients in the intensive care setting. Mobile right-heart thrombi essentially confirm the diagnosis of PE and are associated with high early mortality, especially in patients with RV dysfunction.

COMPRESSION ULTRASONOGRAPHY

In the majority of cases, PE originates from DVT in a lower limb, and only rarely from upper-limb DVT (mostly following venous catheterization). In a study using venography, DVT was found in 70% of patients with proven PE.[36] Nowadays, lower-limb CUS has largely replaced venography for diagnosing DVT. CUS has a sensitivity >90% and a specificity of 95% for proximal symptomatic DVT. CUS shows DVT in 30–50% of patients with PE, and finding a proximal DVT in patients suspected of having PE is considered sufficient to warrant anticoagulant treatment without further testing. However, patients in whom PE is indirectly confirmed by the presence of a proximal DVT should undergo risk assessment for PE severity and the risk of early death.

MARKERS OF MYOCARDIAL INJURY

Elevated plasma troponin concentrations on admission may be associated with a worse prognosis in the acute phase of PE. Cardiac troponin I or T elevation is defined as concentrations above the normal limits, and thresholds depend on the assay used. Of patients with acute PE, between 30 (using conventional assays) and 60% (using high sensitivity assays) have elevated cardiac troponin I or T concentrations. Elevated troponin concentrations were associated with an increased risk of mortality, both in unselected patients [odds ratio (OR) 5.2; 95% confidence interval (CI) 3.3–8.4] and in those who were hemodynamically stable at presentation (OR 5.9; 95% CI 2.7–13.0). On their own, increased circulating levels of cardiac troponins have relatively low specificity and positive predictive value for early mortality in normotensive patients with acute PE.

MARKERS OF RIGHT VENTRICULAR DYSFUNCTION

Right ventricle pressure overload due to acute PE is associated with increased myocardial stretch, which leads to the release of BNP and NT-proBNP. Thus, the plasma levels of natriuretic peptides reflect the severity of RV dysfunction and hemodynamic compromise in acute PE. Similar to cardiac troponins (see above), elevated BNP or NT-proBNP concentrations possess low specificity and positive predictive value (for early mortality) in normotensive patients with PE, but low levels of BNP or NT-proBNP are capable of excluding an unfavorable early clinical outcome, with high sensitivity and a negative predictive value.

INTEGRATION OF AGGRAVATING CONDITIONS AND COMORBIDITY INTO RISK ASSESSMENT OF ACUTE PULMONARY EMBOLISM

In addition to the clinical, imaging, and laboratory findings, which are directly linked to PE severity and PE-related early death, baseline parameters related to aggravating conditions and comorbidity are necessary to assess a patient's overall mortality risk and early outcome. Of the clinical scores integrating PE severity and comorbidity, the Pulmonary Embolism Severity Index (PESI) **(Table 5)** is the one that has been most extensively validated to date, especially its simplified version.

In view of the complexity of the original PESI, which includes 11 differently weighed variables, a simplified version (sPESI; **Table 5**) has been developed and validated.[37] As with the original version of the PESI, the strength of the sPESI lies in the reliable identification of patients at low risk for 30-day mortality. The diagnosis of concomitant DVT has been identified as an adverse prognostic factor, being independently associated with death within the first 3 months after acute PE. Concomitant DVT is generally regarded as an indicator of significant comorbidity in acute PE.

TREATMENT IN THE ACUTE PHASE

Hemodynamic and Respiratory Support

Oxygen Therapy and Ventilation

Hypoxemia is one of the features of severe PE, and is mostly due to the mismatch between ventilation and perfusion. Administration of supplemental oxygen is indicated in patients with PE and SaO_2 <90%. Severe hypoxemia/respiratory failure that is refractory to conventional oxygen supplementation could be explained by right-to-left shunt through a patent foramen ovale or atrial septal defect. Further oxygenation techniques should also be considered, including high-flow oxygen (i.e., a high-flow nasal cannula) and mechanical ventilation (noninvasive or invasive) in cases of extreme instability (i.e., cardiac arrest), taking into consideration that correction

TABLE 5: Original and simplified Pulmonary Embolism Severity Index.

Parameter	Original version	Simplified version
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 bpm	+20 points	1 point
Systolic BP <100 mm Hg	+30 points	1 point
Respiratory rate >30 breaths per minute	+20 points	–
Temperature <36°C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhemoglobin saturation <90%	+20 points	1 point
Risk strata		
	• Class I: ≤65 points; very low 30-day mortality risk (0–1.6%) • Class II: 66–85 points; low mortality risk (1.7–3.5%)	0 points = 30-day mortality risk 1.0% (95% CI 0.0–2.1%)
	• Class III: 86–105 points; moderate mortality risk (3.2–7.1%) • Class IV: 106–125 points; high mortality risk (4.0–11.4%) • Class V: 125 points; very high mortality risk (10.0–24.5%)	≥1 point(s) = 30-day mortality risk 10.9% (95% CI 8.5–13.2%)

(BP: blood pressure; CI: confidence interval)

of hypoxemia will not be possible without simultaneous pulmonary reperfusion. Patients with RV failure are frequently hypotensive or are highly susceptible to the development of severe hypotension during induction of anesthesia, intubation, and positive-pressure ventilation. Consequently, intubation should be performed only if the patient is unable to tolerate or cope with noninvasive ventilation. When feasible, noninvasive ventilation or oxygenation through a high-flow nasal cannula should be preferred; if mechanical ventilation is used, care should be taken to limit its adverse hemodynamic effects. In particular, positive intrathoracic pressure induced by mechanical ventilation may reduce venous return and worsen low cardiac output due to RV failure in patients with high-risk PE; therefore, positive end-expiratory pressure should be applied with caution. Tidal volumes of approximately 6 mL/kg lean body weight should be used in an attempt to keep the end-inspiratory plateau pressure <30 cm H_2O. If intubation is needed, anesthetic drugs more prone to cause hypotension should be avoided for induction.

Pharmacological Treatment of Acute Right Ventricular Failure

Acute RV failure with resulting low systemic output is the leading cause of death in patients with high-risk PE. An overview of the current treatment options for acute RV failure is provided in **Table 6**.

If the central venous pressure is low, modest (≤500 mL) fluid challenge can be used as it may increase the cardiac index in patients with acute PE. However, volume loading has the potential to overdistend the RV and ultimately cause a reduction in systemic cardiac output. Cautious volume loading may be appropriate if low arterial pressure is combined with an absence of elevated filling pressures. If signs of elevated central venous pressure are observed, further volume loading should be withheld. Use of vasopressors is often necessary, in parallel with (or while waiting for) pharmacological, surgical, or interventional reperfusion treatment. Norepinephrine can improve systemic hemodynamics by bringing about an improvement in ventricular systolic interaction and coronary perfusion, without causing a change in pulmonary vascular resistance (PVR). Its use should be limited to patients in cardiogenic shock.

Mechanical Circulatory Support and Oxygenation

The temporary use of mechanical cardiopulmonary support, mostly with venoarterial ECMO, may be helpful in patients with high-risk PE, and circulatory collapse or cardiac arrest. Survival of critically ill patients has been described in a number of case series.[38,39] Use of ECMO is associated with a high incidence of complications, even when used for short periods, and the results depend on the experience of the center as well as patient selection. The increased risk of bleeding related to the need for vascular access should be considered, particularly in patients undergoing thrombolysis.

Advanced Life Support in Cardiac Arrest

Acute PE is part of the differential diagnosis of cardiac arrest with nonshockable rhythm against a background of pulseless electrical activity. The decision to treat acute PE must be taken early, when a good outcome is still possible. Thrombolytic therapy should be considered; once a thrombolytic drug is administered, cardiopulmonary resuscitation should be continued for at least 60–90 minutes before terminating resuscitation attempts.

TABLE 6: Treatment of right ventricle (RV) failure in acute high-risk pulmonary embolism.

Strategy	Properties and use	Caveats
Volume optimization		
Cautious volume loading, saline, or Ringer's lactate, ≤500 mL over 15–30 minutes	Consider in patients with normal low central venous pressure (due, e.g., to concomitant hypovolemia)	Volume loading can overdistend the RV, worsen ventricular interdependence, and reduce CO
Vasopressors and inotropes		
Norepinephrine, 0.2–1.0 µg/kg/min	Increases RV inotropy and systemic BP, promotes positive ventricular interactions, and restores coronary perfusion gradient	Excessive vasoconstriction may worsen tissue perfusion
Dobutamine, 2–20 µg/kg/min	Increases RV inotropy, lowers filling pressures	May aggravate arterial hypotension if used alone, without a vasopressor; may trigger or aggravate arrhythmias
Mechanical circulatory support		
Venoarterial ECMO/extracorporeal life support	Rapid short-term support combined with oxygenator	Complications with use over longer periods (>5–10 days), including bleeding and infections; no clinical benefit unless combined with surgical embolectomy; requires an experienced team

(BP: blood pressure; CO: cardiac output; ECMO: extracorporeal membrane oxygenation; RV: right ventricle)

INITIAL ANTICOAGULATION

Parenteral Anticoagulation

In patients with high or intermediate clinical probability of PE, anticoagulation should be initiated while awaiting the results of diagnostic tests. This is usually done with subcutaneous, weight-adjusted low-molecular-weight heparin (LMWH) or fondaparinux, or intravenous unfractionated heparin (UFH). Based on pharmacokinetic data, an equally rapid anticoagulant effect can also be achieved with a non-vitamin K antagonist oral anticoagulant (NOAC), and phase III clinical trials have demonstrated the noninferior efficacy of a single-oral drug anticoagulation strategy using higher doses of apixaban for 7 days or rivaroxaban for 3 weeks. LMWH and fondaparinux are preferred over UFH for initial anticoagulation in PE, as they carry a lower risk of inducing major bleeding and heparin-induced thrombocytopenia. Neither LMWH nor fondaparinux requires routine monitoring of anti-Xa levels. Use of UFH is nowadays largely restricted to patients with overt hemodynamic instability or imminent hemodynamic decompensation in whom primary reperfusion treatment will be necessary. UFH is also recommended for patients with serious renal impairment [creatinine clearance (CrCl) ≤30 mL/min] or severe obesity.[40,41]

Non-vitamin K Antagonist Oral Anticoagulants

Non-vitamin K antagonist oral anticoagulants are small molecules that directly inhibit one activated coagulation factor, which is thrombin for dabigatran and factor Xa for apixaban, edoxaban, and rivaroxaban. Owing to their predictable bioavailability and pharmacokinetics, NOACs can be given at fixed doses without routine laboratory monitoring. Compared with vitamin K antagonists (VKAs), there are fewer interactions when NOACs are given concomitantly with other drugs. In the phase III VTE trials, the dosages of dabigatran, rivaroxaban, and apixaban were not reduced in patients with mild–moderate renal dysfunction (CrCl between 30 and 60 mL/min), whereas edoxaban was given at a 30-mg dose in these patients. Patients with CrCl <25 mL/min were excluded from the trials testing apixaban, whereas patients with CrCl <30 mL/min were excluded from those investigating rivaroxaban, edoxaban, and dabigatran. Phase III trials on the treatment of acute VTE, as well as those on extended treatment beyond the first 6 months, demonstrated the noninferiority of NOACs compared with the combination of LMWH with VKA for the prevention of symptomatic or lethal VTE recurrence, along with significantly reduced rates of major bleeding.[42]

In a meta-analysis, the incidence rate of the primary efficacy outcome was 2.0% for NOAC-treated patients and 2.2% for VKA-treated patients [relative risk (RR) 0.88; 95% CI 0.74–1.05].[43] Major bleeding occurred in 1.1% of NOAC-treated patients and 1.7% of VKA-treated patients for an RR of 0.60 (95% CI 0.41–0.88). Compared with VKA-treated patients, critical site major bleeding occurred less frequently in NOAC-treated patients (RR 0.38; 95% CI 0.23–0.62); in particular, there was a significant reduction in intracranial bleeding (RR 0.37; 95% CI 0.21–0.68) and in fatal bleeding (RR 0.36; 95% CI 0.15–0.87) with NOACs compared with VKAs.[43]

Vitamin K Antagonists

Vitamin K antagonists have been the gold standard in oral anticoagulation for >50 years. When VKAs are used, anticoagulation with UFH, LMWH, or fondaparinux should be continued in parallel with the oral anticoagulant for ≥5 days and until the international normalized ratio (INR) value has been 2.0–3.0 for 2 consecutive days. Warfarin may be started at a dose of 10 mg in younger (e.g., aged <60 years) otherwise healthy patients and at a dose ≤5 mg in older patients. The daily dose is adjusted according to the INR over the next 5–7 days, aiming for an INR level of 2.0–3.0. The implementation of a structured anticoagulant service appears to be associated with increased time in the therapeutic range and improved clinical

outcome, compared with control of anticoagulation by the general practitioner. Finally, in patients who are selected and appropriately trained, self-monitoring of VKA is associated with fewer thromboembolic events and increased time in the therapeutic range compared with usual care.

REPERFUSION TREATMENT

Systemic Thrombolysis

Thrombolytic therapy leads to faster improvements in pulmonary obstruction, pulmonary artery pressure (PAP), and PVR in patients with PE, compared with UFH alone; these improvements are accompanied by a reduction in RV dilation on echocardiography.[44] The greatest benefit is observed when treatment is initiated within 48 hours of symptom onset, but thrombolysis can still be useful in patients who have had symptoms for 6–14 days.[45] Unsuccessful thrombolysis, as judged by persistent clinical instability and unchanged RV dysfunction on echocardiography after 36 hours, has been reported in 8% of high-risk PE patients. A meta-analysis of thrombolysis trials that included (but were not confined to) patients with high-risk PE, defined mainly as the presence of cardiogenic shock, indicated a significant reduction in the combined outcome of mortality and recurrent PE. This was achieved with a 9.9% rate of severe bleeding and a 1.7% rate of intracranial hemorrhage.[46] The approved regimens and doses of thrombolytic agents for PE, as well as the contraindications to this type of treatment, are given in **Table 7**. Accelerated intravenous administration of recombinant tissue-type plasminogen activator (rtPA; 100 mg over 2 hours) is preferable to prolonged infusions of first-generation thrombolytic agents (streptokinase and urokinase). Preliminary reports on the efficacy and safety of reduced-dose rtPA[47] need confirmation by solid evidence before any recommendations can be made in this regard. UFH may be administered during continuous infusion of alteplase (rtPA), but should be discontinued during infusion of streptokinase or urokinase.

It remains unclear whether early thrombolysis for (intermediate or high risk) acute PE has an impact on clinical symptoms, functional limitation, or chronic thromboembolic pulmonary hypertension (CTEPH) at long-term follow-up. A small randomized trial of 83 patients suggested that thrombolysis might improve functional capacity at 3 months compared with anticoagulation alone.[44]

Percutaneous Catheter-directed Treatment

Mechanical reperfusion is based on the insertion of a catheter into the pulmonary arteries via the femoral route. Different types of catheters are used for mechanical fragmentation, thrombus aspiration, or more commonly a pharmacomechanical approach combining mechanical or ultrasound fragmentation of the thrombus with in situ reduced-dose thrombolysis. Most knowledge about catheter-based embolectomy is derived from registries and pooled results from case series.[48,49] The overall procedural success rates (defined as hemodynamic stabilization, correction of hypoxia, and survival to hospital discharge) of percutaneous catheter-based therapies reported in these studies have reached 87%. One randomized clinical trial (RCT) compared conventional heparin-based treatment and a catheter-based therapy combining ultrasound-based clot fragmentation with low-dose in situ thrombolysis in 59 patients with intermediate-risk PE. In that study, ultrasound-assisted thrombolysis was associated with a larger decrease in the RV/left ventricle diameter ratio at 24 hours, without an increased risk of bleeding.[50] Data support the improvement in RV function, lung perfusion, and PAP in patients with intermediate- or high-risk PE using this technique. Intracranial hemorrhage was rare, although the rate of Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) severe and moderate bleeding complications was 10%. These results should be interpreted with caution, considering the relatively small numbers of patients treated, the lack of studies directly comparing catheter-directed with systemic thrombolytic therapy, and the lack of data from RCT on clinical efficacy outcomes.

Surgical Embolectomy

Surgical embolectomy in acute PE is usually carried out with cardiopulmonary bypass, without aortic cross-clamping and cardioplegic cardiac arrest, followed by incision of the two

TABLE 7: Thrombolytic regimens, doses, and contraindications.

Molecule	Regimen	Contraindications to fibrinolysis
rtPA	• 100 mg over 2 hours • 0.6 mg/kg over 15 min (maximum dose 50 mg)	*Absolute*: History of hemorrhagic stroke or stroke of unknown origin. Ischemic stroke in previous 6 months. Central nervous system neoplasm. Major trauma, surgery, or head injury in previous 3 weeks. Bleeding diathesis. Active bleeding *Relative*: • Transient ischemic attack in previous 6 months. Oral anticoagulation. Pregnancy or first postpartum week. Noncompressible puncture sites. Traumatic resuscitation • Refractory hypertension (systolic BP >180 mm Hg). Advanced liver disease. Infective endocarditis. Active peptic ulcer
Streptokinase	• 250,000 IU as a loading dose over 30 min, followed by 100,000 IU/h over 12–24 hours • *Accelerated regimen*: 1.5 million IU over 2 hours	
Urokinase	• 4,400 IU/kg as a loading dose over 10 min, followed by 4,400 IU/kg/h over 12–24 hours • *Accelerated regimen*: 3 million IU over 2 hours	

(rtPA: recombinant tissue-type plasminogen activator)

main pulmonary arteries with the removal or suction of fresh clots. Recent reports have indicated favorable surgical results in high-risk PE, with or without cardiac arrest, and in selected cases of intermediate-risk PE.[51,52] Among 174,322 patients hospitalized between 1999 and 2013 with a diagnosis of PE in New York state, survival and recurrence rates were compared between patients who underwent thrombolysis (n = 1,854) or surgical embolectomy (n = 257) as first-line therapy.[51] Overall, there was no difference between the two types of reperfusion treatment regarding 30-day mortality (15% and 13%, respectively), but thrombolysis was associated with a higher risk of stroke and reintervention at 30 days. No difference was found in terms of 5-year actuarial survival, but thrombolytic therapy was associated with a higher rate of recurrent PE requiring readmission compared with surgery (7.9% vs. 2.8%). However, the two treatments were not randomly allocated in this observational retrospective study, and the patients referred for surgery may have been selected. Recent experience appears to support combining ECMO with surgical embolectomy, particularly in patients with high-risk PE with or without the need for cardiopulmonary resuscitation.

Vena Cava Filters

The aim of vena cava interruption is to mechanically prevent venous clots from reaching the pulmonary circulation. Most devices in current use are inserted percutaneously and can be retrieved after several weeks or months, or left in place over the long term, if needed. Potential indications include VTE and absolute contraindication to anticoagulant treatment, recurrent PE despite adequate anticoagulation, and primary prophylaxis in patients with a high risk of VTE. Other potential indications for filter placement, including free-floating thrombi, have not been confirmed in patients without contraindications to therapeutic anticoagulation.

A systematic review and meta-analysis of published reports on the efficacy and safety of vena cava filters included 11 studies, with a total of 2,055 patients who received a filter versus 2,149 controls.[53] Vena cava filter placement was associated with a 50% decrease in the incidence of PE and an approximately 70% increase in the risk of DVT over time. Neither all-cause mortality nor PE-related mortality differed between patients with or without filter placement. The broad indication for placement of a venous filter in patients with recent (<1 month) proximal DVT and an absolute contraindication to anticoagulant treatment is based mainly on the perceived high risk of recurrent PE in this setting, and the lack of other treatment options. Complications associated with vena cava filters are common and can be serious. A systematic literature review revealed penetration of the venous wall in 1,699 (19%) of 9,002 procedures; of these cases, 19% showed adjacent organ involvement and ≥8% were symptomatic.[54] Lethal complications were rare (only two cases), but 5% of the patients required major interventions such as surgical removal of the filter, endovascular stent placement or embolization, endovascular retrieval of the permanent filter, or percutaneous nephrostomy or ureteral stent placement.[54] Further reported complications include filter fracture and/or embolization and DVT occasionally extending up to the vena cava **(Tables 8 and 9)**.[54]

TABLE 8: Recommendations for acute-phase treatment of high-risk pulmonary embolism (PE).

Recommendations	Class	Level
It is recommended that anticoagulation with UFH, including a weight-adjusted bolus injection, be initiated without delay in patients with high-risk PE	I	C
Systemic thrombolytic therapy is recommended for high-risk PE	I	B
Surgical pulmonary embolectomy is recommended for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed	I	C
Percutaneous catheter-directed treatment should be considered for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed	IIa	C
Norepinephrine and/or dobutamine should be considered in patients with high-risk PE	IIa	C
ECMO may be considered, in combination with surgical embolectomy or catheter-directed treatment, in patients with PE and refractory circulatory collapse or cardiac arrest	IIb	C

(ECMO: extracorporeal membrane oxygenation; UFH: unfractionated heparin)

TABLE 9: Recommendations for acute-phase treatment of intermediate- or low-risk pulmonary embolism (PE).

Recommendations	Class	Level
Initiation of anticoagulation		
Initiation of anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE, while diagnostic workup is in progress	I	C
If anticoagulation is initiated parenterally, LMWH or fondaparinux is recommended (over UFH) for most patients	I	A
When oral anticoagulation is started in a patient with PE who is eligible for an NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), an NOAC is recommended in preference to a VKA	I	A
When patients are treated with a VKA, overlapping with parenteral anticoagulation is recommended until an INR of 2.5 (range 2.0–3.0) is reached	I	A
NOACs are not recommended in patients with severe renal impairment, during pregnancy and lactation, and in patients with antiphospholipid antibody syndrome	III	C
Reperfusion treatment		
Rescue thrombolytic therapy is recommended for patients with hemodynamic deterioration on anticoagulation treatment	I	B
As an alternative to rescue thrombolytic therapy, surgical embolectomy or percutaneous catheter-directed treatment should be considered for patients with hemodynamic deterioration on anticoagulation treatment	IIa	C
Routine use of primary systemic thrombolysis is not recommended in patients with intermediate- or low-risk PE	III	B

(INR: international normalized ratio; LMWH: low-molecular-weight heparin; NOAC: non-vitamin K antagonist oral anticoagulant; UFH: unfractionated heparin; VKA: vitamin K antagonist)

INTEGRATED RISK-ADAPTED DIAGNOSIS AND MANAGEMENT

Diagnostic Strategies

Various combinations of clinical assessments, plasma D-dimer measurements, and imaging tests have been proposed and validated for PE diagnosis. These strategies have been tested in patients presenting with suspected PE in the emergency department or during their hospital stay or in the primary care setting. Withholding anticoagulation without adherence to evidence-based diagnostic strategies is associated with a significant increase in the number of VTE episodes and sudden cardiac death at 3-month follow-up. However, it is recognized that the diagnostic approach for suspected PE may vary, depending on the availability of, and expertise in, specific tests in various hospitals and clinical settings.

Suspected Pulmonary Embolism with Hemodynamic Instability

The clinical probability is usually high and the differential diagnosis includes cardiac tamponade, acute coronary syndrome, aortic dissection, acute valvular dysfunction, and hypovolemia. The most useful initial test in this situation is bedside TTE, which will yield evidence of acute RV dysfunction if acute PE is the cause of the patient's hemodynamic decompensation. In a highly unstable patient, echocardiographic evidence of RV dysfunction is sufficient to prompt immediate reperfusion without further testing. This decision may be strengthened by the (rare) visualization of right-heart thrombi. Ancillary bedside imaging tests include TEE, which may allow direct visualization of thrombi in the pulmonary artery and its main branches, especially in patients with RV dysfunction. TEE should be performed cautiously in hypoxemic patients. Moreover, bedside CUS can detect proximal DVT. As soon as the patient is stabilized using supportive treatment, final confirmation of the diagnosis by CT angiography should be sought. For unstable patients admitted directly to the catheterization laboratory with suspected acute coronary syndrome, pulmonary angiography may be considered as a diagnostic procedure after the acute coronary syndrome has been excluded, provided that PE is a probable diagnostic alternative and particularly if percutaneous catheter-directed treatment is a therapeutic option.

Suspected Pulmonary Embolism without Hemodynamic Instability

Strategy Based on Computed Tomography Pulmonary Angiography

In patients admitted to the emergency department, measurement of plasma D-dimer is the logical first step following the assessment of clinical probability and allows PE to be ruled out in approximately 30% of outpatients. D-dimer should not be measured in patients with a high clinical probability of PE, owing to a low negative predictive value in this population. It is also less useful in hospitalized patients because the number that needs to be tested to obtain a clinically relevant negative result is high. In most centers, multidetector CTPA is the second-line test in patients with an elevated D-dimer level and the first-line test in patients with a high clinical probability of PE. CTPA is considered to be diagnostic of PE when it shows a clot at least at the segmental level of the pulmonary arterial tree. False-negative results of CTPA have been reported in patients with a high clinical probability of PE;[28] however, such discrepancies are infrequent and the 3-month thromboembolic risk was low in these patients.[28]

Strategy Based on Ventilation/Perfusion Scintigraphy

Hospitals in which V/Q scintigraphy is readily available, it is a valid option for patients with an elevated D-dimer and a contraindication to CTPA. Also, V/Q scintigraphy may be preferred over CTPA to avoid unnecessary radiation, particularly in younger patients and in female patients in whom thoracic CT might raise the lifetime risk of breast cancer. V/Q lung scintigraphy is diagnostic (with either normal- or high-probability findings) in approximately 30–50% of emergency ward patients with suspected PE.[55] The proportion of diagnostic V/Q scans is higher in patients with a normal chest X-ray, and this might support the use of a V/Q scan as a first-line imaging test for PE in younger patients, depending on local availability. The number of patients with inconclusive findings may further be reduced by taking into account clinical probability. Thus, patients with a nondiagnostic lung scan and low clinical probability of PE have a low prevalence of confirmed PE, and the negative predictive value of this combination is further increased by the absence of a DVT on lower-limb CUS. If a high-probability lung scan is obtained from a patient with low clinical probability of PE, confirmation by other tests should be considered.

TREATMENT STRATEGIES

Emergency Treatment of High-risk Pulmonary Embolism

Primary reperfusion treatment, in most cases systemic thrombolysis, is the treatment of choice for patients with high-risk PE. Surgical pulmonary embolectomy or percutaneous catheter-directed treatments are alternative reperfusion options in patients with contraindications to thrombolysis, if expertise with either of these methods and the appropriate resources are available on-site. Following reperfusion treatment and hemodynamic stabilization, patients recovering from high-risk PE can be switched from parenteral to oral anticoagulation. As patients belonging to this risk category were excluded from the phase III new oral anticoagulant trials, the optimal time point for this transition has not been determined by existing evidence but should instead be based on clinical judgment. The specifications concerning the higher initial dose of apixaban or rivaroxaban (for 1 and 3 weeks after PE diagnosis, respectively), or the minimum overall period (5 days) of heparin anticoagulation before switching to dabigatran or edoxaban, must be followed.

Treatment of Intermediate-risk Pulmonary Embolism

Normotensive patients with at least one indicator of elevated PE-related risk, or with aggravating conditions or comorbidities, should be hospitalized. In this group, patients with signs of RV dysfunction on echocardiography or CTPA, accompanied by a positive troponin test, should be monitored over the first hours or days due to the risk of early hemodynamic decompensation and circulatory collapse. Routine primary reperfusion treatment, notably full-dose systemic thrombolysis, is not recommended, as the risk of potentially life-threatening bleeding complications appears too high for the expected benefits from this treatment. Rescue thrombolytic therapy or, alternatively, surgical embolectomy or percutaneous catheter-directed treatment should be reserved for patients who develop signs of hemodynamic instability. It appears reasonable to leave patients with intermediate-high-risk PE on LMWH anticoagulation over the first 2–3 days and ensure that they remain stable before switching to oral anticoagulation. The specifications concerning the increased initial dose of apixaban or rivaroxaban, or the minimum overall period of heparin anticoagulation before switching to dabigatran or edoxaban, must be followed.

Management of Low-risk Pulmonary Embolism: Triage for Early Discharge and Home Treatment

As a general rule, early discharge of a patient with acute PE and continuation of anticoagulant treatment at home should be considered if three sets of criteria are fulfilled: (1) The risk of early PE-related death or serious complications is low, (2) there is no serious comorbidity or aggravating condition(s) that would mandate hospitalization, and (3) proper outpatient care and anticoagulant treatment can be provided, considering the patient's (anticipated) compliance, and the possibilities offered by the healthcare system and social infrastructure. Randomized trials and prospective management cohort studies that investigated the feasibility and safety of early discharge, and home treatment, of PE adhered to these principles, even though slightly different criteria or combinations thereof were used to ensure the above three requirements. In patients who were included in prospective cohort studies and treated at home, with or without a short hospitalization period, the 3-month rates of thromboembolic recurrence, major bleeding, and death were 1.75%, 1.43%, and 2.83%, respectively.

Regimens and Treatment Durations

All patients with PE should be treated with anticoagulants for ≥3 months **(Table 10)**.[56] Beyond this period, the balance between the risk of VTE recurrence and that of bleeding, which has been used to select candidates for extended anticoagulation after a first VTE event in the VKA era, is currently being revisited based on the lower bleeding rates with NOACs. However, despite the improved safety of these drugs compared with VKAs treatment with new oral anticoagulants is not without risk. Phase III clinical trials on the extended treatment of VTE have shown that the rate of major bleeding may be approximately 1% and that of clinically relevant nonmajor (CRNM) bleeding as high as 6%. Bleeding rates may be higher in everyday clinical practice.[57] At present, NOACs are not an alternative to VKAs in patients with antiphospholipid syndrome (testing triple positive for lupus anticoagulant, anticardiolipin, and anti-β-glycoprotein I).

TABLE 10: Recommendations for the regimen and duration of anticoagulation after pulmonary embolism (PE).

Recommendations	Class	Level
Therapeutic anticoagulation for >3 months is recommended for all patients with PE	I	A
Patients in whom discontinuation of anticoagulation after 3 months is recommended		
For patients with first PE/VTE secondary to a major transient/reversible risk factor, discontinuation of therapeutic oral anticoagulation is recommended after 3 months	I	B
Patients in whom extension of anticoagulation beyond 3 months is recommended		
Oral anticoagulant treatment of indefinite duration is recommended for patients presenting with recurrent VTE (i.e., with at least one previous episode of PE or DVT) not related to a major transient or reversible risk factor	I	B
Oral anticoagulant treatment with a VKA for an indefinite period is recommended for patients with antiphospholipid antibody syndrome	I	B
Patients in whom extension of anticoagulation beyond 3 months should be considered		
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE and no identifiable risk factor	IIa	A
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a persistent risk factor other than antiphospholipid antibody syndrome	IIa	C
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a minor transient or reversible risk factor	IIa	C
NOAC dose in extended anticoagulation		
If extended oral anticoagulation is decided after PE in a patient without cancer, a reduced dose of the NOACs apixaban (2.5 mg bid) or rivaroxaban (10 mg od) should be considered after 6 months of therapeutic anticoagulation	IIa	A
Extended treatment with alternative antithrombotic agents		
In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin or sulodexide may be considered for extended VTE prophylaxis	IIb	B
Follow-up of the patient under anticoagulation		
In patients who receive extended anticoagulation, it is recommended that their drug tolerance and adherence, hepatic and renal function, and bleeding risk be reassessed at regular intervals	I	C

(DVT: deep vein thrombosis; NOAC: non-vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonist; VTE: venous thromboembolism)

Chronic Thromboembolic Pulmonary Hypertension

Chronic thromboembolic pulmonary hypertension is a disease caused by the persistent obstruction of pulmonary arteries by organized thrombi, leading to flow redistribution and secondary remodeling of the pulmonary microvascular bed. CTEPH has been reported with a cumulative incidence of between 0.1 and 9.1% in the first 2 years after a symptomatic PE event; the large margin of error is due to referral bias, the paucity of early symptoms, and the difficulty of differentiating acute PE from symptoms of preexisting CTEPH.[58] The hallmark of CTEPH is fibrotic transformation of a pulmonary arterial thrombus, causing fixed mechanical obstruction of pulmonary arteries and leading to overflow of the open pulmonary arterial bed. Together with collateral supply from systemic arteries downstream of pulmonary arterial occlusions, this contributes to microvascular remodeling causing a progressive increase in PVR. Owing to this complex pathophysiology, there is no clear correlation between the degree of mechanical obstruction found at imaging and hemodynamics, which can deteriorate in the absence of recurrent PE. In CTEPH, mean PAP >30 mm Hg is related to poor survival, similar to that reported for idiopathic pulmonary arterial hypertension.

Clinical symptoms and signs are nonspecific or absent in early CTEPH, with signs of right-heart failure only becoming evident in advanced disease. Thus, early diagnosis remains a challenge in CTEPH, with a median time of 14 months between symptom onset and diagnosis in expert centers. When present, the clinical symptoms of CTEPH may resemble those of acute PE or pulmonary arterial hypertension; in the latter context, edema and hemoptysis occur more often in CTEPH, while syncope is more common in pulmonary arterial hypertension. The diagnosis of CTEPH is based on findings obtained after at least 3 months of effective anticoagulation to distinguish this condition from acute PE. The diagnosis requires a mean PAP of ≥25 mm Hg along with a pulmonary arterial wedge pressure of ≤15 mm Hg, documented at right-heart catheterization in a patient with mismatched perfusion defects on V/Q lung scan. Specific diagnostic signs for CTEPH on multidetector CTPA or conventional pulmonary cineangiography include ring-like stenoses, webs, slits, and chronic total occlusions. Planar V/Q lung scan is a suitable first-line imaging modality for CTEPH as it has 96–97% sensitivity and 90–95% specificity for the diagnosis.[59]

Computed tomography pulmonary angiography is gaining ground as a diagnostic modality in CTEPH,[60] but it should not be used as a stand-alone test to exclude the disease. Newer diagnostic tests include dual-energy CT. Cone-beam CT, angioscopy, intravascular ultrasound, and optical coherence tomography are more suitable for the characterization of lesions during interventional treatment than for diagnosis.

Treatment of Chronic Thromboembolic Pulmonary Hypertension

Surgical pulmonary endarterectomy (PEA) is the treatment of choice for operable CTEPH. Over the past decade, balloon pulmonary angioplasty (BPA) has emerged as an effective treatment for technically inoperable CTEPH. It allows dilatation of obstructions down to subsegmental vessels, which are inaccessible to surgery. BPA is a stepwise procedure requiring several (usually 4–10) separate sessions. While most of the BPA procedures are performed in technically inoperable patients, this method has also been used for sequential treatment for pulmonary hypertension persisting after PEA. Optimal medical treatment for CTEPH consists of anticoagulants as well as diuretics and oxygen in cases of heart failure or hypoxemia. Lifelong oral anticoagulation with VKAs is recommended, and also after successful PEA or BPA. To date, the only drug approved for inoperable CTEPH or persistent/recurrent pulmonary hypertension after PEA is riociguat, an oral stimulator of soluble guanylate cyclase.

CONCLUSION

Diagnosis of PE can reliably be made especially in presence of underlying conditions, most commonly orthopedic and other major surgeries, cancers and prolonged immobilization. Clinical suspicion, ECG, echocardiogram and CT pulmonary angiogram are indispensable tools in diagnosis and management of acute PE. The patients should be risk stratified based on presentation using PE scores and approached accordingly for further management. Prevention of VTE is mandatory as directed in guidelines.

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CHAPTER 27

Management of Primary Pulmonary Hypertension

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ABSTRACT

Pulmonary hypertension (PH) is a chronic and complex disease. PH is classified into five groups by the World Health Organization (WHO). Echocardiography is the initial investigation, and right heart catheterization is the gold standard for the diagnosis and guidance to treatment. Multidisciplinary approach is recommended for the care of PH patients. Advances in treatment are for the subset of PH patients. Newer drugs for target therapy and interventional therapies are in the experimental or trial phase. Early diagnosis and no delay in treatment are the keys to improve the outcome of PH patients.

DEFINITION OF PULMONARY HYPERTENSION

In 1961, a report of the World Health Organization (WHO) Expert Committee on chronic cor pulmonale mentioned clearly that the mean pulmonary artery pressure (mPAP) does not normally exceed 15 mm Hg when the subject is at rest in a lying position, and that the value was little affected by age and never exceeded 20 mm Hg.

Since the first World Symposium on Pulmonary Hypertension (WSPH) organized by the WHO in Geneva in 1973, pulmonary hypertension (PH) has been defined as mPAP ≥ 25 mm Hg measured by right heart catheterization (RHC) in the supine position at rest and >30 mm Hg on exercise. This meeting was devoted to primary PH (PPH), a severe form of PH, some years after an outbreak related to the intake of the anorexic drug aminorex. In the report of the meeting, it was recognized that this upper limit of normal (ULN) mPAP of 25 mm Hg was somewhat empirical and arbitrarily defined. However, this conservative cut-off value allowed physicians to discriminate severe PH due to PPH from other forms of PH (mainly due to lung diseases) characterized by a lower mPAP.[1] This definition remained unchanged during the subsequent WSPH meetings from 1998 to 2013, at least in part to preclude potential overdiagnosis and overtreatment of PH.

In 2009, Kovacs et al. reviewed data pertaining to RHC in healthy adults at rest and exercise. Data on 1,187 individuals from 47 studies in 13 countries were included. They noted that pulmonary arterial pressure (Ppa) at rest is virtually independent of age and rarely exceeds 20 mm Hg, exercise P_{pa} is age-related and frequently exceeds 30 mm Hg, especially in elderly individuals, which makes it difficult to define normal P_{pa} values during exercise. They concluded that, while Ppa at rest is virtually independent of age and rarely exceeds 20 mm Hg, exercise Ppa is age-related and frequently exceeds 30 mm Hg, especially in elderly individuals, which makes it difficult to define normal Ppa values during exercise.[2] This has been cited as an evidence base on which the present recommendations on the cut off for mPAP are based.

However, the description of PH cannot be made on the basis of mPAP alone as this, in isolation, does not identify the pathological process at play and is influenced by a number of factors including increase in cardiac output (CO), left-to-right cardiac shunts, and elevation of pulmonary arterial wedge pressure (PAWP) in left heart disease and hyperviscosity, apart from pulmonary vascular disease (PVD), thereby bringing into play a requirement for defining the status of the pulmonary vascular resistance (PVR). Since the third WSPH held in 2003, precapillary PH of group 1 [pulmonary arterial hypertension (PAH)] has been defined by the presence of elevated PVR ≥ 3 Wood units (WU).[3-5] This cut-off value of PVR ≥ 3 WU is also quite arbitrary since some data suggest that PVR > 2 WU could be also considered abnormal.[4] In this sense, the value of PVR ≥ 3 WU is considered clinically relevant in different clinical situations, suggesting the presence of a significant PVD, e.g., it is already used as the threshold value for which the correction of congenital systemic-to-pulmonary shunts becomes questionable[6] and a PVR above which there is poor survival after heart transplantation.[7-11]

TABLE 1: Hemodynamic classification of pulmonary hypertension.

Definitions	Characteristics	Clinical groups
Precapillary PH	• mPAP > 20 mm Hg • PAWP ≤ 15 mm Hg • PVR ≥ 3 WU	1, 3, 4, and 5
Isolated postcapillary PH (IpcPH)	• mPAP > 20 mm Hg • PAWP > 15 mm Hg • PVR < 3 WU	2 and 5
Combined pre- and postcapillary PH (CpcPH)	• mPAP > 20 mm Hg • PAWP > 15 mm Hg • PVR ≥ 3 WU	2 and 5

(mPAP: mean pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance)

Evaluation of patients with borderline (21–24 mm Hg) mPAP with regard to future progression has shown that this subgroup of patients is at a higher risk of progression to overt PH.

Pulmonary hypertension has been classified by WSPH into three broad groups as shown in **Table 1**. A new entity, exercise PH has been introduced and defined as mPAP/cardiac output (CO) slope >3 mm Hg/L/min between rest and exercise. Still there are patients who have mPAP >20 mm Hg but low PVR (≤2 WU) and low PAWP (≤15 mm Hg). Such patients are called "unclassified PH".

Based upon these data, recommendations have been framed by the sixth WSPH as shown in **Table 1**.

THE DIFFICULT ISSUE OF DEFINING EXERCISE PULMONARY HYPERTENSION

In continuation with the existing norms, in 2004, PH was defined as an mPAP of >25 mm Hg at rest or an mPAP of >30 mm Hg during exercise.[6] At the fourth WSPH in 2008, however, the "exercise" part of the definition was removed.[3] The idea of defining PH in relation to exercise is appealing because the disease is clinically silent until late in its natural history, when most of the distal pulmonary arteries (PAs) have been obliterated. Rise in resting PH pressure is a late event in the natural history of PVDs, because of microvascular "reserves." PAP rises only when ≥50% of the microcirculation has been lost.[12] Lau et al. evaluated the response of PAP to increase in CO in healthy volunteers and patients with PAH with dobutamine stress echocardiography (DSE), which demonstrated abnormal response of the PAH to exercise: The average dobutamine-induced mPAP-Q (CO) slope was 1.1 ± 0.7 mm Hg/L/min in healthy control subjects and 5.1 ± 2.5 mm Hg/L/min in patients with PAH ($p < 0.001$).[13]

The changes in mPAP with exercise are dependent on the age and CO. Again, the PVR which is dependent upon mPAP, PAWP, and CO [PVR = (mPAP – PAWP)/CO] varies with exercise because the PAWP is dependent upon CO. So this necessitates the determination of PAWP in such patients. Generating such data is, however, challenging as exercise RHC measurements are time consuming, difficult, and potentially complicated by errors due to rapid respiratory cycles and inaccuracies in exercise CO and PAWP measures. Hence, in spite of an attractive premise, the determination of criteria for a routine measurement of exercise PH remains elusive.

DIAGNOSTIC STRATEGIES IN PULMONARY HYPERTENSION

The diagnosis of PH is hampered by the protean, insidious, and nonspecific presentation of the disease. It is manifested by shortness of breath, fatigability, weakness, light headedness, and occasionally, cough. Advanced cases may present with features of right-sided heart failure. Physical examination is reflected in the jugular venous pressure (JVP), a loud P2, right ventricular (RV) dilatation, murmur of tricuspid regurgitation (TR) or ascites, edema, and hepatomegaly in advanced cases. The cornerstone, hence, in the diagnosis of PH is a high threshold of suspicion with screening and specific evaluation where indicated. After the diagnosis of PH per se, an etiological search should be undertaken. We will focus on the basic evaluation, especially echocardiography required to establish the minimum diagnosis of PH.

Chest X-ray and Electrocardiogram

In spite of providing valuable clues leading to a suspicion of PH, including prognostic information,[14] these are largely nonspecific and have limited utility to arrive at the diagnosis.

Echocardiography

In spite of the diagnosis of PH, as per definition being a diagnosis obtained from catheterization, echocardiography is often used at the diagnostic modality to arrive at the conclusion due to its noninvasive nature and ubiquitous availability. It is an accurate and robust tool for the assessment of PH.

The measurement of the RV systolic pressure is obtained most commonly from the peak tricuspid regurgitant jet velocity which is then used to calculate the pressure gradient from the modified Bernoulli equation and added to the estimated right atrial pressure (RAP).[6,15] A peak TR velocity value of ≤2.8 m/sec is considered normal.

$$\text{Pulmonary artery systolic pressure (PASP)} = (\text{peak TR velocity})^2 + \text{estimated RAP}$$

However, the TR assessment may be fallacious in the presence of right ventricular outflow tract (RVOT) obstruction or RV systolic dysfunction where the PASP may be underestimated and in high output states such as anemia or pregnancy where it may be overestimated.

Approximately 10% of the patients with PH will have pulmonary regurgitation (PR). The mPAP may be calculated conventionally from the PR velocity or the RVOT acceleration time.

Mean pulmonary artery pressure = 4 (PR peak velocity)^2 + estimated RAP. Also, mPAP = 90 – (0.62 × RVOT acceleration time) (Dabestani–Mahan equation)

Based on a single-center sample, an RVOT acceleration time >120 milliseconds could be used to estimate a normal PASP ≤25 mm Hg.[16] Systolic deceleration or "notching" of the RVOT Doppler flow velocity envelope is associated with an elevated pulmonary vessel impedance.[17]

A "notched" Doppler signal strongly suggests an increased resistance and poor vascular compliance. mPAP can also be calculated by adding the velocity time integral (VTI) of the TR jet to estimated RAP.[18]

Also, the mean pulmonary pressure can be calculated as per various formulae from the peak systolic RV pressure as measured from the TR velocity. They have been subsequently validated.[19,20]

Mean pulmonary artery pressure = 0.61 × (PASP) + 2 mm Hg (Chemla et al.)[21]

Mean pulmonary artery pressure = 0.65 × (PASP) + 0.55 mm Hg (Syyed et al.)[22]

Echocardiographically, estimation of the RAP can be made from the inferior vena cava (IVC) dimension and collapsibility. Also, echocardiography will provide invaluable estimation of the RV function, and clues to etiology in the presence of congenital heart disease or left ventricle (LV) dysfunction. It is also important to identify other findings of PAH in echocardiography, which adds to the echocardiographical certainty of PAH. The European Society of Cardiology (ESC) 2015 guidelines on PH[6] details the stratification of probability of PH according to the TR gradient and other echocardiographic variables into low, intermediate, or high. These include the right ventricle (RV)/LV basal diameter ratio >1.0, left ventricular eccentricity index >1.1, right atrial area (end systole) >18 cm^2, RVOT Doppler acceleration time <105 milliseconds and/or mid systolic notching, PA diameter >25 mm, early diastolic PR velocity >2.2 m/sec, and IVC diameter >21 mm with decreased inspiratory collapse.

The ratio of peak tricuspid regurgitant velocity (in milliseconds) to the RVOT VTI (in centimeter) obtained by Doppler echocardiography [TR velocity (TRV)/VTI-RVOT] has been suggested[23] to provide a reliable method to determine PVR. However, its use has been disputed in patients with high PVR[24] and in patients with chronic thromboembolic pulmonary hypertension (CTEPH).[25]

Other Investigations

Other investigations to the diagnosis of PH include pulmonary function test [delineation of restrictive/obstructive pulmonary disease, low diffusing capacity of the lungs for carbon monoxide (DLCO) in PH], chest imaging with high-resolution computed tomography (HRCT) to examine the lung parenchyma, computed tomography (CT), pulmonary angiography, or ventilation/perfusion (V/Q) scan for the detection of CTEPH in appropriate situations, and RHC.

MANAGEMENT OF PRIMARY PULMONARY HYPERTENSION

The current treatment strategy for PAH can be broadly divided into general measures and PAH-specific therapies.

General Supportive Measures

- *Restriction of salt and fluid intake to reduce volume overload in light of their limited RV reserve*: Weight gain is one of the first signs of fluid retention in patients with RV failure (RVF), and therefore, weight should be monitored at every patient visit and by the patient at home. The cause of edema may be factors other than RVF. Patients who have recently commenced PAH treatment with endothelin receptor antagonists (ERAs) exhibit signs of peripheral edema due to increased vascular permeability. There are numerous other causes of fluid retention. Notably, one cause which may be overlooked is a high $PaCO_2$ in patients who develop respiratory failure.[26]
- Supplemental oxygen therapy should be used if needed to maintain systemic oxygen saturation above 90% as it improves exercise capacity. Although O_2 administration has been demonstrated to reduce the PVR in patients with PAH, there are no randomized data to suggest that long-term O_2 therapy is beneficial in PAH or in Eisenmenger syndrome.[27]
- Exercise training is advocated in PAH. Exercise training increases 6-minute walk test (6MWT), peak oxygen uptake, and quality of life in PAH. Low-level, symptom-limited, aerobic exercises are preferred. Use of exercise testing as adjunct to conventional therapy is gaining ground and it remains to be seen whether this confers an additional survival benefit.[28,29]
- Vaccination against influenza and pneumococcal pneumonia is recommended.
- *Contraception*: Pregnancy is associated with substantial mortality in PAH.[30] Hysteroscopic sterilization is the preferred method of contraception, but other options include progesterone-only intrauterine devices and pills and tubal ligation. Estrogen-containing contraceptives and injectable progesterone are contraindicated because they increase the risk of thrombosis.[31]
- *Background therapies for PAH*:
  - Diuretics: Diuretics are used to treat venous congestion resulting from RVF.
  - Digoxin: Short-term use of intravenous (IV) digoxin in idiopathic pulmonary arterial hypertension (IPAH) produces a modest increase in CO and a significant reduction in circulating norepinephrine.[32] However, there is inadequate and conflicting long-term data concerning its use in terms on survival benefit.[33,34]
  - Anticoagulation: In situ thrombosis occurs in the small resistance PAs of PAH patients. The evidence for anticoagulant therapy in patients with PAH is from two single-center, nonrandomized trials.[35,36] In the COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) registry, the use of anticoagulation was associated with a 21% improvement in survival in patients with IPAH but no benefit in those with associated pulmonary arterial hypertension (APAH).[37]. The REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) registry found no survival benefit with anticoagulation in IPAH and reduced survival in APAH.[38] Long-term warfarin therapy is recommended only in IPAH, heritable PAH (HPAH), or anorexigen-associated PAH patients with an international normalized ratio goal of 1.5–2.5.

Specific Management for Idiopathic Pulmonary Arterial Hypertension

Calcium Channel Blocker

In 1987, Rich and Brundage[39] studied 13 patients with PH who were given an initial test dose of 60 mg diltiazem or 20 mg nifedipine followed by consecutive hourly doses until a 50% fall in PVR and a 33% fall in pulmonary arterial pressure were achieved or untoward side effects developed. Among these patients, eight responded. These patients were discharged on high-dose (up to 720 mg/day diltiazem or 240 mg/day nifedipine) calcium channel-blocking drugs as a long-term therapy. On follow-up four patients showed improvement in terms of hemodynamic profile and electrocardiographic and echocardiographic regression of right ventricular hypertrophy (RVH). Subsequent studies have shown a significant survival benefit over a 5-year period when compared to nonresponders to vasodilator therapy and when compared to the NIH registry cohort.[35]

However, only a minority of patients with IPAH benefit from long-term treatment with oral calcium channel blocker (CCB). This depends upon the question of hemodynamic response of the patient to CCB which needs to be initially ascertained, failing of which the imposition of a CCB-based regimen may actually be nonbeneficial and indeed deleterious for the patient. The mechanisms for the deleterious adverse reactions to CCB remain uncertain. Potential explanations are depression in the myocardial contractility, activation of endogenous neurohormonal systems such as renin–angiotensin system, which have an adverse effect on cardiovascular performance, and hypotension leading to reduced coronary perfusion and as a result ischemic myocardial dysfunction.[40]

Pulmonary vasodilator testing establishes the relative contribution of reversible vasoconstriction versus fixed stenosis in patients with PAH. Multiple criteria for a positive pulmonary vasodilator test have been suggested. Data from acute vasoreactivity testing (AVT) have been derived predominantly from studies in patients with idiopathic pulmonary fibrosis (IPF) and hereditary PAH. A decrease of the mPAP of at least 10 mm Hg to reach an absolute value of 40 mm Hg or less without a decrease in CO is currently recommended to consider a pulmonary vasodilator test as positive.[41-43] This revised definition of positive pulmonary vasodilator test (Sitbon criteria), replaced the older definition that considered a test positive when the mPAP and PVR decreased by at least 20% (Rich criteria), motivated by a poor identification of the patients likely to benefit as by applying the more inclusive older criteria. The sensitivity, specificity, positive, and negative predictive values of pulmonary vasodilator testing, using the new criteria, are 69%, 87%, 78%, and 81%, respectively.[41] The percentage of positive tests is observed in about 10–15% of patients using the current criteria. Half of the patients with a positive test will experience long-term benefits with CCBs. Sustained benefit with CCBs is defined by the improvement of dyspnea to New York Heart Association (NYHA) class II or less in concert with sustained hemodynamic improvement after a year of treatment. The lack of sustained benefit in some responders is presumably due to permanent vascular changes which are related to intimal proliferation, fibrosis, and thrombosis.

These Sitbon criteria are currently recommended in international guidelines for adult patients with PAH, but not for children. In children, the Barst criteria[44] [decrease in mPAP of ≥20%, unchanged or increased cardiac index, and decreased or unchanged PVR to systemic vascular resistance (SVR) ratio] are frequently used. In IPAH, the proportion of patients with an acute vasodilator response (AVR, i.e., a positive AVT) has been reported to be much higher in children (up to 50%) than in adults (10–15%), but this may be due to the heterogeneity of the criteria used to define such a finding. The "Barst criteria" were modified by the European Pediatric Pulmonary Vascular Disease (PVD) Network, 2016. They defined that in patients with IPAH/HPAH, the hemodynamic change defines a positive response to AVT in PH without shunt [ratio of pulmonary to systemic flow for children should be considered as a >20% fall in mean PAP and indexed PVR (PVRi)/indexed SVR (SVRi) ratio without a decrease in CO].[44] Inhaled nitric oxide (NO) and oxygen, aerosolized prostanoids (iloprost), and treprostinil are usually recommended for AVT in children, although oral sildenafil or IV epoprostenol infusion can be used.

The agents currently recommended to evaluate the pulmonary vasoresponsiveness include inhaled NO, IV adenosine, or epoprostenol.[3,45] In addition, inhaled iloprost also has acquired substantial evidence for this use. There is lack of consensus on the preferred agent for determining acute pulmonary vasoreactivity. In the absence of evidence-based guidelines, the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) 2009 Expert Consensus Document on PH recommends inhaled NO as the preferred vasodilator agent and considers IV epoprostenol and adenosine as acceptable alternatives.[45]

There are no baseline predictors of patients who respond to vasoreactivity testing as compared to the other patients. However, acute responders have less severe disease, as demonstrated by a higher proportion of patients in the NYHA functional class I or II, a better 6MWT, and a lower PVR. Interestingly, a higher proportion of syncope was found in the history of acute responders, probably because these patients have less severe disease and are able to perform more vigorous activities.

Finally, acute responders had a significantly longer duration of symptoms before diagnosis, in addition to a less severe disease.[41]

The CCBs that have been predominantly used in reported studies for therapeutic use in patients with positive AVT are nifedipine, diltiazem, and amlodipine, with particular emphasis on nifedipine and diltiazem. The choice of CCB is based on the patient's heart rate at baseline, with a relative bradycardia favoring nifedipine and amlodipine and a relative tachycardia favoring diltiazem. The daily doses of these drugs that have shown efficacy in IPAH are relatively high: 120–240 mg for nifedipine, 240–720 mg for diltiazem, and up to 20 mg for amlodipine. It is advisable to start with an initial lower dose, e.g., 30 mg of slow release nifedipine twice a day or 60 mg of diltiazem three times a day (tid) or 2.5 mg of amlodipine once a day, and increase cautiously and progressively to the maximum tolerated dose.[44] Patients with IPAH who meet the criteria for a positive vasodilator response and are treated with CCBs should be followed closely for reasons of both safety and efficacy, with

a complete reassessment after 3–4 months of therapy including RHC. If the patient does not show an adequate response, defined as being in WHO-functional class (FC) I or II and with a marked hemodynamic improvement (near normalization), additional PAH therapy should be instituted.

A long-term CCB response was rare in patients with portal hypertension or HIV and absent in coronary heart disease (CHD), and the vast majority of connective tissue disease (CTD).[46,47]

Endothelin Antagonist

Endothelin (ET) is overexpressed in the lungs and plasma of patients with PAH. ET is a potent vasoconstrictor and smooth muscle mitogen. It acts through endothelin A (ETA) and endothelin B (ETB) receptors. In PPH patients, immunoreactivity for endothelin-converting enzyme-1 (ECE-1) is augmented in the endothelium of diseased PAs and ETB receptors are upregulated in the distal vessels. Therefore, almost all components of the ET system are upregulated in the PAs and are correlated with the severity of the disease.[48-50]

Ambrisentan is an ERA that preferentially binds with ET receptor type A. Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study 1 and 2 (ARIES-1 and ARIES-2) were concurrent, double-blind, placebo-controlled studies that randomized 202 and 192 patients with PAH, respectively, to placebo or ambrisentan (ARIES-1, 5, or 10 mg; ARIES-2, 2.5, or 5 mg) orally once daily for 12 weeks. The 6-minute walk distance (6MWD) increased in all ambrisentan groups; mean placebo-corrected treatment effects were 31 and 51 m in ARIES-1 for 5 and 10 mg ambrisentan, respectively, and 32 and 59 m in ARIES-2 for 2.5 and 5 mg ambrisentan, respectively. No patient treated with ambrisentan developed aminotransferase concentrations >3 times the ULN. In 280 patients completing 48 weeks of treatment with ambrisentan monotherapy, the improvement from baseline in 6-minute walk at 48 weeks was 39 m. In a study of 64 patients, the incidence of adverse events were mild and unrelated to dose, including the incidence of elevated serum aminotransferase concentrations >3 times the ULN (3.1%).[51] This was unrelated to the higher doses of ambrisentan used. In another study, the authors have concluded that in 36 patients ambrisentan did not cause elevations in aminotransferase levels above three times the ULN at doses of 10 tds over a long duration of follow-up (102 months) and thereby ambrisentan treatment may be an option for patients who have discontinued bosentan and/or sitaxentan therapy due to liver function test (LFT) result abnormalities.[52] Similar conclusion was drawn from the ARIES trials regarding transaminitis. Another selective ETA antagonist sitaxentan was evaluated at doses of 100 and 300 mg. Although the 300-mg group increased peak $\dot{V}O_2$ compared with placebo, none of the other endpoints derived from cardiopulmonary (CP) exercise testing were met. However, both the 100- and the 300-mg dose, compared with placebo, increased 6MWD; FC, cardiac index, and PVR also improved.[6]

Bosentan and macitentan are dual ERAs, blocking both ETA and ETB receptors. Bosentan is the first molecule of its class to be synthesized. It has been evaluated in PAH [idiopathic, associated with CTD and Eisenmenger syndrome] in six randomized controlled trials (RCTs; Study-351, BREATHE-1, BREATHE-2, BREATHE-5, EARLY, and COMPASS-2),[53-57] which showed improvement in exercise capacity, functional capacity, hemodynamics, echocardiographic and Doppler variables, and time to clinical worsening. Doses of bosentan used in the study ranged from 62.5 mg of bosentan twice daily for 4 weeks followed by either of the two doses of bosentan (125 or 250 mg twice daily) for a minimum of 12 weeks. BREATHE-5 showed the utility of bosentan in Eisenmenger syndrome. Increases in hepatic aminotransferases occurred in approximately 10% of the patients and were found to be dose dependent and reversible after dose reduction or discontinuation. For these reasons, LFT should be performed monthly in patients receiving bosentan. Other adverse effects of bosentan include flushing, edema, nasal congestion, teratogenicity, and mild anemia. Macitentan 3 and 10 mg daily reduces a composite endpoint of long-term morbidity and mortality by 30% and 45%, respectively. Importantly, this is driven exclusively by the reduction in worsening of PAH, and no reduction is seen in either all-cause or PAH-related mortality [SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome) trial].[58] While liver toxicity is uncommon, reduction in blood hemoglobin (Hb) ≤8 g/dL was observed in 4.3% of patients receiving 10 mg of macitentan.[6]

In a meta-analysis comparing the side-effect profile of, with placebo, bosentan but not macitentan or ambrisentan significantly increased the risk of abnormal liver function. Bosentan and ambrisentan but not macitentan significantly increased the risk of peripheral edema. Bosentan and macitentan but not ambrisentan significantly increased the risk of anemia. ERAs were not found to increase other reported adverse events compared with placebo.[59]

Phosphodiesterase Inhibitors

The discovery in the late 1980s of NO as the endothelium-derived relaxing factor a key discovery, leading to Nobel Prize for Physiology or Medicine in 1998 for the pioneers in this field. NO mediates its biological effects by activating soluble guanylate cyclase (sGC) and increasing cyclic guanosine monophosphate (cGMP) synthesis which, in turn, activates certain proteins. cGMP actions are terminated by phosphodiesterase-5 (PDE-5) enzyme. Corbin et al.[60] demonstrated a high level of PDE-5 in lungs, approximately as high as that in penile corpus cavernosum, and suggested that the abundance of PDE-5 in lung vascular smooth muscle may provide a strong molecular basis for PDE-5 inhibitor treatment of PAH. It is postulated to exert its effect in PAH by NO-mediated vasodilation and antiproliferative effects.[61]

Evaluation of effects of PDE-5i sildenafil and tadalafil was done on the basis of three trials involving a total of 950 patients. In a study comprising PAH treatment-naïve patients, three dosing regimens of sildenafil (20, 40, or 80 mg orally three times daily for 12 weeks) were studied. The distance walked in 6 minutes increased from baseline in all sildenafil groups, all sildenafil doses reduced the mean pulmonary artery pressure, and improved the WHO-FC.[62] Another study [PHIRST (Pulmonary Arterial HypertensIon and ReSponse to Tadalafil) trial] assigned 405 patients with PAH (idiopathic or associated), either treatment-naive or on background therapy

with the ERA bosentan, to placebo or tadalafil 2.5, 10, 20, or 40 mg orally once daily. Tadalafil increased the distance walked in 6 minutes in a dose-dependent manner; only the 40-mg dose met the prespecified level of statistical significance. The degree of improvement was found to be higher in the bosentan-naïve group. Tadalafil 40 mg improved the time to clinical worsening, incidence of clinical worsening, and health-related quality of life. The changes in WHO-FC were not statistically significant.[61] Another trial evaluated the additional benefit of sildenafil in 267 patients with PAH who were receiving long-term IV epoprostenol therapy whereby patients were randomly assigned to receive placebo or sildenafil, 20 mg three times daily, titrated to 40 and 80 mg three times daily, as tolerated, at 4-week intervals. In some patients with PAH, the addition of sildenafil to long-term IV epoprostenol therapy improved exercise capacity, hemodynamic measurements, time to clinical worsening, and quality of life, but not Borg dyspnea score. These improvements were most prominent among patients with baseline 6MWD of 325 m or more.[61] The most common side effects reported in these studies were visual disturbances, headache, flushing, diarrhea, and limb pain.

Vardenafil is a twice daily oral PDE-5i. 66 patients with PAH were randomized 2:1 to vardenafil (5 mg once daily for 4 weeks then 5 mg twice daily; $n = 44$) or placebo ($n = 22$) for 12 weeks. Patients completing this phase were then treated with open-label vardenafil (5 mg twice daily) for a further 12 weeks. Vardenafil increased the mean placebo-corrected 6MWD, cardiac index, and decreased mPAP and PVR. Vardenafil was associated with only mild and transient adverse events.[63]

Soluble Guanylate Cyclase Stimulator

In PAH, sGC is often dysfunctional because it is oxidized or has lost its heme group.[64] Riociguat directly stimulates sGC independent of NO, resulting in increased cGMP and pulmonary vasodilation. In the first study of riociguat an sGC stimulator in patients with PAH, 19 subjects were studied and it was found that riociguat significantly improved pulmonary hemodynamic parameters and cardiac index in patients with PH in a dose-dependent manner, to a greater extent than inhaled NO.[63]

In a large trial (PATENT-1), 443 patients with symptomatic PAH were randomized to receive placebo or riociguat in individually adjusted doses of up to 2.5 mg three times daily (2.5 mg–maximum group), or riociguat in individually adjusted doses that were capped at 1.5 mg three times daily (1.5 mg–maximum group). Prespecified subgroup analyses showed that riociguat improved the 6MWD both in patients who were receiving no other treatment for the disease and in those who were receiving ERA or prostanoids. There were significant improvements in PVR, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, WHO-FC, time to clinical worsening, and Borg dyspnea score.[65] The most common serious adverse event was syncope. In the follow-up of this study, patients completing PATENT-1 were eligible to enter the PATENT-2, an open-label, extension study, which assessed the long-term safety and efficacy of riociguat in patients with PAH. The maximum dose of riociguat employed was 2.5 mg three times daily. The improvements in 6MWD and WHO-FC, observed in the riociguat groups in the 12-week PATENT-1 study were sustained for up to 1 year in the PATENT-2 study.[66] Improvements in the patients' 6MWD and WHO-FC observed in PATENT-1 persisted for up to 1 year in PATENT-2. The safety profile of riociguat in PATENT-2 was similar to that observed in PATENT-1, with cases of hemoptysis and pulmonary hemorrhage also being observed. Also patients under long-term treatment with riociguat showed significantly reduced right heart size and improved RV function in PAH and CTEPH (RIVER trial).[67]

Phosphodiesterase-5 inhibitors and riociguat should not be given concurrently due to the chance of causing hypotension.

Prostacyclin Analogs and Prostacyclin Receptor Agonists

Prostacyclin is produced predominantly by endothelial cells and induces potent vasodilation of all vascular beds. This compound is the most potent endogenous inhibitor of platelet aggregation and also appears to have both cytoprotective and antiproliferative activities. Dysregulation of the prostacyclin metabolic pathways has been shown in patients with PAH as assessed by a reduction of prostacyclin synthase expression in the PAs and of prostacyclin urinary metabolites.[68] Depending on the preparation and specific molecule, prostanoids can be given as a continuous IV infusion (epoprostenol and treprostinil) or subcutaneous (SC) infusion (treprostinil), via inhalation (iloprost and treprostinil), or orally (treprostinil and beraprost).

Epoprostenol (synthetic prostacyclin) has a short half-life (3–5 minutes) and is stable at room temperature for only 8 hours; it requires cooling and continuous administration by means of an infusion pump. It was the first Food and Drug Administration (FDA)-approved treatment for advanced PPH (1980). The first study on epoprostenol including patients with PAH showed that continuous IV infusion of epoprostenol produced symptomatic and hemodynamic improvement, as well as improved survival in patients with severe PPH. Serious complications included four episodes of catheter-related sepsis and one thrombotic event.[69] Similar results were found in patients with PH with scleroderma spectrum of disease.[70] A study[71] was conducted to evaluate the long-term impact of patients being treated with epoprostenol including 162 consecutive patients with PPH treated with epoprostenol between November 1, 1991 and December 31, 2001, from the Rush Heart Institute, Center for Pulmonary Heart Disease's customized patient database to collect specific variables on every patient treated with epoprostenol. Each patient was followed up for a mean of 31 months. Observed survival with epoprostenol therapy at 1, 2, and 3 years was 87.8%, 76.3%, and 62.8%, respectively and was significantly greater than the expected survival of 58.9%, 46.3%, and 35.4% based on historical data. The major morbidity of this therapy was related to the indwelling catheter. Over the entire observation period, our patients had 119 local infections at the exit site (0.24 per person-year), 70 episodes of sepsis (0.14 per person-year), 10 tunnel infections (0.02 per person-year), and 72 instances where the catheter had to be replaced (0.15 per person-year). Treatment with epoprostenol is initiated at a dose of 2–4 ng/kg/min, with doses increasing at a rate limited by side effects (flushing, headache, diarrhea, leg pain). The optimal

dose varies between individual patients, ranging in the majority between 20 and 40 ng/kg/min.

Treprostinil is an analog of epoprostenol, stable at room temperature, with a longer half-life (3 hours) and administrable through IV, SC, and inhalational routes. In a 12-week, double-blind, placebo-controlled multicenter trial in 470 patients with PAH, either primary or associated with CTD or congenital systemic-to-pulmonary shunt, exercise capacity and 6MWD improved with treprostinil and were unchanged with placebo. Improvement in exercise capacity was greater in the sicker patients and was dose related, but independent of disease etiology. Concomitantly, treprostinil significantly improved indices of dyspnea, signs and symptoms of PH, and hemodynamics. The most common side effect attributed to treprostinil was infusion site pain (85%) leading to premature discontinuation from the study in 8% of patients. Three patients in the treprostinil treatment group presented with an episode of gastrointestinal hemorrhage.[72] An RCT was performed with IV treprostinil in PAH patients, but the enrollment of this trial was closed because of safety considerations after 36% of the planned 126 patients had been randomized.[73] The data generated from the survivors after the randomized phase (23 active and 8 placebo) are not considered reliable. In the TRIUMPH-1 trial,[74] 235 PAH patients with NYHA functional class III (98%) or IV symptoms and a 6MWD of 200–450 m while treated with bosentan (70%) or sildenafil were randomized to inhaled treprostinil (up to 54 μg) or inhaled placebo four times daily. This trial showed that, among PAH patients who remain symptomatic on bosentan or sildenafil, inhaled treprostinil improves exercise capacity and quality of life and is safe and well-tolerated. A trial comprising 349 treatment-naïve patients showed a beneficial effect of oral treprostinil on the 6MWD.[75] Oral treprostinil therapy was generally well tolerated; the most common adverse events (intent-to-treat) were headache (69%), nausea (39%), diarrhea (37%), and pain in jaw (25%). In the FREEDOM-C and FREEDOM-C2 trials no benefit, however, was demonstrated for the use of oral treprostinil in PAH patients on ERA or PDE-5i therapy.[76,77] In response to risks associated with external delivery systems, an implantable IV infusion system was developed. A multicenter, prospective, single-arm, clinical trial (DelIVery for PAH) was conducted to evaluate this system for treprostinil in PAH. The procedure for inserting a fully implantable system for treprostinil was successfully performed, with few complications.[78] An implantable pump, Lenus Pro®, in the treatment of PAH with IV treprostinil has also been evaluated.[79]

Iloprost is a chemically stable prostacyclin analog available for IV, oral, or aerosol administration. Inhaled iloprost has been evaluated in one RCT in which daily repetitive iloprost inhalations (six to nine times, 2.5–5 μg/inhalation, median 30 μg daily) were compared with placebo inhalation in patients with PAH and CTEPH.[80] The study showed an increase in exercise capacity and hemodynamics and clinical events in enrolled patients. A second RCT involving 60 patients already treated with bosentan showed an increase in exercise capacity ($p < 0.051$) in the subjects randomized to the addition of inhaled iloprost compared with placebo.[81] The most common side effect associated with the use of iloprost is flushing and jaw pain.

Selexipag, an orally available, selective IP receptor agonist targeting the prostacyclin pathway, is chemically and pharmacologically distinct from prostanoids. In a pilot RCT done in 2012, 43 adult patients with symptomatic PAH (receiving stable ERA and/or a PDE-5i therapy) were randomized three to one to receive either selexipag or placebo. Dosage ranged from a starting dose of 200 to a maximum allowed dose of 800 μg twice daily. Change in PVR at week 17 expressed as a percentage of the baseline value was the primary efficacy end-point, and a statistically significant 30.3% reduction in geometric mean PVR was observed after 17 weeks' treatment with selexipag compared with placebo.[82]

In the GRIPHON study,[83] 1,156 patients were randomized to placebo or selexipag; 20% were PAH therapy naive, 47% were on monotherapy (ERA or PDE-5i), and 33% were on combination therapy (ERA and PDE-5i) at baseline. Selexipag reduced the risk of mortality/morbidity events compared to placebo by 40%. The treatment effect was consistent across age, gender, etiology, baseline functional capacity, and background PAH therapy subgroups. The most frequent adverse events were headache, diarrhea, nausea, jaw pain, myalgias, pain in extremity, flushing, and arthralgia. A follow-up study for the same subset of patients conclude that among patients with PAH, the risk of the primary composite end point of death or a complication related to PAH was significantly lower among patients who received selexipag than among those who received placebo, driven by differences in disease progression and hospitalization. There was no significant difference in mortality between the two study groups.[84]

Selexipag is started at 200 μg twice daily and increased weekly to a maximum of 1,600 μg twice daily **(Table 2)**.

Interventional Therapies

Balloon Atrial Septostomy

In 1983, Rich and Lam first performed balloon atrial septostomy in a patient with PAH. It was observed that patients with Eisenmenger syndrome live longer with lower right-sided heart failure than in patients with primary PAH. Evidence shows that interatrial shunt shows benefit in patients with PAH **(Fig. 1)**.

TABLE 2: Elimination half-life of pharmacotherapy for pulmonary hypertension.

Drugs	Half-life
Bosentan	5.4 hours
Ambrisentan	9–15 hours
Macitentan	Macitentan, ACT-064992 (2 h) active metabolite, ACT-I 32577 (8.4 h)
Epoprostenol	2–3 minutes
Iloprost	30 minutes
Treprostinil	4.5 hours
Beraprost*	35–40 minutes
Sildenafil (for PAH)	3.7 hours
Tadalafil (for PAH)	18 hours
Riociguat	5–10 hours

*Beraprost has been approved in Japan and South Korea, but not in the US or Europe for PAH.

(PAH: pulmonary arterial hypertension)

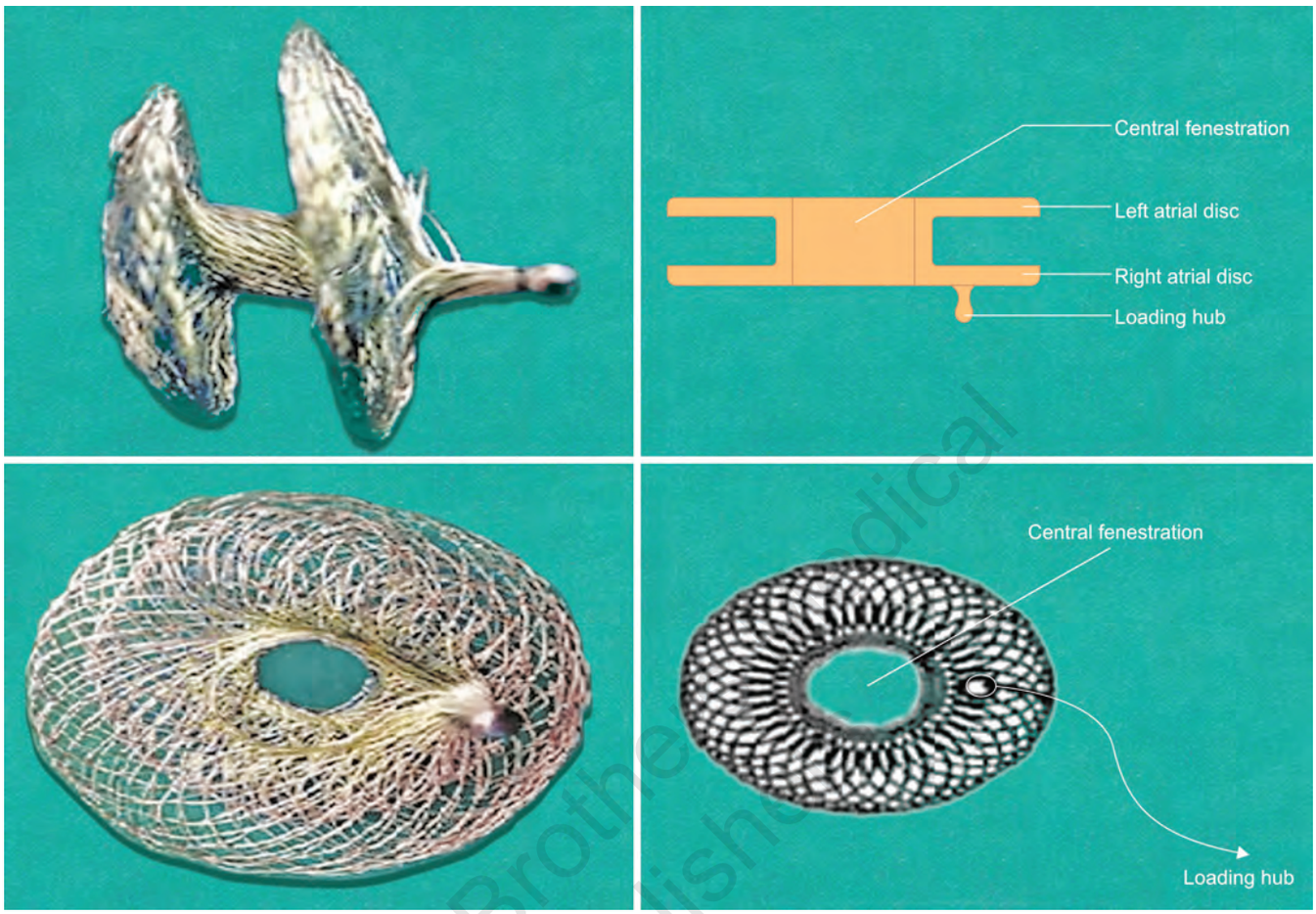


FIG. 1: Fenestrated devices for creation of right-to-left shunt.

Interatrial shunt causes right-to-left shunt which increases the systemic output and decreases the right-sided pressure, RV wall stress, and O_2 demand.

Ideal candidates for septostomy are WHO-FC 3 with RV dysfunction with syncope on maximum medical therapy.

Potts Shunt

It is an anastomosis between descending aorta and left pulmonary artery (LPA) causing left-to-right shunt to increase systemic output. It prevents desaturation in the upper part of the body, brain, and coronary arteries.

Balloon Pulmonary Angioplasty

It is indicated in the patient with CTEPH who are either inoperable or residual PAH after pulmonary endarterectomy (PEA) nonresponder to PAH medication **(Figs. 2A to D)**.

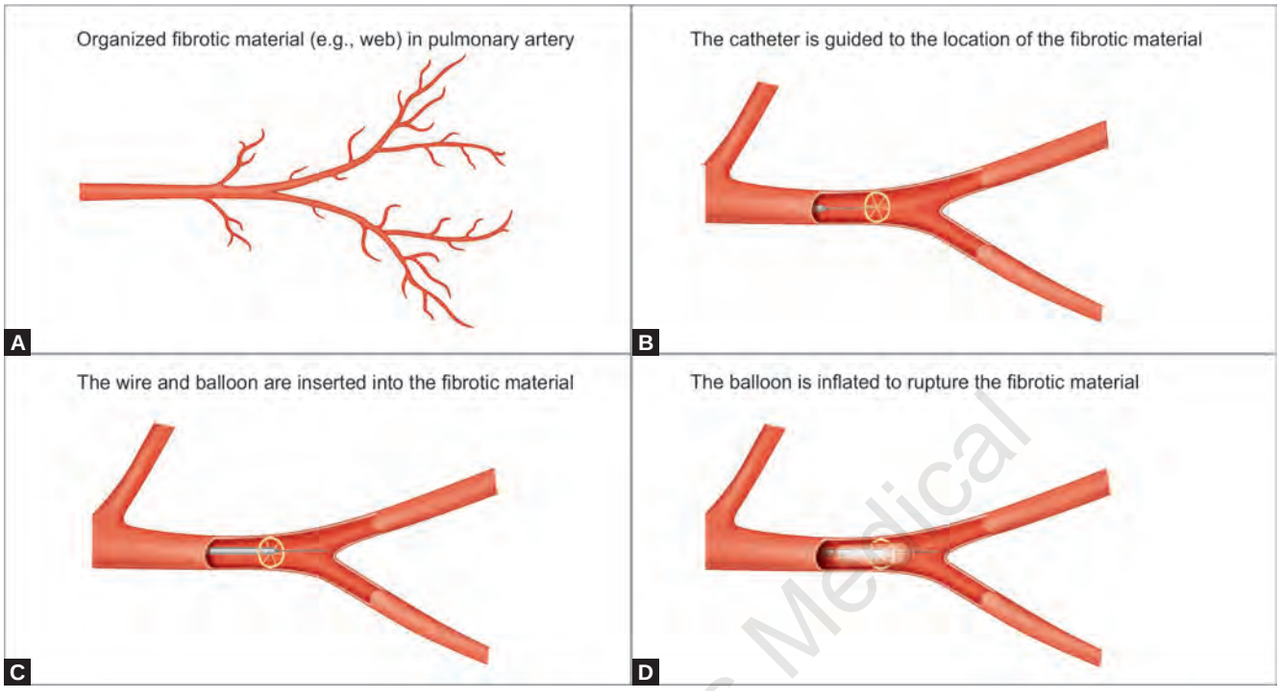
Pulmonary Artery Denervation

Pulmonary artery denervation (PADN) is an innovative catheter-based ablation technique targeting the afferent and efferent fibers of a baroreceptor reflex in the main PA trunk and its bifurcation. This reflex is involved in the elevation of the PA pressure seen in PH. Since 2013, both animal trials and human trials have shown the efficacy of PADN in improving PAH, including improved hemodynamic parameters, increased functional capacity, decreased PA remodeling, and much more. PADN has been shown to decrease the rate of rehospitalization, PH-related complications, and death, and is an overall safe procedure.[85] Transthoracic pulmonary artery denervation (TPADN) in rats completely and accurately removed the main sympathetic nerves (SNs) around PAs and attenuated pulmonary arterial hypertensive progression by inhibiting excessive activation of the sympathetic nervous system and renin–angiotensin–aldosterone system neurohormone–receptor axes.[86]

Therapeutic Intravascular Ultrasound

It is a therapeutic ultrasound done in the PA causing ablation of the nerves without injury to the vessel wall.

Treatment of Pulmonary Hypertension 1 (TROPHY1) was a multicenter, international, open-label trial undertaken at eight specialist centers. Patients with 18–75 years of age with PAH were eligible on dual oral or triple nonparenteral therapy and not responsive to acute vasodilator testing. Shown reduction in PVR and increases in 6MWD and daily activity in patients with PAH on dual or triple therapy **(Fig. 3)**.



FIGS. 2A TO D: Percutaneous balloon angioplasty for CTEPH.

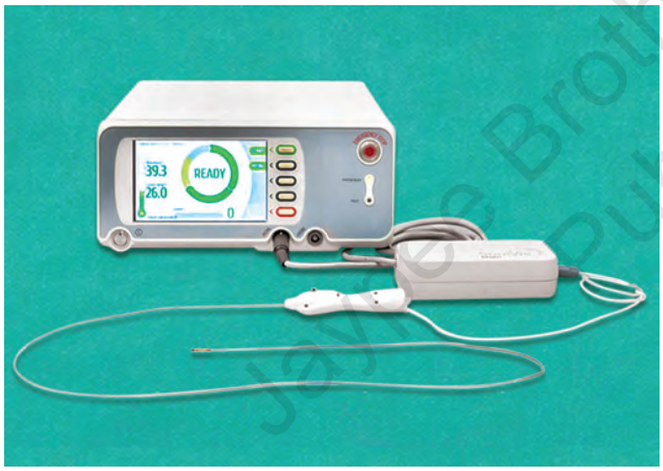


FIG. 3: TIVUS ultrasound system for pulmonary arterial hypertension.

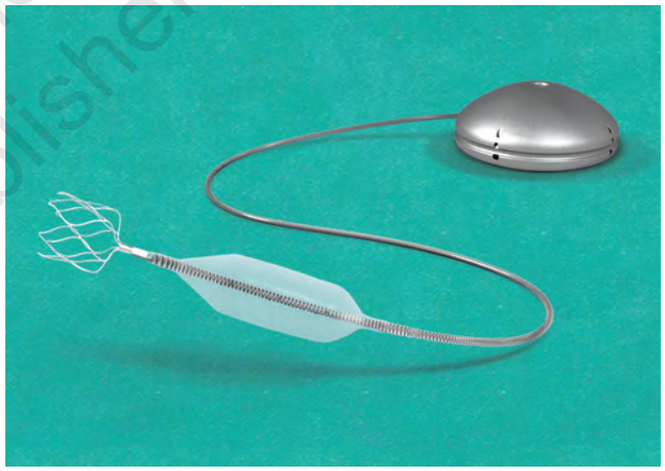


FIG. 4: ARIA CV PH system.

ARIA CV PH System

This device consists of reservoir, conduit, balloon, and nitinol anchor which causes decrease in right-sided workload and increase in CO.

A trial on acute assessment of the device in patient with WHO group 2 and 3 PAH is ongoing **(Fig. 4)**.

Experimental Compounds and Strategies

Circulating Hormones

Sex Hormones

The best hormone-related phenomenon is the "estrogen paradox": Women have a higher incidence of IPAH and HPAH than men, but female patients with PAH have better outcomes than male patients.

Some of the estradiol (E2) metabolites have proliferative effects (e.g., 16α-hydroxyestrone), while others also have antiproliferative and anti-inflammatory properties (e.g., 2-hydroxyestradiol and 2-methoxyestradiol). High E2 levels were associated with PAH in male patients and reduced exercise capacity in female patients, but E2 may also have protective effects on the RV (reviewed in.[87]

Moreover, genes of the Y-chromosome are upregulated in PH and have protective anti-remodeling properties in hypoxic mice.[88] Decreasing circulating E2 by inhibiting conversion of androgens to E2 using the aromatase inhibitor anastrozole

and inhibition of the E2 receptor with tamoxifen inhibited PH in different animal models of PH, partly in a sex-dependent way.[87] By contrast, supplementation with E2 increased exercise capacity in male and female rats with severe PH, probably by exerting protective effects on the RV.[89]

An open-label trial of the estrogen antagonist fulvestrant was completed; due to the low number of enrollment, no final conclusions on the effects of fulvestrant on PAH could be drawn.[90]

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a steroid hormone that acts as a precursor for both estrogen and testosterone synthesis. DHEA prevented and reversed PH and RV dysfunction in different animal models of PH.[91]

Accordingly, higher levels of E2 and lower levels of DHEA were associated with increased risk of PAH in men and increased risk and severity of PAH in postmenopausal women. DHEA treatment significantly improved 6MWD, pulmonary hemodynamics, and diffusion capacity of patients with PH associated with chronic obstructive pulmonary disease, without worsening gas exchange.

Dehydroepiandrosterone is tested in a crossover trial in a small number of patients with PAH [Effects of DHEA in PH (EDIPHY)]. The primary outcome is change in RV longitudinal strain, as determined by cardiac magnetic resonance imaging (MRI).

Renin–angiotensin–aldosterone System

Antagonists of the receptor for aldosterone, a steroid hormone that binds the mineralocorticoid receptor in the heart and pulmonary vasculature, have been used for the patient with PAH.

In animal studies, aldosterone antagonists decrease or partially reverse PH. The "Combination Ambrisentan Plus Spironolactone in Pulmonary Arterial Hypertension Study" (CAPS-PAH)—a study to investigate whether the addition of spironolactone to ambrisentan affects exercise capacity in patients with PAH—was terminated because of low enrollment.

Another target to the peptidase angiotensin-converting enzyme-2 (ACE2) which converts the peptide hormones angiotensin I and II to their vasodilator derivatives with a preference for angiotensin II degradation.

An open-label pilot study on acute hemodynamic responses after a single infusion of recombinant human ACE2 in patients with PAH showed improved CO without a significant change in mPAP or systemic pressures, and reduced markers of oxidant and inflammatory stress.

Atrial Natriuretic Peptide

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are released from atrial cardiomyocytes or the ventricles, respectively. Natriuretic peptides increase renal sodium excretion, cause vasodilation via cGMP release, and decrease heart fibrosis. Natriuretic peptides are degraded by the metalloprotease neprilysin.

The efficacy and safety of the neprilysin inhibitor racecadotril were tested in an RCT in PAH. Acute administration increased plasma ANP and cGMP levels and slightly decreased PVR but mPAP did not change significantly. Systemic blood pressure (BP) was not decreased significantly, and plasma ET levels did not change following the exposure to racecadotril. Further studies are required to determine the effect on PAH.

Neurohormonal Regulation

Neurohormonal regulation plays an important role in pulmonary vascular tone and RV function. Animal studies shows that β-blockers may have beneficial effects on RV dysfunction and maladaptive remodeling. Several small studies tested the effect of β-blockers on RV function and functional capacity with different outcomes but longer studies are required to establish the benefit of β-blockers in PAH. Currently, the use of β-blockers is not recommended in patients with PAH unless required for comorbidities.

Serotonin

Serotonin has been implicated in the development of PAH since anorexigens, which increase the availability of 5-hydroxytryptamine (5-HT) by inducing its release from platelets and inhibiting its reuptake and degradation by monoamine oxidase (MAO), were noted to increase the risk of PAH.

The 5-HT2A and 5-HT2B receptor inhibitor terguride showed no clinical benefit in a phase II study in PAH but prespecified subgroup analysis indicated an improvement of PVR in patients on PAH background therapy with ERAs. A trial with the 5-HT uptake inhibitor escitalopram was completed in 2008, but shows no benefit.

Other Hormones

Vasoactive intestinal peptide (VIP) is a peptide hormone that stimulates contractility in the heart and causes dilation of smooth muscles of different organs, including blood vessels. In spite of the failure of a previous clinical trial with inhaled administration of VIP, a future study with a SC injected, sustained-release analog of VIP (PB1046) is planned.

G-protein-coupled Receptor Pathways

Rho-associated Protein Kinase

Rho-associated protein kinase (ROCK) belongs to serine–threonine kinases family and can be activated via the GTPase Ras homolog family member A (RhoA) by several cellular receptors, including G-protein-coupled receptors (GPCRs) which are stimulated by various vasoactive substances such as angiotensin II or 5-HT.

Rho-associated protein kinase is involved in many cellular functions, for example, smooth muscle cell contraction, cell migration, and stress fiber formation, and has been implicated in the pathogenesis of PAH.

Rho-associated protein kinase inhibitors have shown promising results in animal studies. But in a clinical trial, the 6MWD was not improved by the ROCK inhibitor fasudil. Newer ROCK inhibitors are under development.

Apelin

Apelin is an endogenous vasodilatory and inotropic peptide acting via the G-protein-coupled apelin receptor.

Apelin is downregulated in human PAH and can inhibit PH in animal models. The effect of apelin infusion on CP performance in healthy volunteers and patients with IPAH was recently investigated in a small clinical trial. Results are awaited.

Cytosolic Calcium and Ion Channels

Increased cytosolic calcium contributes to the contractile, hyperproliferative, and antiapoptotic phenotype of pulmonary artery smooth muscle cells (PASMCs). Ca^{2+} is regulated by several ion channels that control calcium influx, as well as Ca^{2+} sequestration within the sarcoplasmic reticulum and mitochondria, and its effect is modulated by Rho kinase activation. Although there is little debate that calcium concentrations are elevated in PAH PASMCs, the relative importance of excessive calcium entry via store-operated channels and/or Ca channels (which are therapeutically targeted by CCBs) versus impaired organelle uptake of calcium (in mitochondria and endoplasmic reticulum) versus calcium sensitization (by rho kinase) remains uncertain.[92]

- Decreased expression of Kv1.5 potassium channels, which normally maintain PASMC membrane potential, leads to membrane depolarization and influx of Ca^{2+} through voltage-dependent calcium channels. In rodent models of PH, restoring Kv1.5 expression through adenoviral gene transfer improves hemodynamics.[93]
- Rho kinase activation in PAH causes calcium sensitization, leading to greater vasoconstriction for a given level of cytosolic calcium. Moreover, the vasoconstriction caused by rho kinase activation is not reversed by conventional vasodilators and likely contributes to vascular stiffening.[94] A liposomal delivery system of fasudil was evaluated in rats, that will preferentially accumulate in the PAH lungs.[95] Rho kinase inhibitors, such as fasudil, have been studied in limited human PAH cohorts. They seem to be safe and effective and may reduce mortality in PAH patients with RVF in a study of 209 patients with right heart failure (RHF) who were treated with 30 mg of IV fasudil three times daily over 30 minutes, until they experienced relief of RHF symptoms. Fasudil decreased both in-hospital mortality and 30-day rehospitalization.[96]
- *Mitochondrial metabolic dysfunction and the Warburg phenotype*: In the presence of PAH, the PASMCs metabolize glucose through upscaled and uncoupled anaerobic pathway, dissociated from mitochondrial oxidation,[97] a pattern of metabolism referred to as Warburg metabolism, as it was first identified by Otto Warburg in cancer cells. Similar metabolic and mitochondrial changes occur in pulmonary artery endothelial cells (PAECs) and adventitial fibroblasts and cardiomyocytes of PAH patients. In PAH, oxidative phosphorylation is actively suppressed by upregulated expression of pyruvate dehydrogenase kinase (PDK). PDK phosphorylates and inhibits pyruvate dehydrogenase (PDH).[98] This shifts the cell to rely on glycolysis, which is energetically inefficient.
    - Emerging metabolic therapies that exploit this include the small molecule PDK inhibitor dichloroacetate (DCA). DCA reverses the Warburg phenotype in PASMCs and RV cardiomyocytes and regresses PAH in preclinical models.[98,99] In a 4-month, open-label study,[100] DCA (3–6.25 mg/kg bid) administered to patients with IPAH already on approved IPAH therapies led to reduction in mean PA pressure and PVR and improvement in functional capacity, but with a range of individual responses. Lack of clinical response was associated with the presence of functional variants of sirtuin 3 (SIRT3) and uncoupling protein 2 (UCP2) that predict reduced protein function. Impaired function of these proteins causes PDK-independent mitochondrial suppression and PH in mice.
    - Mitochondrial calcium uniporter (MCU) is the major functional subunit of the MCU complex that allows for the influx of Ca^{2+} into the mitochondrial matrix. Reduced expression of MCU increases Ca^{2+} in PAH while lowering intramitochondrial calcium. Increased Ca^{2+} promotes vasoconstriction and enhances mitochondrial fission and proliferation.[101] MCU downregulation in PAH is epigenetically mediated by increases in the micro-RNAs miR25 and miR138. *Anti-miRs* or *MCU* gene transfer reverses the mitochondrial phenotype in PAH PASMCs and regresses PAH in the monocrotaline-induced PAH in rat model.[102]

Inflammatory Mediators

Immune modulation is an established concept in PAH, but classic anti-inflammatory drugs such as corticosteroids or acetylsalicylic acid have shown beneficial effects only in specific forms of PAH or no beneficial effects.

Several immune modulatory approaches have shown to be beneficial in animal models, including an interleukin-1 (IL-1) receptor antagonist, IL-6 antibodies, mycophenolate, dexamethasone, cyclosporine, tacrolimus, LTB4 pathway inhibitors, and tumor necrosis factor (TNF)-related apoptosis inducing ligand, but no benefit in treatment of human PAH beyond CTD-PAH.

A clinical trial of the anti-CD20 monoclonal antibody rituximab (which targets B-lymphocytes) in PAH associated with systemic sclerosis (SSc) shows improved 6MWD and potentially effective and safe adjuvant treatment for SSc-PAH.

The safety of anakinra (IL-1 inhibitor) in PAH was recently evaluated in an open-label study. After 14 days of treatment, high-sensitivity C-reactive protein and symptom burden were significantly reduced.

The trial of the IL-6 inhibitor tocilizumab in PAH (TRANSFORM-UK) showed no significant change in PVR from baseline at 6 months in the 19 patients who completed the study protocol.

A phase II open-label extension study with ubenimex was recently terminated after the original study failed to demonstrate efficacy.

Growth Factor Receptors

Receptor Tyrosine Kinases

Receptor tyrosine kinases (RTKs) are cell surface receptors for growth factors, cytokines, and hormones. RTKs which have been implicated in PAH include platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth

factor (FGF), vascular endothelial growth factor (VEGF), and nerve growth factor receptors.

Several RTK inhibitors are imatinib, dasatinib, and nilotinib (inhibiting the PDGF receptor), the multikinase inhibitors sorafenib and sunitinib (inhibiting the PDGF and VEGF receptors), and nilotinib (inhibiting the BCR-ABLTK).

The PDGF receptor inhibitor imatinib was the first RTK used in clinical PAH and the first drug used in PAH to directly target vascular remodeling. In spite of reducing PVR and increasing mean placebo-corrected 6MWD (by 32 m) in a clinical phase III trial [Imatinib in PAH, a Randomized Efficacy Study (IMPRES)], imatinib was not approved for PAH owing to an unfavorable risk–benefit ratio.

A clinical trial with nilotinib was terminated due to severe adverse events.

Exposure to dasatinib was even associated with the development of PAH.

Sorafenib was tested in an open-label study and showed some efficacy (improvement of BNP, uric acid, and cardiothoracic ratio of >10% from the original value continued for 1 month) in two out of nine patients. However, CO also decreased in most patients treated with sorafenib, raising serious concerns about further trials of sorafenib in PAH.

Transforming Growth Factor Beta Superfamily of Growth Factors

An imbalance in transforming growth factor beta (TGFβ)/bone morphogenetic protein (BMP) signaling known as an important pathogenetic mechanism in PAH, since mutations in BMP receptor type 2 (BMPR2), a TGFβ receptor (TGFβR) subtype, were identified in HPAH.

Bone morphogenetic protein receptor type 2 activation, tacrolimus (FK506) was found to promote BMPR2-Smad1/5/8 signaling by interacting with its pharmacological target, 12-kDa FK506-binding protein (FKBP12), thereby removing FKBP12 from all three BMP type 1 receptors (ALK1, ALK2, and ALK3), including those preferred by BMPR2. Tacrolimus prevented the development of PAH in mice with endothelial deletion of BMPR2 and reversed established PAH in two rat models. A phase II clinical trial of tacrolimus in patients with PAH showed favorable safety, but efficacy was low.

Another target is TGFβ signaling that involves inhibition of the Smad 2/3 signaling pathway using sotatercept, an activin receptor type 2A fusion protein that acts as a ligand trap. A phase II RCT (PULSAR) shows an improvement in 6MWT and a decrease in NT-proBNP levels, but thrombocytopenia and an increased Hb level were the most common hematologic adverse events, causing a reduction in PVR in patients on background therapy for PAH.

Systemic Metabolic Alterations

Pulmonary arterial hypertension has been associated with glucose intolerance and insulin resistance. Glucose intolerance was found to be a predictor of increased mortality in PAH. It is not known whether alterations contribute to the pathogenesis of PH or are consequences of PH.

A phase II clinical trial showed that the effect of 12 weeks of metformin did not change 6MWD but significantly improved RV fractional area change, though other echocardiographic parameters were unchanged. RV triglyceride content decreased in eight out of nine patients.

Inhibitors of dipeptidyl peptidase 4 (gliptins) sitagliptin alleviated PH induced by monocrotaline, bleomycin, or hypoxia in rats.

The glucagon-like peptide 1 (GLP-1) receptor agonist liraglutide both prevented and reversed monocrotaline-induced PH, RVH, and pulmonary vascular wall remodeling. The idea of using statins to improve PAH by targeting systemic lipid metabolism has been unsuccessful.

Another target identified is iron metabolism. Iron deficiency, in the absence of anemia, is common in patients with IPAH and HPAH and is associated with a worse clinical outcome. Although the underlying mechanisms are not completely understood, an open-label study showed that IV iron supplementation in patients with PAH increased exercise endurance capacity, though 6MWD was not changed significantly. This study included only patients without anemia, and blood Hb content did not change significantly after iron infusion. In this regard, several groups have shown that iron deficiency in the absence of anemia is common and associated with reduced survival in PAH.

A double-blind study of iron infusion in iron-deficient patients with PAH is a placebo-controlled, 12-week crossover study, in which 39 patients in Europe received a single infusion of ferric carboxymaltose (Ferinject) (1,000 mg or 15 mg/kg if weight <66.7 kg) or saline as placebo, and 17 patients in China received iron dextran (CosmoFer) (20 mg iron/kg body weight) or saline placebo. All patients had IPAH or HPAH and iron deficiency at entry as defined by a serum ferritin <37 μg/L or iron <10.3 μmol/L or transferrin saturations <16.4% shows both iron treatments were well tolerated and improved iron status. There was no effect on any measure of exercise capacity (using CP exercise testing or 6MWT) or CP hemodynamics, as assessed by RHC, cardiac magnetic resonance, or plasma NT-proBNP (N-terminal pro-hormone BNP) at 12 weeks.

Combination Therapy

Despite the advancements in the pharmacotherapy of PAH showing promising findings, a significant proportion of PAH patients had unsatisfactory clinical response on monotherapy and long-term prognosis remained poor, with a high mortality rate. The rationale obviously as in the case of other chronic diseases such as heart failure and hypertension being that targeting simultaneously multiple pathways involved in the disease's pathogenesis rather than increasing doses is expected to lead to additive or even synergistic beneficial effects, while minimizing adverse events.

Changing Paradigm of Clinical Trials (Table 3)

Many of the early clinical trials documented improvement in functional capacity, exercise capacity, and pulmonary hemodynamics with combination therapy compared to monotherapy, while others failed to demonstrate a significant improvement in their primary endpoint.[103,104] In 2011, adding to the already conflicting literature, findings from a systematic

TABLE 3: Clinical trials in pulmonary hypertension therapeutics.

	Background therapy	Number of participants	Study duration (weeks)	Primary endpoint	Secondary endpoint	Main adverse events
AIR (iloprost)	None	203	12	6MWD	• NYHA functional class • Mahler dyspnea index • Quality of life • Death (NS)	• Flushing • Jaw pain
AMBITION (ambrisentan vs. tadalafil vs. dual)	None	500	74	Time to first clinical failure	• 6MWD • WHO-FC (NS) • Borg dyspnea index	• Peripheral edema • Headache • Nasal congestion
ARIES-1 (ambrisentan)	None	202	12	6MWD	• TTCW (NS) • WHO-FC • Quality of life (NS) • Borg dyspnea score • BNP	• Peripheral edema • Headache • Flushing
ARIES-2 (ambrisentan)	None	192	12	6MWD	• TTCW • WHO-FC (NS) • Quality of life • Borg dyspnea score • BNP	• Peripheral edema • Headache • Nasal congestion
Badesch and colleagues (epoprostenol)	None	111	12	6MWD	• Hemodynamics • NYHA functional class	• Jaw pain • Diarrhea • Nausea and vomiting infection
Barst and colleagues (epoprostenol)	None	81	12	6MWD	• WHO-FC hemodynamics (NS) • Survival	• Jaw pain • Flushing • Headaches • Catheter-related sepsis
BREATHE-1 (bosentan)	None	213	12	6MWD	• Borg dyspnea index • WHO-FC • TTCW	Abnormal hepatic function
BREATHE-2 (bosentan)	Epoprostenol	33	16	TPR (NS)	• CI (NS) • PVR (NS) • 6MWD (NS) • WHO-FC (NS)	Mainly related to epoprostenol therapy
COMPASS-2 (bosentan)	Sildenafil	334	38 months	Time to first morbidity or mortality event (NS)	• 6MWD • WHO-FC (NS) • PAH-related admissions (NS)	Abnormal hepatic function
EARLY (bosentan)	None or sildenafil	185	24	6MWD (NS) PVR	• TTCW • WHO-FC • Quality of life	Abnormal liver function test

(BNP: brain natriuretic peptide; CI: cardiac index; 6MWD: 6-minute walk distance; NS: not significant; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; TPR: total pulmonary resistance; TTCW: time to clinical worsening; WHO-FC: World Health Organization functional class)

review and meta-analysis[105] suggested that combining PAH-targeted therapies did not offer any advantage over monotherapy except a modest increase in exercise capacity (weighed mean difference 25.1 m). Several factors behind contemporary study designs may have contribute to this finding:

- Importantly, clinical trials conducted at that time were mainly of short-term duration and used the 6MWD as the primary endpoint. Although baseline and final 6MWD seems to be an important marker of outcome at the time of diagnosis, it was not a very good marker for disease progression and mortality outcomes, hospitalization, or lung transplantation.[106-108]
- A "ceiling" effect[109] in patients who have already been stabilized on background monotherapy, leaving little room

for improvement when another therapy was added had to be taken into consideration.
- Direct assessment of mortality was not feasible for a disease like PAH, as PAH is a rare disease and mortality incidence is low in clinical trials.

The concept of clinical worsening emerged in an attempt to represent events that are undesirable and clinically relevant for patients, including hospitalization, symptomatic progression of disease, treatment escalation, transplantation, atrial septostomy, and death.[110] This was proven to effectively predict subsequent mortality events in an observational study from the REVEAL registry[111] and was shown to be consistently reproducible when adjudicated by an independent committee.

We have thus witnessed a progressive change in the design of clinical trials, from smaller-scale short-term trials using clinical worsening as a secondary endpoint to large-scale event-driven trials evaluating combination therapy versus monotherapy of PAH-targeted drugs in which clinical worsening was the primary efficacy endpoint. Adoption of this design has led to the conclusion that combination therapy is indeed and rationally plausible, superior to monotherapy, and is the order of the day as per latest analyses and guidelines in this regard.[6,104,112-114]

Sequential Combination Therapy

Sequential combination therapies target successive pathogenetic mechanisms behind the development and propagation of PAH, with evidence backing this approach. However, not all combinations have shown to be equally efficacious and safe.

- *Prostanoids in addition to ERAs and/or PDE-5i*: In the STEP trial, inhaled iloprost added to background bosentan was not associated with a significant increase in 6MWD but was associated with improvements in functional status, pulmonary hemodynamics, and time to clinical worsening.

  The COMBI trial that had a very similar study design and population failed to show any benefit with this combination.[80,115] Disappointing results were also seen with the addition of oral treprostinil to ERAs, PDE-5i, or both. Conversely, inhaled treprostinil in addition to background therapy with ERAs or PDE-5i improved exercise capacity.[74] More recently, the GRIPHON study[83] showed that the addition of selexipag was associated with a 40% decrease in the risk of clinical worsening when compared with placebo in 1,156 PAH patients on background therapy. Subgroups of patients receiving an ERA, a PDE-5i, or a combination of the two experienced similar treatment benefit.
- *ERAs in addition to PDE-5i or prostanoids*: Predefined subgroup analyses in the SERAPHIN study[58] showed that macitentan delayed time to first PAH-related events in both treatment-naïve and pretreated patients (PDE-5i or nonparenteral prostaglandins), confirming that sequential combination therapy improves long-term outcomes in PAH. More recently, however, the COMPASS-2[57] study where 334 patients on baseline sildenafil were randomized to bosentan or placebo, failed to demonstrate a reduction in the risk of morbidity/mortality. Importantly, the COMPASS-2 trial had an important amount of missing data due to premature discontinuation of the study; also, the trial was designed to detect a treatment effect of 40% with combination therapy and the events encountered in the trial were too few. Thus, the study may have lacked statistical power to detect a smaller difference between treatments.
- *PDE-5i or sGC stimulation in addition to prostanoids or ERAs*: In the PACES-1 study,[116] the addition of sildenafil in patients with poor exercise capacity despite background IV epoprostenol was associated with significant delay in clinical worsening, improvements in exercise capacity, and hemodynamics. Riociguat also improved exercise capacity after 12 weeks in both treatment-naïve patients and those on background PAH therapy.

Initial Upfront Combination Therapy

Only two RCTs compared initial upfront combination therapy versus monotherapy in treatment-naïve patients.

In the BREATHE-2 trial,[56] upfront combination of epoprostenol and bosentan was associated with a non-significantly greater decrease of total pulmonary resistance from baseline to week 16, as compared with the epoprostenol/placebo group. Unfortunately, with a small number of patients (n = 33), it lacked power to detect significant difference between treatments.

The AMBITION trial[117] has brought new evidence in favor of upfront combination therapy in treatment-naïve patients. In this RCT, 500 patients with WHO-FC II–III were randomized into three treatment arms: Ambrisentan and tadalafil in upfront combination or monotherapy of ambrisentan or tadalafil combined with placebo.

Upfront combination therapy led to a 50% reduction in clinical failure compared with the combined monotherapy arms. Patients on combination therapy also had better performance on the 6MWD and larger decrease of NT-proBNP. There was no difference among groups for serious adverse events and treatment discontinuation. More recently, a post-hoc analysis of the AMBITION study[118] evaluating survival at 7 days after the termination of each individual patient's randomized treatment suggested a lower mortality in patients initially treated with combination therapy.

Finally, a recent retrospective analysis of real-world data including 97 patients suggested that these effects were similar regardless of the combination regimen used (ambrisentan/bosentan and tadalafil/sildenafil), consistently over a duration of 30 months.[119]

Triple Combination Therapy (Table 4)

There is paucity of data on triple combination therapy designed specifically to assess the benefits of adding a third therapy to a dual combination therapy regimen. However, three RCTs have included a large population of patients on dual background therapy, thereby providing an opportunity to investigate the effect of triple versus dual combination therapy. In the first two, FREEDOM-C (n = 350) and FREEDOM-C2 (n = 310), a large proportion of patients were on dual combination therapy at baseline (45% in FREEDOM-C and 40% in FREEDOM-C2). In these short-term trials, addition of oral treprostinil failed to demonstrate any significant benefit on the primary endpoint

TABLE 4: Dual and triple drug therapy.

Combination drugs	No. of subjects	Major WHO-FC status of subjects	Follow-up time	Primary endpoint	Primary endpoint meets the defined significance	Type of combination
Bosentan + inhaled iloprost (STEP)	67	III (94%)	12 weeks	6MWD	No	Sequential combination
Bosentan + inhaled iloprost (COMBI)	40	III (100%)	12 weeks	6MWD	No	Sequential combination
Bosentan or sildenafil + inhaled treprostinil (TRIUMPH-1)	235	III (98%)	12 weeks	6MWD	Yes	Sequential combination
ERA or PDE-5 inhibitors or both + oral treprostinil (FREEDOM-C)	350	II (21%), III (76%)	16 weeks	6MWD	No	Sequential combination
ERA or PDE-5 inhibitors or both + oral treprostinil (FREEDOM-C2)	310	II (26%), III (73%)	16 weeks	6MWD	No	Sequential combination
Epoprostenol + sildenafil (PACES)	267	II (25%), III (66%), IV (6%)	16 weeks	6MWD	Yes	Sequential combination
Epoprostenol + bosentan (BREATHE-2)	33	III (76%), IV (24%)	16 weeks	Hemodynamic evaluation	No	Upfront combination
Epoprostenol + bosentan + sildenafil	19	III (42%), IV (58%)	Median exposure 39.2 months	6MWD and PVR	Yes	Upfront combination

(ERA: endothelin receptor antagonist; 6MWD: 6-minute walk distance; PDE-5: phosphodiesterase-5; PVR: pulmonary vascular resistance; WHO-FC: World Health Organization functional class)

of change in 6MWD, either as dual or triple combination therapy. In the GRIPHON[83] study, 376 patients (32.5% of the total population) were on dual ERA and PDE-5i therapy at baseline.

Administration of selexipag or placebo to these patients allowed triple versus dual combination therapy to be studied. A prespecified analysis evaluating the composite primary endpoint of morbidity/mortality demonstrated that selexipag reduced the risk of a primary endpoint event in patients receiving dual combination therapy at baseline by 37%.

Upfront triple therapy is at a nascent stage of evolution. A pilot study with 19 patients gave favorable evidence for the institution of triple therapy at diagnosis with respect to improvement of hemodynamic and clinical parameters.[120] TRITON, a multicenter, double-blind study, evaluated initial triple (macitentan, tadalafil, and selexipag) versus initial double (macitentan, tadalafil, and placebo) oral therapy in newly diagnosed, treatment-naive patients with PAH. Patients were assigned to initial triple (n = 123) or initial double therapy (n = 124). At week 26, both treatment strategies reduced PVR compared with baseline (by 54% and 52%), with no significant difference between groups.[121] Exploratory and post hoc analyses on long-term outcomes suggest a signal for reduced risk for disease progression with initial triple versus initial double oral therapy. These findings should be interpreted with caution because of their exploratory nature.

Currently as per the latest recommendations, macitentan added to sildenafil, riociguat added to bosentan, and selexipag added to and/or ERA/PDE-5i enjoy a class I recommendation in the ESC 2015 PH guidelines.[6]

Follow-up of Patients with Primary Pulmonary Hypertension

The goals of therapy have been gradually redefined as the management has evolved. Rather than simply abate the progression of the disease the goals of therapy now aim at improvement in functional status to WHO class 1/2 and a 6MWD of 440 m and hemodynamic status [RAP <8 mm Hg, cardiac index >2.5 L/min/m^2, venous oxygen saturation (SVO_2) >65%], which would improve the risk profile patients with PAH.[6]

WHO Functional Class

The WHO-FC, although a subjective parameter, is highly relevant to the determination of the prognosis and is widely used in clinical trials as an endpoint for the determination of outcomes. The goals of treatment are an improvement in the FC or maintaining WHO-FC 1 or 2.

Functional Assessment by 6-minute Walk Test

The 6MWT is an extremely important, semiobjective and simple parameter that has been extensively used to quantify exertional intolerance and serially assess the progression of the patient. It also serves as an important prognostic marker.[122,123] 6MWD, however, is influenced by many factors including age, height, weight, gender, ethnicity, comorbid conditions, supplemental O_2 use, encouragement level, corridor length used for testing, learning effect, and mood. The guidelines for this test have been laid out by the American Thoracic Society in a 2002,[124] and when properly performed according to guidelines provides a simple and reproducible insight into the patient's functional

capacity. In a meta-analysis of 22 RCTs, the 6MWD was found to have a strong inverse correlation with the PVR.[107] According to the REVEAL registry,[125] the survival was significantly better in patients with a 6MWD of >380 m. In another large study, the survival was better in patients with a 6MWD of >440 m.[116] The 6MWD should be recorded at the baseline and at an interval of every 3–6 months on follow-up visits, and after change of therapy.[6]

Cardiopulmonary Exercise Testing

The routine use of CP exercise testing outside of research has understandably been subdued due to complicated, cumbersome nature and difficulties in arranging and performing this test for routine clinical use.

Biomarkers

Among many biomarkers associated with PH, BNP and NT-proBNP have been used for the follow-up of patients with PH. According to Nagaya et al. for a mean follow-up period of 24 months, survival was strikingly worse for patients with a supramedian value of follow-up BNP (≥180 pg/mL) than for those with an inframedian value.[126] Also patients with initial NT-proBNP levels >1,800 ng/L that subsequently improved with therapy to values below this threshold had almost identical outcomes to patients with persistently low NT-proBNP levels at baseline and follow-up, conversely, patients who developed a titer beyond this threshold demonstrated a poorer outcome.[125,127]

Echocardiography

The use of echocardiography in follow-up provides useful information about the assessment of right-sided and pulmonary pressures as per the details above, RV function, and the development of pericardial effusion, which is an important adverse prognostic marker. It is advocated after every 3–6 months, and after the change of therapy or clinical worsening.

Right Heart Catheterization

The use of RHC has primarily been advocated to assess the response to change in therapy and in the event of clinical worsening.

CONCLUSION

Primary PH has evolved from an inexorable calamity to rapidly emerging exciting new frontiers in management which has significant successes in deferring the course of the illness. It remains a study in evolution.

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CHAPTER 28

Anticoagulation, Dual Antiplatelet Therapy, and Perioperative Management

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ABSTRACT

Anticoagulant and antiplatelet drugs are commonly encountered during perioperative workup during noncardiac surgery. Anticoagulants are usually encountered in patients of atrial fibrillation, while antiplatelets are encountered postangioplasty. The risk of ischemic events on stoppage of these agents must be weighed against bleeding risk if they are continued. The indication and timing of stopping these agents are therefore, crucial. While most cases can allow stoppage of these drugs at appropriate times, very high-risk cases may require bridging molecules. Emergency surgery may require the use of reversal agents in very selected cases. These aspects are dealt with in this chapter.

INTRODUCTION

Managing antithrombotic agents during the periprocedural period has always been a challenging area in clinical practice. Management of patients on antithrombotic therapy who are referred for surgical procedures involves consideration of the risk of thrombosis, the consequences of delaying the surgical procedure, and the increased intra- and periprocedural bleeding risk and possible consequences of such bleeding if drug is continued. Given the complexity of these considerations, a multidisciplinary approach—involving interventional cardiologists, cardiologists, anesthetists, hematologists, and surgeons—is required to determine the patient's risk for bleeding and thrombosis and to choose the best management strategy. Recommendations from different authorities are mostly based on expert opinions as data from randomized trials or well-designed observational studies are lacking. Clinical judgment for individual cases is essential and plays a crucial role in the final outcome. First, we will discuss about perioperative issues in relation to anticoagulation and then we shall discuss about antiplatelets.

MANAGING ANTICOAGULANTS

Interruption of anticoagulation temporarily increases thromboembolic risk, and continuing anticoagulation increases the risk of bleeding associated with invasive procedures; both of these outcomes can increase mortality rates.[1]

Decision-making can be aided by the interactive format presentation on the Thrombosis Canada website (https://thrombosiscanada.ca/).[2]

While deciding the approach, it is convenient to stratify the procedures according to the risk of bleeding **(Box 1)** and risk of thromboembolism **(Table 1)**.

Taking into consideration bleeding versus thrombotic risk, the next step is to decide whether or not to interrupt anticoagulation.

Whether to Interrupt Anticoagulation

Once the thromboembolic and bleeding risks have been estimated, a decision can be made about whether the anticoagulant should be interrupted or continued.[3] Data comparing the relative benefits of continuing anticoagulation versus interrupting an anticoagulant are limited, and decisions that balance thromboembolic and bleeding risks must be made on a case-by-case basis. No scoring system can substitute for clinical judgment in this decision-making. Patient factors can also contribute to bleeding risk; these patient-related risks can be quantified using bleeding risk scores such as HAS-BLED score.[4]

In general, the anticoagulant must be discontinued if the surgical bleeding risk is high. Those at very high or high thromboembolic risk should limit the period without anticoagulation to the shortest possible interval; in some cases, this involves the use of a bridging agent.

BOX 1 Stratification of bleeding risk.

Low (minor nondental procedure)
- Cataract surgery
- Dermatologic procedures (e.g., biopsy)
- Gastroscopy or colonoscopy without biopsies
- Coronary angiography
- Permanent pacemaker insertion or internal defibrillator placement (if bridging anticoagulation is not used)
- Selected procedures (e.g., thoracentesis, paracentesis, arthrocentesis)

Low (minor dental procedure)
- Dental extractions (one or two teeth)
- Endodontic (root canal) procedure
- Subgingival scaling or other cleaning

Moderate
- Abdominal surgery (e.g., cholecystectomy, hernia repair, colon resection)
- Other local surgery (e.g., breast)
- Noncataract ophthalmologic surgery
- Gastroscopy or colonoscopy with biopsies
- Selected procedures (e.g., bone marrow biopsy, lymph node biopsy)
- Complex dental procedure (e.g., multiple tooth extractions)

High
- Any surgery or procedure with neuraxial (spinal or epidural) anesthesia
- Neurosurgery (intracranial or spinal)
- Cardiac surgery (e.g., CABG, heart valve replacement)
- Major vascular surgery (e.g., aortic aneurysm repair, aortofemoral bypass)
- Major orthopedic surgery (e.g., hip/knee joint replacement surgery)
- Lung resection surgery
- Urological surgery (e.g., prostatectomy, bladder tumor resection)
- Extensive cancer surgery (e.g., pancreas, liver)
- Intestinal anastomosis surgery
- Reconstructive plastic surgery
- Selected procedures (e.g., kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy)

(CABG: coronary artery bypass graft)

Source: Adapted from Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. Blood. 2012;120:2954.

The major factors that increase thromboembolic risk are atrial fibrillation (AF), prosthetic heart valves, and recent venous or arterial thromboembolism (e.g., within the preceding 3 months). The risk classifications given are largely based on indirect evidences. Patient-specific factors and clinical judgment should also be incorporated into the risk estimate.[5]

Atrial fibrillation accounts for the highest percentage of patients for whom perioperative anticoagulation questions arise. Patients with AF are a heterogeneous group; risk can be further classified according to clinical variables such as age, hypertension, congestive heart failure, diabetes, prior stroke, and other vascular diseases. The CHA_2DS_2-VASc score[6] incorporates these variables, but the use of risk scores has not been prospectively validated in the perioperative setting. The magnitude of perioperative thrombotic risk was found to be 1.2% in RE-LY trial,[7] 0.3–0.4% in ROCKET AF trial,[8] and 0.35–0.57% in ARISTOTLE trial,[9] where anticoagulation with any agent was interrupted.

The risks of thromboembolism are high in patients with mechanical prosthetic heart valves, especially in the mitral position, non-bileaflet design, and recent history of transient ischemic attack or ischemic stroke. Thromboembolic risk is greater in the immediate period following an event and declines over time. A patient of AF and ischemic stroke <3 months and those with suboptimal anticoagulation in the previous month are at a high risk of recurrent thromboembolic events. Elective surgery must be deferred as far as possible.

In contrast, individuals undergoing selected low bleeding risk surgery often can continue their anticoagulant; in certain cases, continuation of the anticoagulant may be preferable.

Timing of Interruption

If a moderate or high bleeding risk surgery is required urgently or immediately, reversal of the anticoagulant may also be required.

If a decision has been made to interrupt the anticoagulant for surgery with high or moderate bleeding risk, the agent should be stopped in sufficient time to allow anticoagulation to resolve. For some agents such as warfarin, laboratory testing is a reliable indicator that the anticoagulant effect has resolved after discontinuation.

For non-vitamin K oral anticoagulants (NOACs), well-validated and easily accessible testing is not always available. Data to guide the timing of anticoagulant interruption are evolving, especially for NOACs, and much of our practice is based on expert opinion and observational studies as we await results from ongoing trials.[10]

The following applies to NOAC interruption **(Table 2)**:
- These intervals are for individuals with normal kidney function and factor Xa inhibitors regardless of kidney function.
- *For minor bleeding risk*: Stoppage is required only on the day of surgery. It can be restarted after >6 hours.
- *Low/Moderate bleed risk*: For low/moderate bleeding risk surgery, omit the NOAC 1 day before and resume 1 day (~24 hours) after the procedure, provided hemostasis is secure. The total duration of interruption is 2 days **(Fig. 1)**.
- *High bleed risk*: For high bleeding risk surgery, omit the NOAC 2 days before and resume 2 days (~48 hours) after the procedure, provided hemostasis is secure. The total duration of interruption is 4 days. Waiting an additional 1 day before resumption may be appropriate in some cases.
- For individuals with creatinine clearance (CrCl) 30–50 mL/min receiving dabigatran, longer intervals are used (omit from 2 days before a low/moderate bleeding risk procedure; omit from 4 days before a high bleeding risk procedure). For individuals with impaired kidney function (CrCl < 30–50 mL/min) who are taking dabigatran, there is an additional 1day interruption before low/moderate bleeding risk procedures and an additional 2-day interruption before high bleeding risk procedures.

TABLE 1: Stratification of thrombotic risk.

Thrombotic risk	Indication for anticoagulant therapy		
	Mechanical heart valve	**Atrial fibrillation**	**Venous thromboembolism (VTE)**
High thrombotic risk	• Any mitral valve prosthesis • Any caged-ball or tilting disk aortic valve prosthesis • Recent (within 6 months) stroke or transient ischemic attack	• $CHADS_2$ score 5–6 • CHA_2DS_2-VASc score 7–9 • Recent (within 3 months) stroke or transient ischemic attack • Rheumatic valvular heart disease	• Recent (within 3 months) VTE • Severe thrombophilia (e.g., deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Moderate thrombotic risk	Bileaflet aortic valve prosthesis and one or more of the following risk factors: Atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age >75 years	• $CHADS_2$ score 3–4 • CHA_2DS_2-VASc score 4–6	• VTE within the past 3–12 months • Non-severe thrombophilia (e.g., heterozygous factor V Leiden or prothrombin gene mutation) • Recurrent VTE • Active cancer (treated within 6 months or palliative)
Low thrombotic risk	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	• $CHADS_2$ score 0–2 • CHA_2DS_2-VASc score 0–3 (assuming no prior stroke or transient ischemic attack)	VTE >12 months previous and no other risk factors

Source: Modified from Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckmen MH, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e326S. Copyright © 2012. Reproduced with permission from the American College of Chest Physicians.

TABLE 2: Summary of timeline related to stopping and resumption of non-vitamin K oral anticoagulant (NOAC).

Creatinine clearance ($mL/m^2/min$)	Dabigatran		Apixaban Rivaroxaban	
	Low risk	High risk	Low risk	High risk
>80	>24	>48	>24	>48
50–79	>36	>72	>24	>48
30–49	>48	>96	>24	>48
15–29	Not indicated	Not indicated	>24	>48
<15	Not indicated	Not indicated	Not indicated	Not indicated

Notes: No heparin bridging. Start NOAC >24 hours after low-risk surgery and >48 hours after high-risk surgery.

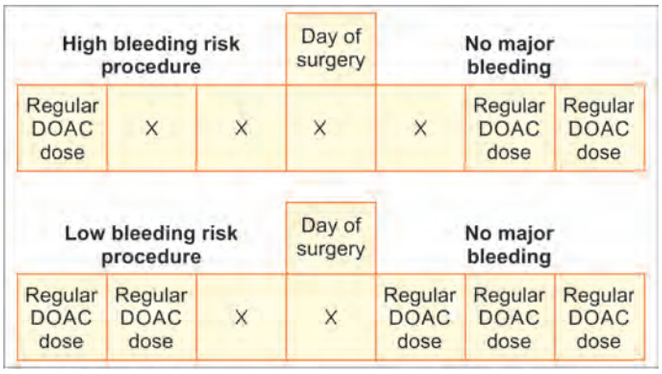


FIG. 1: Protocol for direct oral anticoagulant discontinuation perioperatively. Timing for interruption of a direct oral anticoagulant (DOAC) before and after elective surgery.

Source: Modified from Douketis JD, Lip GH. Perioperative management of patients receiving anticoagulants. UpToDate.

- Direct factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) do not require duration adjustments for kidney function.
- Bridging is not used for NOACs usually. In the patients whose bleeding risk outweighs the cardioembolic risk, or those unable to take orally, post surgery, a venous prophylactic dose of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) may be given. NOACs may be started 12 hours after LMWH discontinuation.
- In patients treated with very low-dose rivaroxaban (2.5 mg twice daily) on top of dual antiplatelet therapy (DAPT), rivaroxaban can be safely discontinued >48 hours before surgical interventions (independent of the bleeding risk).
- The perioperative management from the PAUSE study (a population with AF) can be applied to individuals who are receiving an NOAC for venous thromboembolism (VTE) that was >30 days prior. If the individual had a VTE within the prior 30 days, NOAC interruption should be individualized and may include placement of a temporary inferior vena cava (IVC) filter or shorter periods of NOAC interruption.

The following applies to vitamin K antagonist (VKA) interruption:

- For warfarin, discontinue 5 days before the procedure.
- For those with international normalized ratio (INR) value >1.5, surgery should be postponed till it is 1.5 or less, or if there is an urgency, low-dose oral VKA (1–2 mg) should be given. Usually, INR falls to <1.4 the next day.
- If bridging is needed for a high thromboembolic risk patient, start LMWH at a therapeutic dose approximately 3 days before surgery, with the last preoperative dose approximately 24 hours before surgery.
- Resume warfarin postoperatively once hemostasis is assured (typically the evening of the day of surgery or the day after surgery). Resume LMWH approximately

2–3 days after surgery (determined by the bleeding risk of the procedure) and discontinue LMWH after stable warfarin anticoagulation.
- The overlap period between LMWH and warfarin depends on the patient's thromboembolic risk.

Whether to Bridge or Not?

The intent of bridging is to minimize the time the patient is not anticoagulated, thereby minimizing the risk for perioperative thromboembolism. However, this needs to be balanced with the importance of mitigating the risk of postoperative bleeding. Accumulating evidence suggests that in the vast majority of patients, bridging does not provide a benefit in lowering thromboembolic risk, whereas most data show a consistent increase in bleeding risk.

Evidence to support the limited use of bridging to selected individuals with very high thromboembolic risk comes from several meta-analyses. As an example, a 2020 meta-analysis that included 6 randomized trials and 12 cohort studies found that bridging was associated with an increased risk of bleeding [relative risk (RR) 2.83; 95% confidence interval (CI) 2.00–4.01] with no statistical reduction in thromboembolic risk.[11]

MANAGING ANTIPLATELETS

It is estimated that 5–25% of patients with coronary stents may require noncardiac surgery within 5 years after stent implantation.[12] In stented patients undergoing noncardiac surgery, the rate of major adverse cardiac events (MACE) ranges from 3 to 11%.

In most clinical situations, aspirin provides benefit that outweighs the bleeding risk and should be continued.[13] Possible exceptions to this recommendation include intracranial procedures, transurethral prostatectomy, intraocular procedures, and operations with extremely high bleeding risk.[14]

Identifying High Thrombotic Risk

The foremost factor in deciding the use of antiplatelet during the periprocedural period is the assessment of thrombotic risk of the patient vis-a-vis the bleeding risk. According to the European guidelines, high-risk patients are those who have recent percutaneous coronary intervention (PCI) along with other features as presented in **Box 2**.

Patients who are already implanted with a bioresorbable vascular scaffold are a special category with an increased risk of stent thrombosis when DAPT is withheld prematurely (<1 year). However, as Absorb stent was withdrawn a few years back, we are unlikely to face this clinical dilemma in the future.

DECIDING PERIOPERATIVE STRATEGY

The role of aspirin in the primary prevention of atherosclerotic cardiovascular diseases has been a gray area since long. Its omission during the periprocedural period is justified if the bleeding risk is not low. The real difficulties come while dealing with patients who are on DAPT, mostly following coronary angioplasty with stents.

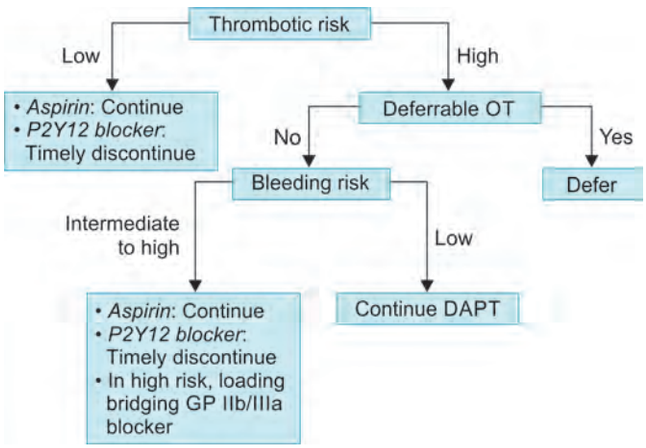
A higher risk of ischemic events in the case of noncardiac surgery has been reported after first-generation drug-eluting stent (DES),[15] and a higher risk for MACE has also been shown during the first weeks after noncardiac surgery in patients with implanted stents. Furthermore, surgery per se, irrespective of the timing of DAPT discontinuation, is associated with pro-inflammatory and prothrombotic effects, thereby increasing the risk of coronary thrombosis at the level of the stented vascular segment as well as throughout the coronary vasculature.[16] Therefore, in patients undergoing noncardiac surgery after recent acute coronary syndrome (ACS) or stent implantation, the benefits of early surgery for a specific pathology (e.g., malignant tumors or vascular aneurysm repair) should be balanced against the risk of cardiovascular events, and the strategy should be discussed by a multidisciplinary team **(Flowchart 1)**.

BOX 2 Patients who have high thrombotic risk.

High thrombotic risk situations
- Post-PCI ≤1 month
- *Post-PCI 1–6 months with:*
  - ACS at presentation
  - Prior stent thrombosis on adequate antiplatelet therapy
  - Stenting of the last remaining patent coronary artery
  - Diffuse multivessel disease, especially in diabetics
  - Chronic kidney disease (eGFR <60 mL/min)
  - At least three stents implanted
  - At least three lesions treated
  - Bifurcation with two stents
  - Total length >60 mm
  - Treatment of chronic total occlusion

(ACS: acute coronary syndrome; eGFR: estimated glomerular filtration rate; PCI: percutaneous coronary intervention)

Source: Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39:213-60.



FLOWCHART 1: Protocol for antiplatelet discontinuation in perioperative management.

(DAPT: dual antiplatelet therapy; GP IIb/IIIa: glycoprotein IIb/IIIa)

Many registries have reported that surgery-associated risk in DES-PCI-treated patients reaches a stable level after 3–6 months.[17] If an emergency procedure is required, consideration of platelet transfusion is viable only if bleeding risk outscores thrombotic risk. After elective coronary stent implantation, elective surgery requiring discontinuation of the P2Y12 inhibitor should be considered after 1 month, irrespective of the stent type, if aspirin can be maintained throughout the perioperative period. In patients at high ischemic risk due to ACS presentation or complex coronary revascularization procedure, delaying surgery up to 6 months after index ACS or PCI may be reasonable **(Flowchart 1)** as an additional safeguard to minimize the risk of peri-surgical myocardial infarction (MI), and based on unmatched retrospective registry data if the risks of further delaying surgery are acceptable.[18]

It is recommended to continue aspirin perioperatively if the bleeding risk allows and to resume the recommended antiplatelet therapy as soon as possible postoperatively.

If both oral antiplatelet agents have to be discontinued perioperatively, a bridging strategy with intravenous antiplatelet agents may be considered, especially if surgery has to be performed within 1 month after stent implantation.

New-generation DES are safer than bare metal stents, and the relative advantage of the former comes between 2 and 6 months postimplant. Till now, the relative advantage of stents with bioresorbable polymer compared to the durable polymer during DAPT discontinuation is yet to be established, and hence similar rules apply for both.[18]

First assessment of the thrombotic risk must be made. If low risk, timely discontinuation of P2Y12 inhibitor should be done and only aspirin continued. In moderate to high risk, an operation must be deferred if feasible. Otherwise, an assessment of the bleeding risk must be done. If it is low, DAPT must be continued. In case of moderate and high risk, timely discontinuation of P2Y12 inhibitor should be done, and only aspirin continued. In selected cases, addition of postprocedure bridging glycoprotein IIb/IIIa (GP IIb/IIIa) blocker in high-risk situations may be considered. **Flowchart 1** gives a simple algorithm for the perioperative protocol of antiplatelets.

Timing of Interruption

In patients needing surgery within a few days, it is recommended to withhold ticagrelor for 3 days, clopidogrel for 5 days, and prasugrel for 7 days prior to surgery whenever feasible **(Fig. 2)**. If P2Y12 inhibitor therapy has been stopped before a surgical procedure, it should be restarted as soon as possible (within 48 hours), given the substantial thrombotic hazard associated with lack of platelet inhibition early after surgery in patients with recent stent implantation and/or an ACS episode.[18]

Bridging Antiplatelet Therapy

In patients with high bleeding and thrombotic risk and where surgery cannot be deferred, a bridging molecule is necessary. Cangrelor, a reversible intravenous P2Y12 inhibitor, can be started up to 3–4 days after prasugrel discontinuation and 2–3 days of clopidogrel and ticagrelor discontinuation to minimize the duration of infusion. Due to very short half-life (3–6 minutes), platelet activity returns by an hour and thus

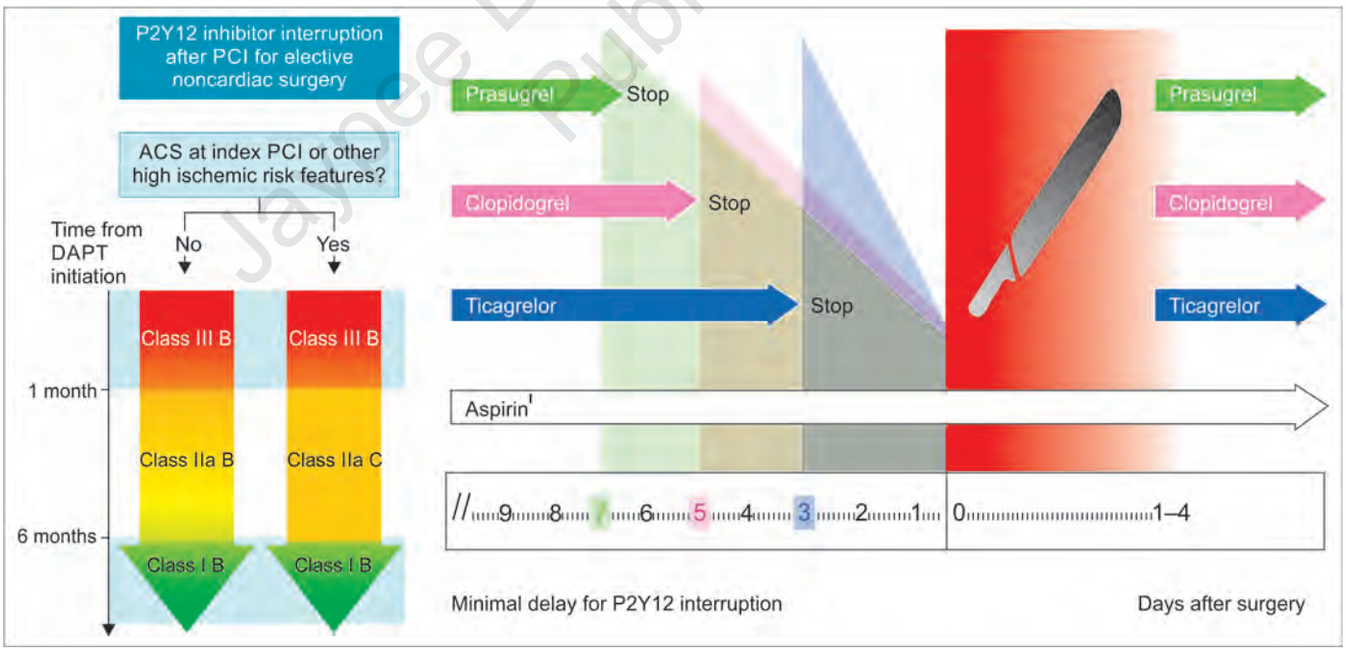


FIG. 2: Antiplatelet timing protocol.

(ACS: acute coronary syndrome; DAPT: dual antiplatelet therapy; PCI: percutaneous coronary intervention)

Source: Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39:213-60.

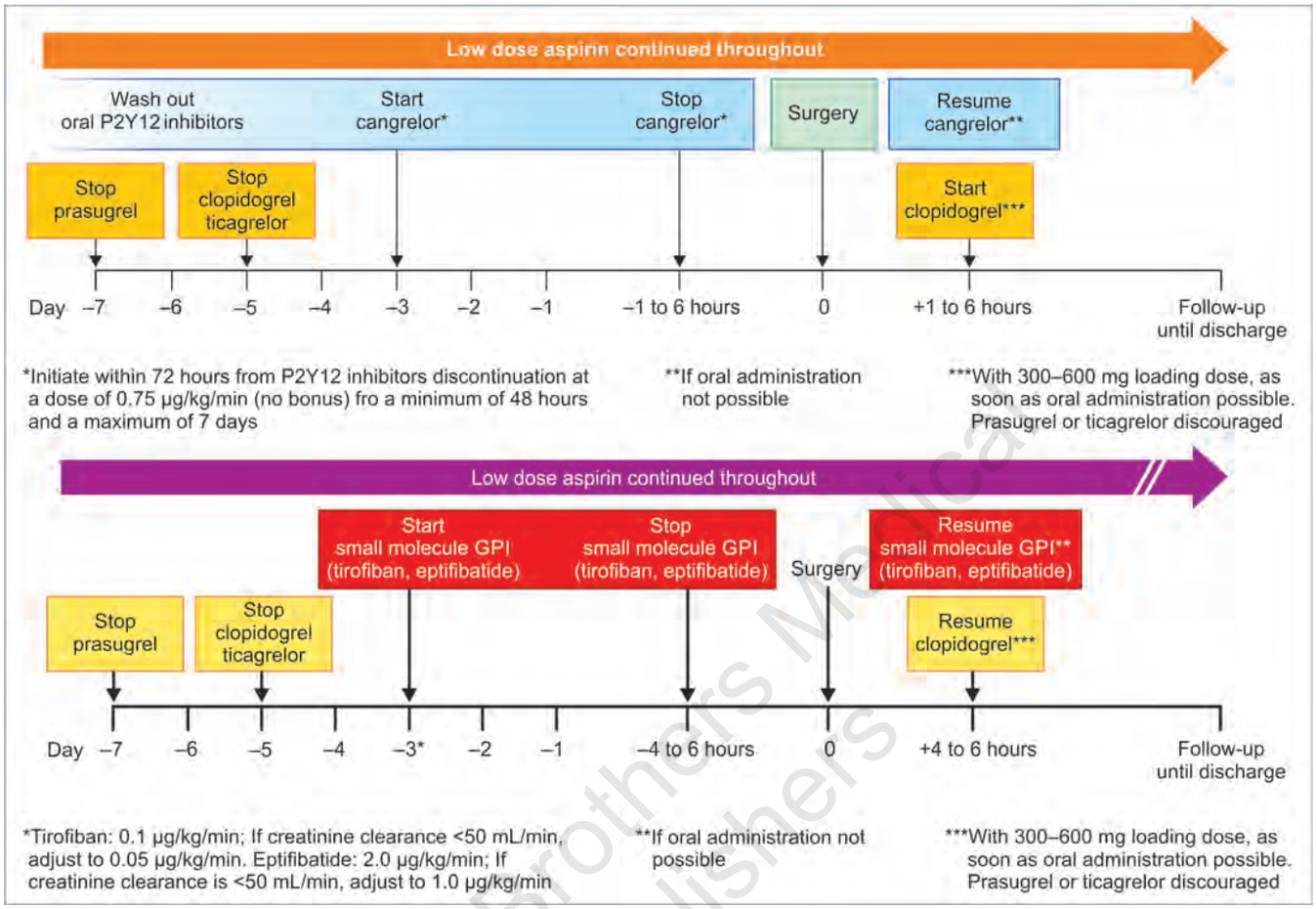


FIG. 3: Time period of interruption of P2Y12 inhibitors and protocols for cangrelor and glycoprotein IIb/IIIa (Gp IIb/IIIa) molecules.

(GPI: glycoprotein IIb/IIIa inhibitors)

Source: Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39:213-60.

can be discontinued just before surgery **(Fig. 3)**. Cangrelor has been tested against placebo as a bridging agent among thienopyridine-treated patients undergoing coronary artery bypass grafting surgery in the BRIDGE (Bridging Antiplatelet Therapy with Cangrelor in Patients Undergoing Cardiac Surgery) trial. A further advantage is that because it is not renally cleared, it can be used in patients with kidney disease. An alternative to cangrelor, when it is not available, are GP IIb/IIIa inhibitors eptifibatide and tirofiban. These drugs should be started 3 days before surgery. However, they have a longer half-life and should be discontinued 4 hours before surgery. Since they are renally cleared, they should be stopped 8 hours before surgery in patients with CrCl <50 mL/h. There is lack of evidence on the use of GP IIb/IIIa molecule as bridging therapy. After successful hemostasis is achieved, oral P2Y12 inhibiting therapy should be resumed within 24–48 hours with the use of a loading dose. In patients with increased bleeding risk, clopidogrel should be preferred over prasugrel or ticagrelor. If the use of oral P2Y12 inhibiting therapy is not possible, for example, if the gastrointestinal function has not yet recovered (e.g., abdominal surgery), intravenous infusion of antiplatelet agents [cangrelor or glycoprotein IIb/IIIa inhibitors (GPI)] should be restarted.

When and How to Restart Antiplatelet Therapy

If aspirin has been interrupted, this should be initiated immediately after surgery. Once successful hemostasis has been obtained, oral P2Y12 inhibitors should be resumed within 24–48 hours after surgery using a loading dose. In patients at increased bleeding risk, clopidogrel should be preferred over prasugrel or ticagrelor. Clopidogrel may be resumed with a 600 mg rather than a 300 mg loading dose in patients with low bleeding risk and high thrombotic risk. However, resumption of antiplatelet drugs after surgery may be deferred and individualized in case of clinically relevant bleeding complications.

DEVICE IMPLANTATION

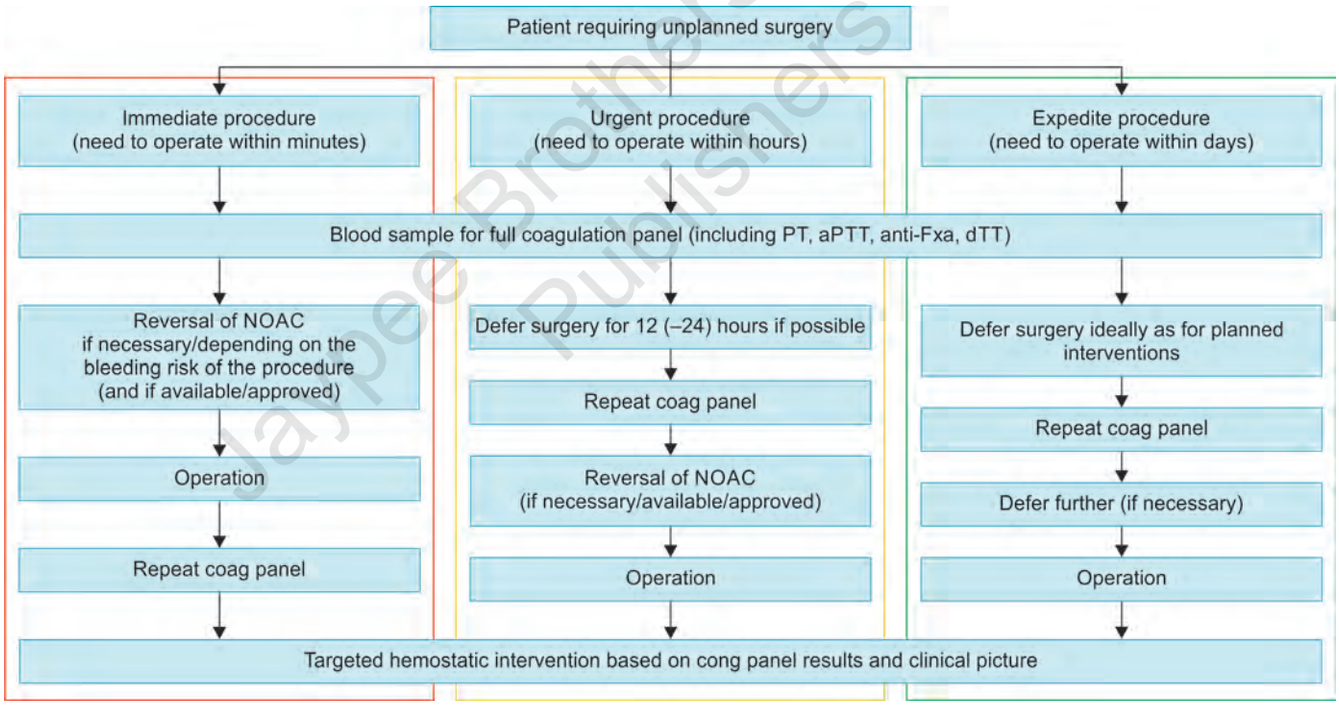
For patients undergoing cardiac implantable electrical device implantation (CIED), VKA-treated patients have lower thromboembolic and bleeding rates if the VKA is continued uninterrupted. For NOAC-treated patients, BRUISE-CONTROL 2 trial demonstrated similar bleeding and embolic rates in patients with the last intake being 48 hours before the implantation for rivaroxaban/apixaban (and based on the glomerular filtration rate for dabigatran) versus continued NOAC until the morning of the procedure.

EMERGENCY PROCEDURES

Immediate procedures (immediate life-, limb-, or organ-saving intervention, typically cardiac, vascular, and neurosurgical emergency procedures) need to be performed within minutes of the decision to operate and cannot be delayed. In these cases, reversal with idarucizumab (in the case of dabigatran) and andexanet alfa (for rivaroxaban, apixaban) may be considered, especially in moderate- to high-hemorrhagic risk procedures. However, there is a significant risk of thrombosis when reversal agents are used, and they should be used with caution, only once and in case of dire necessity. If specific reversal agents are not available, prothrombin concentrate complexes (PCCs) or activated prothrombin concentrate complexes (aPCCs) should be considered despite the lack of evidence for efficacy and safety. In these situations, surgery or intervention should be deferred, if possible, until at least 12 hours and ideally 24 hours after the last dose. Also, coagulation test results can be awaited. In such cases, a normal activated partial thromboplastin time (aPTT) in the case of dabigatran intake and a normal prothrombin time (PT) in the case of rivaroxaban intake (and to a lesser extent, edoxaban) may rule out high plasma levels of the respective drugs. Specific coagulation tests [diluted thrombin time (dTT) or ecarin chromogenic assay (ECA) for dabigatran; anti-factor Xa (anti-FXa) chromogenic assays for FXa inhibitors] and assessment of plasma levels may help in interpreting the current anticoagulant status **(Flowchart 2)**.

CONCLUSION

Managing anticoagulant and antiplatelets during the perioperative period requires a judicious balancing of bleeding and thrombotic risk. Clinical judgment should be done in a case-to-case basis to get the best possible outcome.



FLOWCHART 2: Protocol for non-vitamin K oral anticoagulants (NOACs) in case of emergency surgery.

(anti-FXa: anti-factor Xa; aPTT: activated partial thromboplastin time; dTT: diluted thrombin time; PT: prothrombin time)

Source: Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39:1330-93.

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CHAPTER 29

Emerging Role of Impedance Cardiography: A New Tool

Bhabani Prasad Chattopadhyay, Sudipta Ghosh, Nasim Mandal, Kalyan Saha

ABSTRACT

Electrocardiography (ECG) works by measuring voltage: The electrical conduction in respect of time in a graphical manner. Impedance cardiography (ICG) deals predominantly with the variation of impedance or resistance.

We are familiar with the concept that Pressure (P) = Flow (F) × Resistance (R) which has similarity with Ohm's Law Voltage (V) = Current (I) × Resistance (R) or impedance.

The emerging role of "ICG" is great. It can measure "stroke volume, heart rate, cardiac output, blood pressure, systolic time intervals, preejection period, left ventricular ejection time, total systolic time, total diastolic time" and variation of hemodynamic parameters in health and disease.

Impedance cardiography is cheaper and easy to use. So, it will be very useful tool for day-to-day bedside and OPD assessment of structural and functional aspects of heart in health and disease.

INTRODUCTION

Cardiologists are primarily acquainted with evidence-based treatment. Hard evidence in favor of the diagnosis and treatment protocol is essential in this field. Often one time data acquisition from one investigation is sufficient in concluding diagnosis. But, there are conditions where multiple repetitions or continuous recording of data for some duration for a given investigation is essential. Cardiac catheter laboratory based estimation of pressure data, cardiac output (CO) measurement, and hemodynamic information are examples which are precious but invasive and hence cannot be repeated again and again without reasonably strong indications. On the other hand, impedance cardiography (ICG) derived parameters despite being noninvasive have been validated with invasive catheter laboratory data worldwide inclusive of our catheter laboratory in Medical College and Hospital, Kolkata. This noninvasive modality can be repeated as and when required and can also be utilized for continuous monitoring of the hemodynamic parameters as in case of Holter monitoring and that too in ambulatory state of the patient. The purpose of present article is to highlight the basic principles, outlines of few of our latest research works, and to foresee the future directions of "ICG" as a whole.

BASIC PRINCIPLE OF IMPEDANCE CARDIOGRAPHY

Impedance cardiography is a new tool, yet to be widely utilized in day-to-day cardiological patient care. ICG can give information about the structure and function of the heart. Kubicek[1] et al. were the pioneer to introduce ICG for measuring CO and body fluid composition in 1966. ICG measures the *ionic conduction* of human body. We the clinicians are accustomed to electrocardiography (ECG) which works by measuring the *electrical conduction* in respect of time in a graphical manner. ECG deals with the electrical conduction whereas "ICG" deals predominantly with the variation of impedance or resistance.

Cardiologists are accustomed to the concept that Pressure (P) = Flow (F) × Resistance (R) which has similarity with Ohm's Law Voltage (V) = Current (I) × Resistance (R) or impedance. If some contrast is to be injected into a vessel—the ease or resistance of injecting the dye depends on the emptiness or fullness of the vessel in addition to many other factors. Similarly, if alternating current is injected to the tissue overlying a vessel the ease or resistance to flow of current depends mainly on the instantaneous impedance in the vessel and less on the impedance of its surrounding tissues.

Blood contains electrolytes and charged particles or ions. Blood flows through vessels (arteries and veins). This flow is pulsatile in nature. There is variation or change in volume of blood in the vessels in respect of time and that is attributable to the characteristics of the components of the cardiac cycle. Variation of blood volume is associated with variation of quantity of charged particle in a given segment of vessel under study in respect of time. This variation of volume and hence the quantity of ions results in variation of impedance (to the current injected by ICG device). The variation of volume of arteriovenous blood within a specific part of the body in respect of time is deemed responsible for variation of the static and transient values of electrical conductivity. Before Kubicek the variation in impedance (ΔZ) obtained due to the pulsatile, peripheral blood flow of limbs has been mathematically related to the pulsatile change in volume by Nyboer[2] in the year 1950.

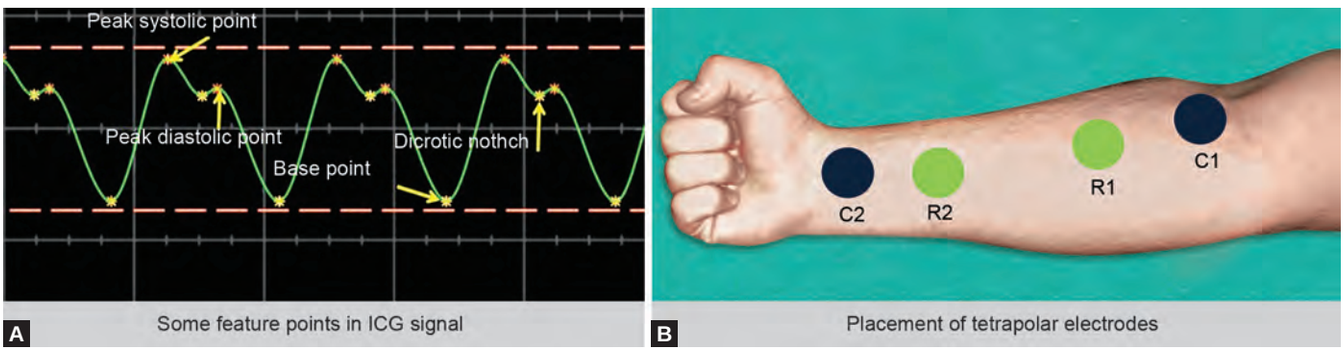
Vessels are considered as "volume conductors". Majority of initial researchers worked on thoracic impedance plethysmography and the volume changes in aorta and inferior vena cava were studied in great detail. Vessel segment in the limbs have also been studied. In this connection, it is necessary to understand the rate of change of impedance (dz/dt) and the maximum rate of change of impedance (dz/dt_{max}).

Both bipolar and tetrapolar electrodes have been used for research. In case of tetrapolar electrodes low intensity high-frequency steady current is injected by outer two electrodes and the receiving of the signal of *variation of impedance (dZ)* at the electrode-skin as well as tissue-vessel interface is acquired by the inner two electrodes. The signal so acquired from a segment of vessel under study is processed and filtered. Demodulation and differentiation of the signal acquired helps extraction of features that corresponds to multiple components of the cardiac cycle. The ICG signal thus acquired resembles conventional aortic pulse waveform in many ways. The extracted features of ICG waveform may be broadly categorized into four major groups: (1) Pressure features, (2) Time features, (3) Area features, and (4) Amplitude features. Algorithm deployed in the ICG device is usually designed in such a way, so that it detects only the complete cardiac cycles and discards incomplete cardiac cycles. Feature points—such as peak systolic point, dicrotic notch, peak diastolic point, and baseline point are of paramount importance. Once the complete cardiac cycles are identified, the amplitudes of the first (P1), second (P2), third (P3), and fourth (P4) peak points are stored, and the difference in amplitudes between these points are calculated. The difference values may be termed as "P1–P2" and "P3–P4". The first order and the second order differentiated ICG waveforms may be used to extract many other remaining feature points **(Figs. 1A and B)**.

Stroke volume (SV) is the absolute volume of blood ejected by concerned ventricle (left) during systole and CO is the product of SV and heart rate. CO measurement can help in monitoring of patients of heart failure in intensive coronary care unit (ICCU) and critical care units, surgical units particularly in the face of judging fluid balance for a given patient. ICG can accurately detect the variation of SV from beat to beat better than the absolute values. Ejection fraction can also be estimated. However, the guideline to fluid therapy may be scientific with the help of ICG—derived data. Blood "pressure (P)" is the product of "flow (F)" and "resistance (R)". ICG derived data can give instantaneous measurement of blood pressure. Depending on storage capacity, etc. ICG can measure ambulatory long-term cuffless blood pressure and can help in reflecting trends of BP in real life day-to-day activities.

Academic cardiologists of earlier generations were very much fond of systolic time intervals (STI). Much to their nostalgia ICG will bring back the reproducibly understandable utility of those time-related parameters in the understanding of disease and its management in the bedside. Role of pre-ejection period (PEP) and left ventricular ejection time (LVET) in aortic stenosis or left ventricular outflow tract (LVOT) obstruction and hemodynamically equivalent disease entities is well established. Medical teachers will find pleasure in making their students understand it in an objective way.

Total systolic time is the summation of ICG derived PEP and LVET. Time interval between closure of aortic valve and beginning of next PEP delineates the "total diastolic time". The rate of rise of LV pressure (dp/dt) and the rate of change of LV volume (dv/dt) can be obtained from ICG signals and hence can give fair idea about status of the contractile function of myocardiumin health and disease. These cover hemodynamic attributes of the ICG derived data. Impedance spectroscopy on the other hand can differentiate tissues and can discriminate healthy and diseased tissues. Work on impedance spectroscopy in the field of cardiology is limited paving the horizon of future research in this arena.



FIGS. 1A AND B: Some feature points in impedance cardiography (ICG) signal as well as placement of tetrapolar electrodes.

FEW RESEARCH WORKS ON ICG DONE IN THE LABORATORIES OF MEDICAL COLLEGE, KOLKATA AND IIT KHARAGPUR

In one study SV ejection fraction and cardiac health monitoring using ICG was carried out details of which is available in our past publication.[3]

Hemodynamic parameters were measured by ECG-gated echo-Doppler study as well as by invasive catheter laboratory procedures in another study. The hemodynamic parameters derived from ICG signals have been clinically validated in that study in the Department of Cardiology, Medical College, Kolkata.[4] Studies carried out in the Department of Cardiology Medical College, Kolkata and IIT Kharagpur on strength of correlation between ICG and coronary angiographic data subjected to "artificial neural network" have also been carried out and the study shows promising results regarding the potential of ICG in predicting the coronary artery involved. In this work, the novel design and method for noninvasive detection and prediction of localization of coronary arterial stenosis using ICG and artificial neural network has been studied. The device used for recording ICG signals was first bench tested and validated in School of Medical Science and Technology (SMST), IIT, Kharagpur, before being clinically used on human subjects in Medical College and Hospital, Kolkata. The subjects who underwent coronary angiography on cardiological indications were subjected to ICG recording. The ICG signal recorded by the device provided by IIT, Kharagpur was used to extract certain feature points. The extracted features were used as input to a trained artificial neural network, for prediction of coronary arterial blockages. The algorithm developed by IIT, Kharagpur is promising and can predict possible findings of coronary angiogram in patients of ischemic heart disease. The tool may serve as a new method for noninvasively predicting and localizing coronary arterial stenosis. Limitation of the study lies in its involvement of small number of patients. Studies on larger number of patients are being carried out.

CONCLUSION AND FUTURE DIRECTIONS

The emerging role of ICG lies in its ability of but is not limited to measurement of SV heart rate, CO blood pressure, STI, PEP, LVET, total systolic time, total diastolic time, and variation of hemodynamic parameters in health and disease. It bears the potential of localizing the culprit coronary artery in patients of acute coronary syndrome as well. In ICCU and critical care units continuous monitoring of hemodynamic parameters will be possible in a noninvasive manner by ICG derived signals. ICG instrument is relatively cheaper, cost-effective and its handling can be done by lay persons and technicians. It can be made widely available even in the rural health center levels. Screening for coronary artery disease, cuffless blood pressure measurement without use of stethoscope, etc., will make ICG popular in the medical practice in near future.

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CHAPTER 30

Women and Valvular Heart Disease

Sujatha Vipperla

ABSTRACT

Valvular heart disease (VHD) contributes to significant morbidity and mortality in India afflicting all ages. Mitral valve is the most commonly affected valve followed by the aortic valve. Mitral stenosis (MS) is seen predominantly in women and is of rheumatic etiology. Mitral regurgitation (MR) due to rheumatic causes and mitral valve prolapse account for the majority of the cases and are also more common in women. Aortic stenosis (AS) is less common in women and is more often degenerative. Women differ in responses mounted to hemodynamic load of valvular disease, clinical presentation, and response to treatment. Women with MS and AS have maternal and fetal adverse outcomes during pregnancy. Prosthetic valves during pregnancy pose challenges to clinicians and anticoagulation during pregnancy should be guideline directed and closely monitored to improve maternal and fetal outcomes.

INTRODUCTION

Valvular heart disease (VHD) in women is a significant problem, which contributes to significant morbidity and mortality. In India, though rheumatic heart disease (RHD) is the most common etiology of VHD, with the aging population, degenerative VHD is also rising. In view of this twin assault, women of all ages suffer from VHD in India. VHD-afflicting pregnancy contributes to maternal and fetal mortality. Sex-related differences in epidemiology, pathophysiology, clinical presentation, and outcomes exist, understanding of which improves patient care.

EPIDEMIOLOGY

Prevalence of VHD in India is estimated to be 1%.[1] RHD continues to be the dominant etiology in India. RHD contributed to 64.3% of VHD in the largest study of echocardiographic patterns in VHD from India. In the same study, mitral valve was involved in 54% and the aortic valve was involved in 36% of patients. One-third of patients had multivalvular disease.[2] In another study from north India, isolated mitral valve disease was seen in 48.7%, combined mitral and aortic valve disease in 34.5%, mixed aortic valve disease in 9.4%, and isolated aortic stenosis (AS) was seen in 4.8%.[3]

MITRAL STENOSIS

Mitral stenosis (MS) is seen predominantly in women (66%) and is predominantly of rheumatic etiology (97.4%).[2] Degenerative MS is rare and is also seen predominantly in women. Low-gradient very severe MS has a higher prevalence in female gender.[4] Percutaneous balloon mitral valvuloplasty (PBMV) has excellent short- and long-term outcomes. Major adverse cardiovascular event [cardiovascular death and need for repeat balloon mitral valvuloplasty (BMV) or mitral valve surgery] free survival at 20 years following PBMV was 36% in one study, which included 83% women. Though a final valve area <1.75 cm was more common in women (30% vs. 17%), male sex was an independent predictor of poor outcomes.[5] However, Cruz-Gonzalez et al., who specifically analyzed sex differences in PBMV women (83% women), had lower procedural success (69 vs. 83%), smaller postprocedural area, and 2.4-fold higher chance of developing mitral regurgitation (MR) compared to men **(Table 1)**.[6]

MITRAL REGURGITATION

Mitral regurgitation can be primary due to involvement of mitral leaflets or secondary due to ventricular dysfunction. Manjunath et al. reported MR in 25.6% of cases. RHD (41.1%)

TABLE 1: Sex differences in common valvular lesions.

	Mitral stenosis (MS)	Mitral regurgitation (MR)	Aortic stenosis (AS)	Tricuspid regurgitation (TR)
Etiology	• More common in women • RHD more common	• More common in women • RHD more common • Anterior or bileaflet prolapse in MVP	• Less common in women • BAV presents as more AS	• More common in women • Rheumatic etiology
Diagnosis	Low-gradient MS common	• Smaller LV volumes • Smaller EROA • Larger EROA/EDV ratio	• Paradoxical low-flow, low-gradient AS • Normal geometry and concentric remodeling • Less myocardial fibrosis • More AV fibrosis, less calcification	More progression to severe TR after successful left-sided surgery
Symptoms	More symptomatic	• Late referral for surgery • Older, higher AF, comorbidities	• More symptomatic at presentation • Older • More HTN, DM • Less CAD, PAD, sternotomies	More symptomatic
Treatment	• PBMV low-procedural success • Smaller postprocedural area • More MR	• More replacement than repair • Higher mortality and morbidity	• Higher vascular complications • Lower 1- and 3-year mortality and better outcomes	• More concomitant TV surgery at MV surgery • Lower event-free survival

(AF: atrial fibrillation; AV: aortic valve; BAV: bicuspid aortic valve; CAD: coronary artery disease; DM: diabetes mellitus; EDV: end-diastolic volume; EROA: effective regurgitant orifice area; HTN: hypertension; LV: left ventricular; MV: mitral valve; MVP: mitral valve prolapse; PAD: peripheral arterial valve; PBMV: percutaneous balloon mitral valvuloplasty; RHD: rheumatic heart disease; TV: tricuspid valve)

and mitral valve prolapse (40.8%) constituted the majority of patients followed by degenerative mitral valve disease in minority. Isolated MR was more common in women in all three subgroups.[2] There are differences in morphology of mitral valve in mitral valve prolapse in women having more anterior and bileaflet prolapse, more leaflet thickening which is more difficult to repair than posterior leaflet prolapse, which is more common in women. Absolute values of left ventricular and left atrial diameters were smaller in women than in men but were larger when indexed to body surface area regardless of the severity of regurgitation.[7]

Guidelines recommend mitral valve surgery in asymptomatic patients when left ventricular ejection fraction (LVEF) is <60% or left ventricular end-systolic dimension is ≥40 mm.[8] Women were less likely to be referred for surgery. At presentation for surgery women, who were older, had a higher incidence of atrial fibrillation and more comorbidities and were more likely to undergo additional surgery for atrial fibrillation and tricuspid disease. Furthermore, women were less likely to receive mitral valve repair and had higher mortality.[9] In a large retrospective analysis[10] of Medicare data, women had a higher mortality rate post mitral valve repair but was similar to that of men after risk adjustment. Mitral valve repair restored normal life expectancy in men but not in women. These differences could be due to late presentation of women for mitral valve surgery. In contrast, mitral valve replacement had similar mortality in men and women in a study by Seeburger et al.[11]—10-year survival in women was 58% as compared to 72% in men. Kislitsina et al.[12] found that women referred for mitral valve surgery were older, had higher STS (Society of Thoracic Surgeons) scores, and had higher concomitant MS, coronary artery disease, and heart failure. Women who received less mitral valve repair had more tricuspid valve intervention and atrial fibrillation ablation. They further performed propensity score matching and found no difference in surgical procedure or surgical outcome and inferred that women were referred later in the disease and had more aggressive mitral valve pathology. Mantovani et al.[13] reported similar mortality in women undergoing surgery for organic MR but higher heart failure during 10-year follow-up. In a study evaluating the sex-based differences in outcomes after surgery for ischemic MR, women had smaller left ventricular volumes, effective regurgitant orifice areas (EROAs), and larger EROA/end-diastolic volume ratio, which indicates disproportionate MR to left ventricular dilatation. Women had higher mortality, major adverse cardiac and cerebrovascular events, and morbidity postsurgery.[14] Transcatheter mitral valve repair (TMVR) is an emerging option in the treatment of patients with primary and secondary MR. A multicenter European registry and the Italian GRASP registry found no differences between men and women in outcomes post-TMVR.[15,16]

AORTIC STENOSIS

Aortic valve disease was seen in 16.2% of patients in India, with mixed disease in 9.8%, isolated AS in 4.8%, and pure aortic regurgitation (AR) in 2.0% of patients. Isolated AS had bimodal

distribution with peaks in first and sixth decades. Degenerative disease was the predominant etiology (58%), followed by bicuspid aortic valve in 25% of patients. Interestingly, in contrast to the west, two-thirds of patients presented at age <60 years. Up to 31% of AS in this study were women.[3] Bicuspid aortic valve is three to four times more common in men than in women and presents more frequently with AS in women and AR in men.[17]

Sex-related differences in myocardial response to AS exist. On cardiac magnetic resonance imaging, normal geometry and concentric remodeling were dominant in women, and concentric and eccentric hypertrophy were predominant in men.[18] In another study for similar severity of AS, men had higher left ventricular volumes, concentric remodeling, and late gadolinium enhancement than women; despite this, women develop symptoms early.[19] Up to 40% of patients have low-gradient AS. Classical low-flow, low-gradient AS is seen in 5–10% of AS population, is more common in men, and is associated with more coronary artery disease and reduced ejection fraction, whereas paradoxical low-flow, low-gradient AS is seen in 10–25% of the AS population and is more common in elderly women. This phenotype resembles heart failure with preserved ejection fraction characterized by restrictive physiology, small hypertrophied left ventricle, normal ejection fraction, and stroke volume <35 mL/m^2.[20] Women have more aortic valve fibrosis than calcification, and hence the American College of Cardiology (ACC) guidelines recommend lower thresholds for diagnosis of severe AS of 1,300 versus 2,000 Agatston units in men.[8]

In an analysis of sex-based differences in a large US database of patients (37% women) who underwent surgical aortic valve replacement (SAVR), women who were older had more hypertension, diabetes, atrial fibrillation, anemia, and obstructive lung disease but less incidence of coronary, peripheral arterial disease, and prior sternotomies. In-hospital mortality was higher even after propensity matching.[21] However, there was no difference in 10-year survival following aortic valve replacement (AVR)—66.8% in men and 67.5% in women.[22] In an analysis of Transcatheter Valve Therapy (TVT) registry,[23] women who were older had less diabetes, atrial fibrillation, and coronary artery disease but higher incidence of porcelain aorta, renal insufficiency, and higher STS scores. In an analysis of five registries with patient-level data, women who were older had higher transvalvular gradients, higher pulmonary artery pressures, and smaller annular sizes.[24] In a large metanalysis[25] (48,000 patients, 49% women), women had fewer comorbidities. Though the 30-day incidence of vascular complications and stroke was higher in women than in men, there was no difference in all-cause or cardiovascular mortality at 30 days. Furthermore, female sex was associated with a lower 1- and 3-year all-cause mortality, possibly due to lower cardiovascular mortality and lower incidence of paravalvular AR. Similar results were replicated in patient-level metanalysis with higher vascular complications and bleeding, lower rate of aortic incompetence but similar procedural and 30-day mortality and lower 1-year mortality.[24] In a meta-analysis of gender-specific subgroup analysis of randomized controlled trials, Panoulas et al.[26] found that transcatheter aortic valve replacement (TAVR) reduced mortality at 1 and 2 years as compared to SAVR in women but not in men. TAVR has 26–31% lower mortality odds than SAVR. All female Transcatheter Aortic Valve Implantation (TAVI) registry (WIN-TAVI) reported a low incidence of early and 1-year mortality and stroke.[27,28]

AORTIC REGURGITATION

Isolated AR was seen in 5.8% of cases in India in a study by Manjunath et al.,[2] which was mostly rheumatic followed by bicuspid aortic valve and congenital heart disease. Rheumatic AR was more common in women as compared to bicuspid and congenital AR, which was more common in men. In a study by Sahu et al.,[3] isolated AR was seen in 2.0% of patients, which was mostly congenital followed by rheumatic etiology. Surgery in current ACC guidelines is recommended in all symptomatic patients and asymptomatic patients when LVEF is 55%, left ventricular end-systolic diameter (LVESD) >50 mm, and LVESD >25 mm/m^2. In one study,[29] women had surgery more for class III or class IV symptoms, unlike men who had surgery due to severe left ventricular enlargement [LVESD >55 mm, left ventricular end-diastolic diameter (LVEDD) >80 mm]. Women had similar operative mortality, but those who survived had higher 10-year mortality and female sex was an independent predictor of mortality. Independent predictors of late survival were different for men (age and ejection fraction) and women (age and concomitant coronary bypass grafting). A later study[30] from the same institute found no difference in survival between women and men but found that larger indexed left ventricular systolic and diastolic dimensions were associated with late mortality. The authors suggested an LVESD cutoff of >25 mm/m^2 as a predictor of mortality, which has been incorporated in the recent ACC guidelines.

TRICUSPID REGURGITATION

Organic involvement of tricuspid valve was seen in 9.7% in Manjunath series.[2] Tricuspid stenosis was rare and was mostly of rheumatic etiology and seen predominantly in association with MS. Tricuspid regurgitation (TR) was mostly rheumatic (70%) in the above series and mostly seen in women. Song et al.[31] after analysis of risk factors for the development of TR after successful left-sided surgery identified age, rheumatic etiology, female gender, and peak pressure gradient of TR as risk factors. Late significant TR was associated with a significantly lower 8-year clinical event-free survival rate. In fact, in patients undergoing mitral valve surgery, concomitant tricuspid valve surgery was mostly performed in women.[11] TR ,whether organic or functional, is an important cause of heart failure post successful left-sided surgery, especially in women, and future research should focus on interventions addressing this issue.

VALVULAR HEART DISEASE IN PREGNANCY

Pregnancy in women with VHD poses unique challenges. Cardiac output increases by about 45%, mainly due to 20–30% increase in heart rate and increase in stroke volume. Increase in cardiac output begins at 10 weeks gestation and peaks at 24 weeks.[32] Gravid uterus can compress the inferior vena cava in a supine position, which is exacerbated in women with valve

disease. Peripartum and postpartum hemodynamics are altered due to uterine contractions, pain during delivery, and blood loss, which are more prominent in valve disease patients. So, women with VHD have a 100-fold higher risk during pregnancy than normal women.

The European Society of Cardiology (ESC) created Registry on Pregnancy and Cardiac Disease (ROPAC), which enrolled 5,739 pregnant women with heart disease. VHD accounted for 29% of heart disease. Majority of patients with VHD (56%) had RHD. Maternal mortality was 1% and heart failure occurred in 17% in this group.[33] RHD accounts for 40–50% of cardiac disease during pregnancy. In an analysis of patterns of VHD in India, RHD constituted 87% of VHD. Mitral valve was the most common valve involved in 69% with severe MS comprising 50% of patients.[34,35]

The World Health Organization (WHO)[36] released a document to risk stratify women with cardiovascular disease into four categories. Women with mechanical heart valves (MHV) are classified as risk category III with significantly increased risk of maternal mortality or severe morbidity. Women with severe MS and severe AS are classified as risk category IV with extremely high risk of maternal mortality or severe morbidity. Pregnancy is contraindicated or termination is advised in this group. Patients with pulmonary arterial hypertension due to VHD also fall in this category.

MITRAL STENOSIS

Increase in cardiac output and heart rate during pregnancy increase the transvalvular gradient by 30% between the first and the second trimesters. Symptoms begin mostly during the second trimester. Cardiac complications occurred in 26, 38, and 67% of patients with mild, moderate, and severe MS, respectively, with pulmonary edema developing in 31% and arrhythmias in 11% of pregnancies.[37] In ROPAC registry, 23% of pregnant women with MS were hospitalized, with rates approaching 50% in women with severe MS. Maternal mortality was 1.9% in this registry but may be higher in developing countries. Prepregnancy New York Heart Association (NYHA) class >1 was an independent predictor of maternal cardiac events.[38] Prematurity rate was 22%, intrauterine growth retardation was 24%, and fetal death was reported in 4% in one study.[39] β-blockers reduce the heart rate, which reduces the diastolic filling time leading to a decrease in left atrial pressure. Diuretics should be used judiciously if there is no relief of symptoms. Prepregnancy counseling should be undertaken to avoid pregnancy in patients with MS and valve area <1.5 cm^2, especially if <1.0 cm^2. Balloon valvuloplasty to reduce the risk during pregnancy should be performed even if asymptomatic. Balloon valvuloplasty should be performed after the 20th week of pregnancy in patients refractory to medical therapy, NYHA class III–IV symptoms and those with pulmonary systolic pressures >50 mm Hg.[40] Abdominal shielding reduces radiation exposure. Various studies of balloon valvuloplasty conducted in India in pregnant women reported good immediate and long-term results with immediate success of 91–98%.[41-43] In a metanalysis[44] of balloon valvuloplasty during pregnancy from low- and middle-income countries, valvuloplasty was successful in 93.6% of patients. MR was the most common cardiac complication reported in 12.7% of patients. Based on these studies, percutaneous valvuloplasty is an acceptable option to optimize outcomes in pregnant women with MS.

AORTIC STENOSIS

Aortic stenosis is mostly congenital and rarely rheumatic in developed countries. In an Indian study,[34,35] AS was seen in 9.8% of pregnancies and was mostly rheumatic. In pregnant women with AS due to increased stroke volume, there is an increase in transvalvular velocity and pressure gradient, and hence AS severity should be assessed by valve area and dimensionless index. In ROPAC registry,[45] 20.8% were hospitalized due to cardiac reasons. This was more common in severe AS than moderate AS (35.3% vs. 12.9%) and was even higher in symptomatic severe AS (42.1%). There was a higher incidence of preterm birth (44%), intrauterine growth restriction (IUGR) (22%), and lower birth weight.[39] Preconception counseling should not deter women from becoming pregnant in moderate AS. In symptomatic patients with severe AS, pregnancy is contraindicated. Most patients can be managed medically and balloon valvuloplasty is performed when medical therapy fails.[45]

MITRAL AND AORTIC REGURGITATION

Regurgitant lesions are tolerated well in pregnancy, but a surprisingly high rate (23%) of heart failure in severe MR was noted in ROPAC registry.[38] Most patients can be managed medically with no untoward consequences.

PROSTHETIC VALVES

Hemodynamic changes during pregnancy in women with prosthetic valves increase transvalvular gradients by approximately 50% with valve area remaining constant.[46] Presence of MHV is associated with maternal mortality and mortality and is classified as modified WHO risk category III.[36] In ROPAC registry, 58% of the patients with an MHV had a pregnancy free of serious adverse events compared with 79% of patients with a tissue heart valve.[47] Maternal mortality was 1.4%. It is controversial whether pregnancy accelerates bioprosthetic valve degeneration but long-term studies found no effect of pregnancy on bioprosthetic valve degeneration.[48] The risk of valve thrombosis during pregnancy is approximately 5%, the higher risk attributed to a hypercoagulable state.

Warfarin has the lowest risk of thromboembolic complications and this should be balanced against the risk of warfarin embryopathy.[49] Warfarin embryopathy occurs with the use of warfarin between 6th and 12th weeks of pregnancy with an incidence of 7.4% and is dose dependent. Women taking <5 mg/day had no embryopathy with a 15% fetal complication rate.[50] Low-molecular-weight heparin (LMWH) is safe for the fetus[49] as it does not cross the placenta but should be dosed to a target anti-Xa level of 0.8–1.2 U/mL, 4–6 hours after dose. Incorrect dosing of LMWH leads to valve thrombosis. Unfractionated heparin (UFH) poses significant challenges in administration and is associated with a small risk of osteoporosis.

Because warfarin is the best form of anticoagulation, 2021 ACC/American Heart Association (AHA) guidelines[8] for the management of VHD recommend continuation of warfarin in all three trimesters if dose is <5 mg/day. If the warfarin dose is >5 mg/day and if monitoring of anti-Xa levels are available, the same guidelines recommend dose-adjusted LMWH for the first trimester followed by warfarin for the second and third trimesters. If anti-Xa monitoring is not available, continuous dose-adjusted UFH is recommended in the first trimester followed by warfarin for the second and third trimesters. Warfarin should be discontinued at least 1 week before delivery and switched to continuous intravenous (IV) UFH or dose-adjusted LMWH. Thirty six hours before delivery, all patients should be switched to continuous IV UFH, which should be stopped 4–6 hours before delivery.[8] Valve thrombosis during pregnancy is life-threatening and all pregnant women with a prosthetic valve should be counseled and managed by the multidisciplinary team to optimize maternal and fetal outcomes.

CONCLUSION

Apart from pregnancy and associated valvular heart disease including prosthetic valves, a problem which is unique to females, there are definite differences in prevalence, presentations and outcomes in general between women and men. Despite so many social advances, women have been less represented in clinical studies and interventions. There have been indications to modify criteria for severity of valvular lesions based on gender. Similarly, outcome of a valvular intervention also has gender differences. Time has come to study the gender related impact on the management of valvular heart disease globally.

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CHAPTER 31

Women and Cardiomyopathy

Meenakshi Subbiah

ABSTRACT

Cardiomyopathies are a heterogeneous group of cardiac muscle abnormality with differences in prevalence, epidemiology, clinical pattern, response to treatment, and outcomes between men and women. Some cardiomyopathies are unique to females such as the peripartum cardiomyopathy (PPCM) and stress cardiomyopathy. Even among the other cardiomyopathies such as dilated cardiomyopathy and hypertrophic cardiomyopathy, gender-specific differences in treatment response and outcomes prevail. The major impact of gender differences is predominantly driven by the sex hormones and their influence on the body mechanisms. The cellular effects of sex hormones on the renin–angiotensin and aldosterone system, endothelial injury, vascular aging, and left ventricular remodeling predominantly drive these sex-specific differences. The psychological and cultural factors, reluctance in disease acceptance, resistance to device therapies, and everyday life approach may differ between men and women leading to difference in approach and prognostic outcomes of the disease pattern. Women are much under-represented in the majority of trials. This under-representation may be a reason for the diagnostic bias and underutilization of treatment. Understanding the gender differences and the influence of the sex on outcomes helps in better strategic planning of treatment and leads to better treatment outcomes in women with cardiomyopathy.

INTRODUCTION

Cardiomyopathy is a heterogeneous group of disorders in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease (CAD), hypertension, valvular heart disease, and congenital heart disease sufficient to cause the observed myocardial abnormality.[1] Cardiomyopathies may be either inherited or acquired and include various types such as dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and nonclassified cardiomyopathies. This heterogeneous group of muscle disorders leads to heart failure (HF), a constellation of signs and symptoms of fluid retention, and is associated with significant morbidity and mortality in both men and women.[2]

There are differences in epidemiology, pathophysiology, clinical presentation, and outcomes between men and women with cardiomyopathy. Some cardiomyopathies such as peripartum cardiomyopathy (PPCM) are specific to women with unique considerations. Cardiomyopathies such as stress cardiomyopathy, HCM, sarcoidosis, and amyloidosis have sex-specific differences in prevalence, treatment, and outcomes. The cellular effects of sex hormones on the renin–angiotensin and aldosterone system, endothelial injury, vascular aging, and left ventricular (LV) remodeling predominantly drive these sex-specific differences. The psychological and cultural factors, reluctance in disease acceptance, resistance to device therapies, and everyday life approach may differ between men and women leading to the difference in approach and prognostic outcomes of the disease pattern. The gender differences are also due to implicit bias leading to underdiagnosis, undertreatment, and under-representation in clinical trials. In this chapter, we will see the differences in epidemiology, pathophysiological patterns, drug response between men and women with cardiomyopathies, and the gender-specific cardiomyopathies unique to women.

GENDER-SPECIFIC DIFFERENCES IN HEART FAILURE

Heart failure is the predominant symptom of cardiomyopathy. It is classified based on ejection fraction (EF) into HF with reduced EF (<40%—HFrEF) and HF with

preserved EF (>50%—HFpEF). HF remains the leading cause of hospitalization and accounts for almost 8% of all cardiovascular deaths.[3] HF affects 2.6 million women and 3.4 million men in the United States.[4]

Heart Failure with Reduced Ejection Fraction

Epidemiology

Heart failure with reduced EF is described as HF with LVEF <40%. The lifetime risk of HFrEF is lower in women (5.8%) compared to men (10.6%).[5,6] Women are more likely to have nonischemic cardiomyopathy and men are more likely to have ischemic cardiomyopathy.[7] Women with HFrEF are older, less likely to have CAD, peripheral artery disease (PAD), and tobacco usage when compared to men. Women have higher levels of natriuretic peptides than men.[8,9] According to the HF trials PARADIGM-HF (Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with Angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and morbidity in Heart Failure) and ATMOSPHERE, women have a worse quality of life compared to men, despite lower mortality and no difference in HF hospitalization.[10]

Sex-based Differences in Medical Therapy

Medical therapy is the cornerstone of HF treatment. Medical therapy has been beneficial in reducing HF hospitalizations, improving quality of life, and reducing mortality and reverse LV remodeling.[11] The understanding of sex differences in response to medical therapy is based on limited data from retrospective and post hoc subgroup analysis of landmark HF clinical trials. The major limitation is under-representation of women in these clinical trials. Despite these limitations, the analysis clearly indicates that men and women do not benefit equally from HF medications.

No definitive benefit of angiotensin-converting enzyme (ACE) inhibitors was observed in women based on two large meta-analyses on ACE inhibitors.[12,13] A large observational study from Canada compared ACE inhibitors and angiotensin-receptor blockers (ARBs) in 10,223 women and 9,475 men with HFrEF and showed that women had better survival on ARB than on ACE inhibitors [adjusted hazard ratio (HR); 95% confidence interval (CI), 0.59–0.80; $p < 0.0001$] with no difference in survival for men [adjusted HR, 1.10 (95% CI, 0.95–1.30); $p = 0.21$].[14] In the PARADIGM-HF trial, which compared angiotensin receptor-neprilysin inhibitor (ARNI) to ACE inhibitors in symptomatic HFrEF patients, there was a reduction in the HF hospitalizations in patients taking ARNI.[15] Plasma renin levels are lower in women compared to men. The expression of angiotensin II type 2 receptor is on the X chromosome and estrogen stimulates increased angiotensin II type 2 receptor expression and activation. This leads to the enhanced inhibitory effect of ARBs in women than in men. This explains the increased efficacy of ARBs and subsequently ARNIs in women relative to ACE inhibitors.[16]

In the DIG (Digitalis Investigation Group) trial, with 1,519 women participants, the trial showed increased mortality and no significant reduction in HF hospitalizations in women with digitalis. The higher mortality was due to higher serum concentrations of digitalis despite similar doses, which was attributed to sex differences in pharmacokinetics and pharmacodynamics.[17] Some trials such as the V-HeFT (vasodilator heart failure trial I) not even included women when comparing prazosin, isosorbide, and hydralazine to placebo in patients with HF.[18] In the SHIFT (Systolic Heart Failure Treatment with I_f Inhibitor Ivabradine trial), 1,535 women participated and ivabradine reduced the combined endpoint of HF hospitalization and cardiovascular death in women, and had similar benefits in men.[19]

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are indicated in symptomatic HF (HFrEF) patients with or without diabetes mellitus. Both empagliflozin (EMPEROR-HF) trial with 893 women participants and dapagliflozin (DAPA-HF trial) with 1,109 women, showed reduction in the combined endpoint of cardiovascular death and HF hospitalization in women.[20,21] Estrogen in the form of hormone replacement therapy has shown significant survival benefit in postmenopausal women with symptomatic HF. The benefits are predominantly driven by the reduced activation of neurohormonal systems and suppression of the sympathetic activity.[22]

Sex-based Differences in Devices and Interventions

Implantable cardioverter defibrillators (ICDs) are recommended for all HF patients with New York Heart Association (NYHA) classes II–III with LVEF <30% to prevent sudden cardiac death.[2] There was underutilization of ICD therapy in eligible women compared to men. One meta-analysis based on the primary prevention ICD trials (DEFINITE, SCD-HeFT, DINAMIT, MUSTT, and MADIT-II) included 934 women and showed no survival benefit for women with ICD.[23] Women with an ICD for primary prevention had fewer appropriate ICD shocks when compared with men (8% vs. 14%) in the EU-CERT-ICD project.[24] The differences in the benefit of ICD for primary prevention between men and women are based on the sex differences in the mode of death with 32% lower risk of sudden cardiac death in women compared to men.[25] Based on the National Cardiovascular Data Registry, women with ICD for primary prevention were more likely to have 30- and 90-day adverse events such as bleeding and mechanical complications [adjusted odds ratio (aOR) 1.39 (95% CI 1.26–1.53); $p < 0.001$] and hospital readmissions within 6 months [aOR 1.32 (95% CI 1.23–1.42); $p < 0.001$] compared to men. Women also had a higher likelihood of major complications such as lead dislodgement.[26,27]

Cardiac resynchronization therapy (CRT) is indicated for patients with HF with LVEF <35% and NYHA classes II–IV, sinus rhythm, and left bundle branch block (LBBB) with QRS duration >150 ms (class I indication) and may be helpful in those with LBBB with wide QRS 120–149 ms, non-LBBB with QRS >150 ms, or those with significant pacemaker dependency.[2] Eligible women were less likely to get the benefits of CRT in spite of indications. Women are more likely than men to benefit from CRT with improved quality of life, ventricular remodeling, HF hospitalizations, and mortality.[28] A meta-analysis of three CRT trials (REVERSE, MADIT-CRT, RAFT) also demonstrated benefits of CRT with narrower QRS complex—LBBB with QRS 130–149 ms.[29]

Baroreflex activation therapy (BAT) with an electrode attached to the bifurcation of the carotid artery reduces the sympathetic activity and increases the parasympathetic activity resulting in reduction in blood pressure and improved venous and arterial compliance. This therapy has been deemed safe and effective in patients with HFrEF and shown improvements in quality of life, in 6-minute walk test, in NYHA functional class, and in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels when compared to guideline-directed medical therapy (GDMT) based on the BeAT-HF (Baroreflex Activation Therapy for HF) trial.[30,31]

Advanced HF refers to patients with symptomatic severe HF despite optimal GDMT and the therapeutic options are limited to mechanical circulatory devices and transplantation. LV assist devices are used as a bridge to transplantation in advanced HF patients and bridge to destination in patients not suitable for a heart transplant. Women with cardiogenic shock had higher mortality compared to men and they were less likely to receive temporary mechanical support devices for cardiogenic shock.[32] Sex differences in adverse events have been demonstrated with durable LV assist devices, based on an international database that included 2,066 women with continuous-flow LV assist devices. Women had a higher risk of mortality during the first 4 months after LV assist devices compared to men and the cause of death was predominantly neurological complications.[33]

According to the International Society for Heart and Lung Transplantation (ISHLT) among the total heart transplantation during 2002–2008, 77% were male recipients.[34] Women were less likely to undergo transplantation and the mortality was higher while waiting for transplantation compared to men.[35] Current criteria for matching a heart based on body weight, blood type, and tissue typing account for the lower rates of transplantation in females. Parous women tend to have elevated panel reactive antibodies, which further decrease their chances of receiving a heart transplant.[34] Women had an increased risk of death within 1-year post-transplantation according to ISHLT. Women with body surface area (BSA) <1.5 and >1.5 m^2 with small thoracic cavities were unable to get ventricular assist devices due to anatomical constraints.[36] With the advent of newer technologies and smaller continuous flow devices, it is hoped that the benefit of mechanical circulatory support may be extended to many women.

Heart Failure with Preserved Ejection Fraction

Epidemiology and Pathophysiology

Heart failure with preserved EF is more prevalent in women than in men at any given age.[37] From a larger analysis of pooled data from FHS (Framingham Heart Study), PREVEND (Prevention of Renal and Vascular End-stage Disease), and CHS (Cardiovascular Health Study), independent predictors of HFpEF are older age, higher systolic blood pressure, increased body mass index, smoking, history of atrial fibrillation, antihypertensive treatment, and previous myocardial infarction.[37,38] Female sex was not a predictor of HFpEF, but the predominance of women was mostly associated with aging.

Another important risk factor contributing to gender-specific differences for HFpEF is obesity. Each 1 standard deviation (SD) increase in body mass index was associated with 34% increase in the incident HFpEF compared to 18% for HFrEF, and this association was more apparent in women than in men. Similarly, waist circumference was associated with HFpEF but not HFrEF in women but both HF subtypes in men. An inflammatory metabolic hypothesis has been proposed. The expanded epicardial adipose tissue mass, microvascular dysfunction, and altered activity of adipocyte-associated inflammatory mediators predispose women to greater risk of HFpEF in the presence of systemic inflammatory conditions such as obesity, diabetes, and the metabolic syndrome.[39]

Women have higher systolic and diastolic elastance than men, which increases as age advances. Greater concentric remodeling, heightened load-induced impairment of LV relaxation, and coronary microvascular dysfunction all contribute to the pathophysiology of HFpEF in women at older ages than in men.[40,41] Pulmonary artery pressures are higher in women, and they are overrepresented with combined precapillary–postcapillary hypertension among HFpEF patients.[42] Sex hormones play an important role in cardiac aging and contribute to the development of HFpEF. Estrogens have been very cardioprotective, and loss of estrogens after menopause leads to the activation of the renin–angiotensin–aldosterone system and coronary microvascular dysfunction due to its proangiogenic properties and abnormal diastolic function, all contributing to higher prevalence of HFpEF in women.[43,44]

Gender Differences in Medical Management

Notable differences in the treatment response of women have been seen in the trials. Post hoc analysis of the aldosterone antagonist therapy for adults with HF and preserved systolic function (TOPCAT) trial analyzed 882 (49.9%) women among the 1,757 participants. Women were older with less comorbidities than men. There were no significant sex differences in the primary outcomes of a composite of cardiovascular mortality, aborted cardiac arrest, or HF hospitalization. But there was a significant reduction in all-cause mortality associated with spironolactone in women but not in men.[45]

In PARAGON HF trial, ARNIs showed a reduction in the primary outcome predominantly driven by the reduction in HF hospitalization rather than mortality and were significant in women with an EF of 45–60%. The greater benefit with ARNI could be explained by the relative natriuretic peptide deficit in women translating to a greater benefit.[46] In a subgroup analysis of empagliflozin outcome trial in patients with chronic HFpEF (EMPEROR PRESERVED), empagliflozin 10 mg/day reduced the combined risk of cardiovascular death or hospitalization for HF more so pronounced in women.[47]

Specific Cardiomyopathies for Women

Some cardiomyopathies are quite peculiar and unique to women such as PPCM and stress (Takotsubo) cardiomyopathy, which need discussion here. Even across the spectrum of DCM and HCM, some features are unique for women. Data on some of the cardiomyopathies such as PPCM and cardiac sarcoidosis are sparse.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy is the leading cause of HF and mortality in pregnancy and postpartum.[48] The 2010 Heart Failure Association of the European Society of Cardiology Working Group definition of PPCM is "an idiopathic cardiomyopathy presenting with heart failure secondary to LV systolic dysfunction toward the end of pregnancy or in the months following delivery, where no other cause of heart failure is found." The diagnostic criteria include an LVEF <45% with or without LV dilatation.[49] The incidence of PPCM varies from 1 in 100 live births in Nigeria to 1 in 20,000 live births in Japan approximately.[50] PPCM is associated with multiple risk factors and the most commonly associated factors include black race, advanced maternal age, gestational hypertension, preeclampsia, multifetal pregnancies, and possibly diabetes and anemia. Familial clustering and 6% co-occurrence of idiopathic DCM suggest the sharing of genetic profile with familial nonischemic DCM in a minority of the patients.[51]

The etiology of PPCM is multifactorial and none of them is proven. The suggested mechanisms included nutritional deficiencies, autoimmune processes, and viral myocarditis, and the hemodynamic stress of pregnancy has also been postulated as a potential etiology. Two vascular-hormonal animal models of pregnancy-associated cardiomyopathy have been suggested as novel mechanisms in humans. The first model was a STAT3 knockout mouse in which oxidative stress led to cleavage of the nursing hormone, prolactin. The 16-kDa prolactin fragment had vascular and pro-apoptotic properties, which led to vascular and myocardial dysfunction, and the effects were reversed by treatment with bromocriptine, a suppressor of prolactin secretion.[52] A second vascular hormonal mouse model of PPCM was developed by cardiac-specific genetic deletion of proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), leading to vasculo-toxicity by activation of the 16-kDa prolactin fragment and decreased expression of the pro-angiogenic vascular endothelial growth factor (VEGF). The cardiomyopathy was partly reversed with bromocriptine in this model and required the addition of VEGF for complete recovery.[53]

Majority of the women present with signs and symptoms of HF and get diagnosed in the first month after delivery. The delay in diagnosis may be due to the overlap of signs and symptoms of HF with those of normal pregnancy. The most common presenting symptoms are shortness of breath, fatigue, orthopnea, paroxysmal nocturnal dyspnea, and chest pain. Tachypnea, tachycardia, elevated jugular venous pulse, pulmonary rales, and peripheral edema are the typical signs. Cardiogenic shock, pulmonary edema, thromboembolic complications, and severe arrhythmias are the presenting features in a minority of patients.

Echocardiogram is the diagnostic test in patients with suspected symptoms of PPCM. Echocardiogram shows LV and right ventricular (RV) dilatation, LVEF <45%, RV dysfunction, biatrial enlargement, functional mitral and tricuspid regurgitation, and pulmonary hypertension. LV thrombus has been identified in the initial echocardiogram in as many as 10–17% of the patients with PPCM and 5–9% of women present with thromboembolic complications.[54,55] NT-proBNP levels are grossly elevated in PPCM. Cardiac magnetic resonance imaging (MRI) is useful in the accurate assessment of LVEF and RV–LV dilatation. Among the various prognostic factors studied, LVEF at the time of presentation is the very major factor deciding on the long-term recovery and outcomes. The other prognostic factors include LV and RV dilatation, LV thrombus, RV dysfunction, concomitant preeclampsia, and obesity. Recovery frequently occurs within the first 3–6 months. Delayed recovery is also reported as late as 2 years following the diagnosis.[56]

Management of PPCM is like any HF, except for the modification of drugs to ensure fetal safety during pregnancy. Almost all HF medications are compatible with breast-feeding. Anticoagulation is suggested in the setting of low EF in PPCM considering the increased thromboembolic manifestations and the hypercoagulable state of pregnancy and early postpartum. The threshold for starting anticoagulation is LVEF <30% according to the American Heart Association, and the European Society of Cardiology recommends an LVEF of 35%. Bromocriptine is a dopamine agonist and it inhibits the release of prolactin. Patients treated with bromocriptine 2.5 mg twice daily for 2 weeks followed by 2.5 mg daily for 6 weeks had greater improvement in LVEF at 6 months (27–58%; $p = 0.012$) than the control group (27–36%) and fewer experienced the composite end point defined as death, NYHA functional class III/IV, or LVEF <35% at 6 months compared with the control group.[57] Until more definitive data become available, bromocriptine should be considered experimental. The 2018 European Society of Cardiology guidelines include a weak recommendation (class IIb, level of evidence B) for the use of bromocriptine.[58] Therapeutic anticoagulation is recommended along with the use of bromocriptine due to its association with thrombotic complications.

In PPCM patients with hemodynamic instability despite ionotropic support, temporary mechanical circulatory support devices such as intra-aortic balloon pump, percutaneous ventricular assist devices, and extracorporeal membrane oxygenation may be considered. Hemodynamic instability despite medical therapy should prompt early delivery. Vaginal delivery should be the mode of delivery unless there are obstetric indications for cesarean section.[59] Fluid overload and pulmonary edema are anticipated in the immediate postpartum due to the removal of the caval compression by the fetus, autotransfusion from the uterine contractions, and increased venous return due to fluid mobilization and resorption into the vascular system.

The 2010 European statement on PPCM advised against breast-feeding based on the prolactin hypothesis.[49] However, women who breast-feed had higher rates of recovery based on a small study of patients enrolled online in the United States.[60] Breast-feeding was not associated with adverse outcomes, inflammatory markers, or persistent myocardial dysfunction. Most of the HF medications are safe during breast-feeding. The HF medications should be continued indefinitely with persistent LV dysfunction. After recovery of cardiac function, the duration of continuation of treatment is unknown. There may be subclinical LV dysfunction, which may be a reason for the continuation of HF medications. HF medications should be weaned in a stepwise fashion with frequent clinical assessment and echocardiographic monitoring every 3–6 months. LV

function should be reassessed after drug discontinuation by annual clinical and echocardiographic assessment. Patients with persistent myocardial dysfunction (LVEF <50%) are at a high risk of recurrent HF and mortality.

Based on these data, the 2018 European Society of Cardiology guidelines discouraged subsequent pregnancy if the LVEF is not >50–55%.[58] The risk associated with subsequent pregnancy depends primarily on the recovery of LV function and the prepregnancy LVEF is the strongest predictor of the outcomes.[61] The importance of contraception should be discussed both by the cardiologists and obstetrician at the time of discharge. The estrogen-containing contraceptives increase the thromboembolic complications and so progesterone-releasing subcutaneous implants and Mirena intrauterine devices are the safe and effective choices.[62]

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a genetic cardiomyopathy with a slight male predominance (55–65%). The autosomal dominant inheritance pattern of HCM should result in a balanced male/female ratio. This unexpected male predominance may be due to the underrecognition and diagnostic bias in women. The estimated prevalence of HCM is between 1:500 and 1:200.[63] Based on a cohort study investigating the differences among 969 patients with HCM in Italy and the United States, women were diagnosed at an older age compared to men. Women were more likely diagnosed after clinical manifestations, whereas men were diagnosed during routine medical examinations.

Women were more likely than men to have symptoms of exertional dyspnea, chest pain, and syncope with higher outflow gradients, worse diastolic function, and severe HF symptoms at presentation.[64] In the study by Rowin et al., 73% of the women had NYHA class II–IV symptoms at presentation (compared to 53% men).[65] Women were more likely to functionally decline or experience death from HF or stroke compared to men.[64] The Mayo Clinic study with 3,673 patients with HCM (45% women) treated over a 37-year period and followed up for a median of 10.9 years also showed similar results. There were no sex differences in the rate of ICD implantation, myectomy, or alcohol septal ablation. In the Mayo Clinic study, women underwent more frequent alcohol septal ablation compared to men and similar frequency of myectomy. Despite this, women had significantly higher mortality at 5 and 10 years even after adjusting for age, NYHA class III–IV symptoms, and comorbidities.[66] The sex differences in mortality and outcomes between the cohorts despite similar therapy may be attributed to the sex differences in disease phenotype or progression at the time of diagnosis and therapy. The diagnostic criterion of LV wall thickness of at least 15 mm for HCM does not account for BSA and may be the reason for underestimation of the disease severity in women. Compared with male patients, women with HCM had greater amounts of fibrosis at the cellular level contributing to the worse outcomes. Sex should be considered a determining variable for risk assessment at all levels of care of HCM patients from disease awareness to management.

Takotsubo Cardiomyopathy

Stress cardiomyopathy, also called Takotsubo cardiomyopathy, apical ballooning syndrome, and broken heart syndrome, refers to a transient and reversible cardiomyopathy in which LV dilatation and acute systolic HF occur typically following a physical or emotional stressor. Worldwide, it is more common in postmenopausal women (male to female ratio 9:1). In Japan, it is predominant in men, mostly after physical stress. Men were younger than women and were more likely to have severe pump failure or require mechanical circulatory support. The pathophysiology of Takotsubo cardiomyopathy is uncertain. The hypotheses include estrogen deficiency and a heightened autonomic system, which leads to sympathetic stimulation.[67] The surge in stress-related hormones contributes to apical ballooning through disruptions in the microvasculature or by myocardial toxicity.

CARDIAC AMYLOIDOSIS

Cardiac amyloidosis is an infiltrative myocardial disease due to deposition of the misfolded amyloid fibrils within the myocardium. The two most common types of cardiac amyloidosis are light-chain amyloidosis (AL) and transthyretin amyloid cardiomyopathy (ATTR-CM). Light-chain amyloidosis occurs due to secretion and overproduction of immunoglobulin light chains. Cardiac involvement occurs in 50–75% of AL amyloid cases.[68,69] AL amyloidosis occurs in the fifth to seventh decade and has a slight male preponderance. There is insufficient data regarding the treatment responsiveness and prognosis of AL cardiomyopathy in men and women. Transthyretin (ATTR) amyloidosis is caused by dissociation of the transthyretin (TTR) tetramer into monomers, which misfold and get deposited in the myocardium. ATTR-CM occurs due to the accumulation of wild-type (ATTR wt) or variant (ATTRv) TTR amyloid fibril deposition. The ATTR wild type being the most common form of cardiomyopathy leads to HFpEF.

Sex differences are more marked in the ATTR-CM wild type with 80–90% patients being men. Increased male prevalence among familial ATTR-CM (ATTRv) amyloidosis is associated with selected mutations including Leu111Met, lleu68Leu, Thr60Ala, and Val122lle, whereas these mutations were observed in only 30% of cases in women.[70] The recent analysis from the Transthyretin Amyloidosis Outcomes Survey (THAOS) registry postulated that the higher prevalence of ATTRv in men compared with women with transthyretin mutations might be due to the protection offered by the female sex hormones against the degree of myocardial involvement in ATTRv amyloidosis.

Women also had higher LVEF, lower interventricular septal thickness, and posterior wall thickness on presentation and were less likely to have an abnormal electrocardiogram (ECG). The THAOS study used LV wall thickness >12 mm to define the ATTRv cardiomyopathy which may partially account for the lower proportion of women (27.8%) in the THAOS registry.[71] Women may require a longer deposition period to reach this prespecified wall thickness measurement. Other genetic studies have shown sex-related differences. A study of women with type A fibrils had significantly lower median septal and posterior wall thicknesses and lower median LV mass compared to men, suggesting lower rates of cardiac infiltration. In another study involving Val122lle mutations, no sex differences were noted in HF severity markers including NYHA functional class, cardiac troponin levels, and mortality despite women being older

than men (76 vs. 69 years of age) suggesting slower disease progression in women compared with men. Based on the existing data, it remains unknown whether ATTR CM occurs predominantly in men or whether the true prevalence of the disease is underestimated.

CARDIAC SARCOIDOSIS

Sarcoidosis is an inflammatory granulomatous condition and tends to be more common in the black women and residents of northern latitude. Cardiac sarcoidosis has an evolving definition that typically involves either histological diagnosis on endomyocardial biopsy or a combination of clinical cardiac manifestations in the presence of biopsy-confirmed extracardiac sarcoidosis. Histopathological examination of the myocardium in sarcoidosis reveals noncaseating granulomas, multinucleated giant cells, and asteroid bodies. The emphasis on tissue diagnosis for diagnostic criteria is limited due to the patchy involvement of the myocardium. The prevalence of cardiac sarcoidosis has increased partly because of new diagnostic imaging modalities and better understanding of the disease. Prospective screening of patients with unexplained conduction abnormalities with fluorodeoxyglucose-positron emission tomography (FDG-PET) found that 34% of patients with atrioventricular block had cardiac sarcoidosis and there were no significant sex differences in those with cardiac sarcoidosis versus idiopathic atrioventricular block.[72]

Of the 110 patients with cardiac sarcoidosis in the Myocardial Inflammatory Diseases in Finland (MIDFIN) study, 71 had isolated cardiac sarcoidosis. Those with isolated cardiac sarcoidosis were more often women and had a higher frequency of LV dysfunction and septal wall motion abnormalities. Sex was not an independent predictor of outcomes in the Finnish cohort in spite of the differences in disease prevalence.[73]

The incidence of supraventricular tachycardia was comparable between men and women in patients with cardiac sarcoidosis.[74] In the United States National Survey, women constituted the significant majority of patients with documented sarcoidosis (n = 200 of 241, 67% women). Women had higher rates of atrial arrhythmias, lower rates of ventricular arrhythmias, and significantly higher in-hospital mortality compared with men (64% vs. 36%; $p < 0.0001$). Women also had lower rates of ICD, CRT with defibrillator (CRT-D), and endomyocardial biopsy compared with men.[75]

Left ventricular dysfunction is the strongest predictor of survival in patients with cardiac sarcoidosis.[76] Patients with cardiac sarcoidosis have worse prognosis in the form of sudden death and HF death than sarcoidosis patients without cardiac involvement. Data on sex differences in cardiac sarcoidosis outcomes are limited and may be attributed to the underutilization of devices (ICD, CRT-D) in women with cardiac sarcoidosis compared to men. Cardiac transplantation has been in the increasing trend for cardiac sarcoidosis and there has been limited data on the comparison of outcomes between men and women post-transplantation with most centers using more immunotherapy to prevent reoccurrence of the disease.

CONCLUSION

Understanding the gender differences in etiology, pathophysiology, and outcomes in cardiomyopathy patients helps in better management and prognostication of women with cardiomyopathy. In everyday clinical practice, gender medicine has progressively gained in importance for the evaluation of patients with cardiovascular disease and for cardiovascular disease prevention and is predominantly driven by the effects of sex hormones. Women should be included in equal numbers in the trials. Adequate representation of women in major trials may give better insights into the disease pattern, diagnosis, and outcomes. Modern medicine nowadays is moving from disease-specific medicine to personalized medicine. Gender medicine is a step toward more personalized medicine. Developing a more targeted risk stratification approach and a more personalized treatment in cardiomyopathy patients is pivotal to drive therapeutic regimens and device therapies, reduce inappropriate treatments, and optimize cost-effectiveness. This personalized approach leads to a better understanding of the treatment outcomes and proper utilization of the available treatment modalities in caring for women with cardiomyopathies.

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CHAPTER 32

Meditation and Cardiac Health

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ABSTRACT

Despite the advances in prevention of atherosclerosis, cardiovascular disease (CVD) remains number one killer across the globe. There has been a search of novel and inexpensive interventions which could potentially be used in primary and secondary prevention of CVD. Yoga and meditation since long has been claimed to be useful in this regard. Present review discusses the scientific data for meditation in primary and secondary prevention of CVD.

INTRODUCTION

Despite advances in the treatment of cardiovascular diseases (CVDs), 27% of deaths due to noncommunicable diseases (NCDs) are contributed by CVD in India, and 45% of CVD deaths occur among 40–69 years age group.[1] According to the global burden of the disease study, the age-standardized CVD death rate is much higher in India (272/100,000) than the global average (235/100,000).[2] Hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, physical inactivity, unhealthy diet, and psychosocial stress are the common risk factors for CVD.

In recent years, the use of complementary therapies has emerged rapidly in various NCD. For example, one-fifth of the patients with NCD practice mind–body therapies as per a recent study in North India.[3] The most common reasons for seeking complementary treatment are higher treatment cost and side effect of modern medicine. In fact, considering the risk factors associated with CVD, mind–body therapies such as meditation play an adjunctive role in the modern medical treatment. For example, most of the risk factors of CVD can be modified through mind–body therapies such as lifestyle and meditation. Apart from the utility of meditation to manage the risk factors of CVD, research regarding the utility of meditation on secondary and tertiary prevention of CVD is also on the rise.

In this chapter, we have tried to collate the evidence available for the utility of various meditation practices for CVD, including the risk factors.

UNDERSTANDING MEDITATION

Meditation has been in existence since ancient times and dates back to 2,500–5,000 years.[4] It is good to understand the nomenclature related to meditation before we get into the details of meditation itself. Meditation is derived from a Latin word called "*mederi*," which means to heal. In Eastern philosophy, the term used is Yoga. There are no English equivalents for this Sanskrit term though the term meditation is commonly used as an alternative to Yoga.

Background Knowledge to Understand the Term Yoga

In Yoga philosophy, the universe is comprised of three important energies—*purusha* (*atma*), *prakriti* (*sthula prapancha*, i.e., the physical world), and *Ishwara* (*paramatma*, God, or *vishesha purusha* as per Maharishi Patanjali).[5] *Prakriti* is matter/material energy (which includes the human body as well), whereas *purusha* and *Ishwara* are spiritual energies. For the convenience of the readers, henceforth, we shall use the terms soul, supreme soul, and physical matter for *atma, paramatma,* and *sthula prapancha,* respectively.

Life in this universe is a beautiful interplay between soul and body (including all other physical matter). In this interplay, as long as the soul is aware that he is the master of his body including the senses, peace, love and joy naturally prevail in life. When soul is influenced by the attractions of physical matter,

especially the senses and body, search for peace, love and joy becomes an elusive and often a never-ending journey. In simple terms, Yoga is all about this journey of reexploring and regaining the sovereignty of soul by managing our mind (Yoga *chitta vritti nirodha*).[5]

From a practice point of view, Yoga has been defined as a process of concentration on an object of one's interest (though concentration itself is not Yoga/meditation). Though there are a variety of objects (body, breath, *guru, jyothi/deepa,* etc.), that are prescribed for concentration, the classical object of focusing by exponents of Yoga like Maharishi Patanjali is supreme soul.[5] Supreme soul is devoid of any effects of either positive or negative (and conceptualized as a Divine light). In this context, classically, Yoga is defined as a link (conscious loveful remembrance) between soul and supreme soul. Here, the conscious communion with supreme soul practically means imbibing his unlimited qualities of peace, love, and joy in our daily routine life.[6] It is in this context that the Ahirbudhnya Upanishad defines Yoga as "*Samyoga yoga ityukto jivatma paramatmanah*" (roughly translated as "Yoga is the union between individual human soul and the supreme soul").[7] In fact, the term Yoga comes from the Sanskrit root "*yuj*" which means communion. Not only the ancient *Upanishads* but also some of the neo-spiritual movements (like the Brahmakumaris spiritual organization) defined Yoga as a loving and intellectual communion of soul with supreme soul.[6] It is important to note here that the term supreme soul is used beyond the context of any religion in a secular manner. As explained in many of the yogic or spiritual text, supreme soul is conceptualized as a divine light. This concept of a higher being/consciousness in the form of divine light is utilized even by practitioners who do not believe in God (e.g., Buddhist meditation).

It is important to understand that although majority of the people who practice *asana* and *pranayama* identify them with Yoga, it is really not so. *Yogasana* and *pranayama* are important tools that may be used to aid the process of Yoga, but they are not Yoga by themselves.[8] They are considered as limbs of Yoga as per *Patanjali yoga sutras*. This is not to disregard the health benefits of *asana* and *pranayama* but to emphasize a proper understanding of Yoga as it is. Similarly, other terms such as *dharana, dhyana,* and *samadhi* are also defined as different limbs of Yoga (such as *asana* and *pranayama*). Henceforth for readers' convenience, we shall use the term meditation, equivalent to Yoga in its classical meaning.

Types of Meditation

Though there are variety of meditation and traditions, the essence of any type of meditation is focusing on an object to gain mastery over the wandering mind. The object of focus can be varied as detailed earlier. Some of the commonly used objects in practice are candlelight or *diya*, breath, thoughts, feelings, or a higher being who is considered as divine and elevated, including supreme soul.

In simple terms, meditation is focusing one's attention on an object of interest, clearing the unintended thoughts, decluttering the mind, and connecting with the supreme soul. In essence, this process of meditation involves two important tasks: (1) Holding the attention on the object of focus and (2) being a detached observer for any other distractions (own past negative memories, negative affect of recent happenings, external distractions, or any other unintended thoughts, feelings and memories, etc.). Accordingly, meditation has been broadly classified into two types: (1) Focused attention (FA) and (2) open monitoring (OM). Roughly, these types may be compared to *dharana* and *dhyana* mentioned in yogic scripture. Apart from these two types which are based on the mental processing in meditation, there are many other types that are mentioned in literature (automatic self-transcending type of meditation, loving-kindness meditation, compassion meditation, etc.).[9] But for practical purpose, FA and OM type is suffice to explain in most of the schools of meditation.

Focused attention type involves focusing the attention on a particular object (e.g., a positive thought, chanting a *mantra*, or visualizing pleasant image) of interest. OM involves observing all the happenings of the mind and body as a detached observer with a sense of self-distancing attitude. As one masters any one of the above types of meditation, it automatically enables one to master the other type as well. Hence for an experienced meditator, there is no distinction as focused awareness or OM can happen back and forth at ones will. As one gains mastery in meditation, one goes beyond these classifications (FA, OM, etc.) and gets absorbed into the experience with dissolution of self-ego boundary leading to the expansion of consciousness and connection with the supreme soul.[6]

It is to be noted that, though meditation traditionally is taught to be done in a static sitting posture, but in practice it extends beyond that. For example, the positive experience one gets in sitting meditation naturally spills into daily routine life. In this context, at the beginning, meditation might be understood as a sitting practice, but as one progresses, it is a feeling of abundance and fulfillment through better connection with self and supreme.

MECHANISM OF HEART DISEASES AND RATIONALE FOR MEDITATION USE

Numerous risk factors are often responsible for triggering the chain of pathophysiological processes that underlie the clinical continuum of CVD manifesting with various symptoms.[10]

Risk factors such as elevated cholesterol, hypertension, diabetes mellitus, smoking, and obesity induce oxidative stress, hence endothelial dysfunction leading to target organ damage. The target organ damage is preceded by numerous mediating events, including vasoactive mediators, inflammatory response, and vascular remodeling **(Fig. 1)**. Interrupting the chain of events anywhere between the origin (risk factors) and the end (end-stage heart disease) would be beneficial in enhancing the cardiac health.

In the pathophysiology of heart disease, psychological stress and negative affect play a major role from the beginning to end in various ways.[11] For example, most of the risk factors causing cardiac problems are causally associated with psychological stress and negative affect. Even after the development of heart disease, comorbid mental health problems such as depression and anxiety add to the existing disease burden, and the pathological process becomes more vicious—stress and mental health problems leading to heart disease and vice versa.

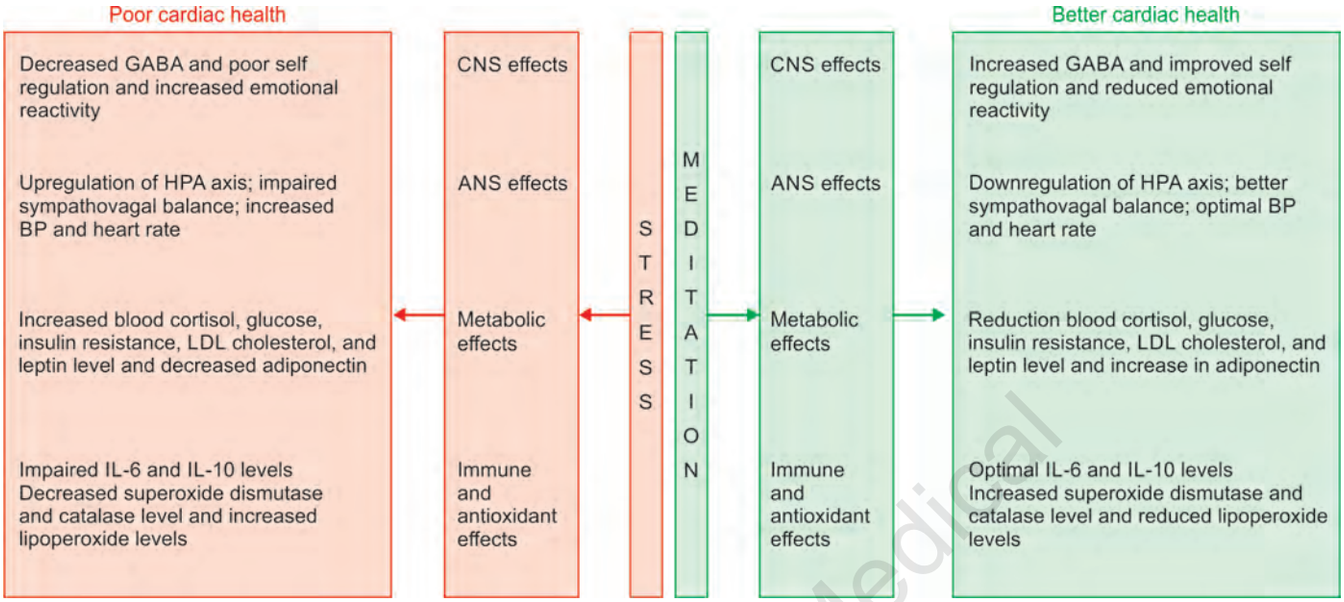

FIG. 1: Rationale for the use of meditation in cardiac diseases.

(ANS: autonomic nervous system; BP: blood pressure; CNS: central nervous system; GABA: gamma-aminobutyric acid; HPA: hypothalamic–pituitary–adrenal; IL: interleukin; LDL: low-density lipoprotein)

Considering the nature of pathophysiology with psychological stress as one of the culprits in the evolution of heart disease, meditation that combats stress efficiently, is well placed as a complementary therapy at various levels in the development of CVD. Psychological stress and the ensuing autonomic imbalance are the roots at which meditation intervenes, and the resulting cascade of events interrupts the pathophysiology of CVD at multiple levels.

Meditation mainly acts on the autonomic nervous system (ANS), especially the parasympathetic nervous system through vagus nerve and restores the sympathovagal balance.[12] Excess sympathetic drive is downregulated, and parasympathetic drive is increased through the process of meditation. It has twofold effects—*behaviorally* it reduces the perceived stress and *physiologically* it reduces the workload of the heart through optimal heart rate, blood pressure (BP), heart rate variability (HRV), and other inflammatory mediators. This twofold psychophysiological effect improves the metabolic profile (insulin resistance, high cholesterol, glucose tolerance, etc.), and hence combats the risk factors (oxidative stress, endothelial dysfunction, and deranged coagulation profile) leading to enhancement of cardiac health.

Apart from its effect on the ANS, meditation directly affects some of the cortical and subcortical regions of the brain involved in self and emotion regulation (which in turn influences the cardiac functioning). This could be one of the possible reasons for reduction in perceived stress with meditation intervention. Hence, meditation works through both bottom-up (through vagal nerve stimulation) and top-down (acting on the prefrontal cortex and the downstream regions) mechanisms in regulating the emotions and also in the functioning of various organ systems, including heart.

ROLE OF MEDITATION IN DIFFERENT DISORDERS INCLUDING RISK FACTORS

Meditation and Cardiovascular Risk Factors

Stress and Negative Affect

Stressful life events, including chronic stressors and high levels of perceived stress, are strongly correlated with cardiac diseases. One meta-analysis suggested that high perceived stress is associated with 27% increase in risk of coronary heart disease (CHD),[11,13] which is equivalent to 50 mg/dL increase in low-density lipoprotein (LDL), a 2.7/1.4 mm Hg increase in BP, or five more cigarettes per day. Even stressful experiences during childhood times also have a serious impact on cardiovascular health through elevated inflammatory markers and metabolic risk factors in later life.[14]

Negative effects, especially anger and hostility, have been linked to an enhanced risk of CHD. A systematic review of observational studies suggests that there is a greater risk of acute coronary syndrome, stroke, and ventricular arrhythmia in the 2 hours following outburst of anger.[15] Another meta-analysis of prospective studies reported increased incidence of CHD due to negative affect not only in healthy populations but also increase in the recurrent events in patients with existing CHD.[16]

Meditation for Managing Stress and Negative Affect

Meditation is one of the commonly used mind–body therapies for managing stress. In simple terms, the effect of meditation on stress is explained by relaxation response proposed by Benson

and colleagues in the 1970s. Meditation causes a myriad of effects which is just opposite to the effects that stress causes at a psychological and physiological level. For example, stress increases the sympathetic nervous system activity, prolongs the hypothalamic–pituitary–adrenal (HPA) axis response to stress and decreases the gamma-aminobutyric acid (GABA) activity, whereas mind–body practices such as meditation do the opposite. Studies that had shown better sympathovagal balance through enhanced HRV, better skin conductance, reduced cortisol, and improved GABA activity among meditators support the above-mentioned destressing effects of meditation and related mind–body practices.[17,18] These results have been favorably applied in clinical conditions as well (such as cardiovascular disorders, anxiety, depression, and epilepsy).

- From a behavioral neuroscience perspective, meditation positively impacts the cognitive and affective mechanisms through enhanced emotion awareness, altered emotion reactivity, cognitive reappraisal (including self-referential thinking), and altered reward processing.[19] Three important neuronal networks which are of relevance in this context are the central executive network (CEN), the salience network (SN), and the default mode network (DMN).[19] The CEN comprises nodes in the prefrontal cortex and parietal cortex. It is involved in the top-down regulation of attention. The SN involves dorsal anterior cingulate cortex (ACC), amygdala, anterior insula, and dopaminergic midbrain regions. The SN helps in preferentially focusing on the most salient stimuli compared to other stimuli. DMN spreads across the midline cortical region with posterior cingulate cortex and medial prefrontal cortex as two major hubs. DMN is involved in processing self-related information. In this context, it is interesting to note the following findings from a recent meta-analysis[20] which included 78 meditation studies with functional neuroimaging: The insular cortex, especially the anterior insula which is involved in interoception (monitoring and conscious awareness of internal body states),[21,22] empathy,[23] and metacognition,[24] is activated across meditation types.[20]
- In both FA and OM types of meditation, significant activations are reported in the dorsal ACC. The dorsal ACC is one of the key players in regulating emotion and attention and monitoring performance.
- The frontopolar/rostrolateral prefrontal cortex showed a large but subthreshold activation in OM type of meditation. But an earlier morphometric study by Lazar et al.[25] reported increased cortical thickness in prefrontal cortex among meditation practitioners across diverse schools of meditation.[26] Frontopolar cortex plays a key role in meta-awareness and metacognition.[24,27] It also plays an important role in switching/distributing attention between internal and external events[28] (for example driving is a task where the attention is focused externally, and at the same time being alert/not being drowsy needs an internal focus as well) as it is a key node of the frontoparietal control network.[29]

A recent review on meditation and neuroimaging studies reported decreased activity in DMN (reduced mind wandering) and increased connectivity between regions of DMN and CEN during rest suggestive of enhanced capacity to regulate self-referential ruminative thinking.[30-32]

Apart from reducing psychological stress, meditation programs also enhance well-being by reducing the negative affect. A recent meta-analysis by Goyal et al.[33] suggests that clinical practitioners should be open to discuss meditation programs with patients for its utility on reducing stress and negative affect; however, more rigorous studies need to be done from research design perspective.

Meditation and Hypertension

Hypertension is one of the important risk factors for CVD. Depending on the stage of hypertension, the mean odds of developing CVD range from 2.0 to 3.6.[34] Complementary therapies, including meditation, are recommended as a supportive and adjunctive modality for hypertension.[35] It is useful especially in early stages of hypertension to avoid or delay the use of medications in clinically appropriate situations.

The first randomized controlled trial (RCT) using meditation intervention among patients with hypertension was conducted in 1975 with 40 subjects (20 in treatment group and 20 in control group)[36] and demonstrated a significant reduction in systolic and diastolic BP following meditation intervention. The medication requirement was also lesser in the meditation group than in the control group. Since then, multiple studies have been conducted using meditation. Various types of meditations have been studied, with transcendental meditation (TM) and mindfulness-based meditation being the most studied ones. The findings of all these studies (12 RCTs—all TM—as per a meta-analysis in 2015[37] and 6 RCTs—all mindfulness-based meditation—as per another meta-analysis in 2021)[38] show that, on an average, meditation intervention lowers the BP by 4–5/2–3 mm Hg (systolic/diastolic) in patients with hypertension compared to control participants. The study duration varied from 2 to 60 months (mean 4 months). A review[39] done exclusively on TM among patients with hypertension analyzed eight meta-analyses and reported a mean fall in BP of 4/2 mm Hg (systolic/diastolic). Another meta-analysis[40] that analyzed 19 studies (studies grouped as transcendental-type meditation intervention and non-TM type of intervention) found similar results for transcendental-type meditation with ambulatory BP measurements. The plausible mechanism by which meditation might work in reducing the BP is shown in **Figure 2**.

Meditation and Metabolic Syndrome

Metabolic syndrome is a complex interrelated metabolic abnormality characterized by hypertension, dyslipidemia, elevated fasting blood glucose, and abdominal obesity. Metabolic syndrome is a risk factor for diabetes mellitus and CVD.[41,42]

Currently, *yogasana*-based mind–body therapies have been widely studied in the context of metabolic syndrome. Only two studies with meditation intervention are available.[43,44] In the two studies that included meditation intervention, one with 103 CHD patients showed significant improvement in insulin resistance, BP, and glucose tolerance with TM intervention.[43] The other study showed significant improvement in waist circumference, blood glucose levels, BP, triglycerides, and high-density lipoprotein (HDL) cholesterol level.[44]

Another meta-analysis which included predominantly yogasana-based interventions[45] analyzed 26 uncontrolled

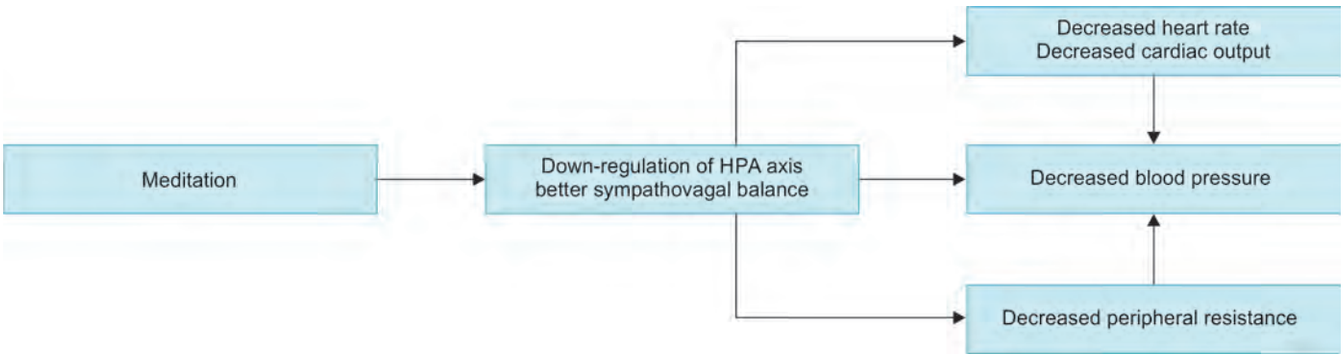

FIG. 2: Effect of meditation on blood pressure.
(HPA: hypothalamic–pituitary–adrenal)

clinical trials, 21 nonrandomized clinical trials, and 22 RCTs and reported beneficial changes in several insulin resistance syndrome (IRS) related risk factors for CVD. It included glucose tolerance and insulin sensitivity, lipid profiles, anthropometric characteristics, BP, oxidative stress, coagulation profiles, sympathetic activation, and cardiovagal function.

A recent meta-analysis (with yogasana-based interventions) synthesized results from 12 RCTs and 2 non-RCTs with prediabetes subjects.[46] The reported results were improvements in BP, fasting blood glucose, total cholesterol, and triglyceride levels compared to controls.

Though most of the studies currently available are yogasana-based studies, considering the key role of stress in the development of metabolic syndrome, relaxation response induced by meditation practices might be therapeutically useful. This is yet to be studied in detail.

Meditation for Cardiovascular Diseases

Meditation and Coronary Heart Disease

Coronary heart disease remains a major cause of death, especially in low- and middle-income countries. Despite the advances in care, it is still responsible for a huge burden on the healthcare system.[47] The role of complementary therapies, such as meditation, including lifestyle modification, has been increasingly realized lately. One of the landmark studies which drew attention of clinicians toward lifestyle modification was Dean Ornish's lifestyle modification program (which also included meditation) for regression of CHD.[48-50] Since then, numerous studies have been published demonstrating the beneficial effects of meditation on CHD.

In a meta-analysis by Linden et al.,[51] the effect of psychosocial interventions, including meditation, was assessed among CHD patients. Linden et al. reported enhanced reduction in all risk factors that worsen CHD in the psychosocial intervention group. In the control group, there was greater mortality and adverse cardiovascular events during the first 2 years of follow-up. The adjusted odds ratio was 1.70 for mortality [95% confidence interval (CI) 1.09–2.64]. However, in another meta-analysis by Younge et al. in 2015,[52] which included subjects of various cardiac diseases including CHD, many of the outcomes assessed improved significantly in the meditation group compared to control group.

Two long-term studies with CHD patients deserve a mention. The first one is a non-RCT by Gupta et al.[53] (Mount Abu Open Heart Trial) which recruited CHD patients with angiographically documented stable coronary artery disease (>50% of stenosis in at least one major epicardial artery). Subjects in the experimental intervention group were taught Raja yoga meditation-based lifestyle, including diet modification and physical exercise. Compared to the control group, the Raja yoga intervention group showed significant reduction in coronary stenosis and cardiac events. There was significant reduction in other risk factors of CHD as well. In this 6.48 years follow-up study, results were better with more adherence to the intervention. Regression of coronary artery stenosis was observed mostly in the compliant subjects. In the second study, a RCT in 201 African men and women CHD patients by Schneider et al.,[54] TM significantly reduced the all-cause mortality including myocardial infarction (MI) and stroke, which were the primary endpoints. There was also 48% risk reduction in the aforesaid primary endpoint at 5.4 year follow-up.

Six studies have also evaluated the impact of meditation on atherosclerosis.[50,53,55-58] The subjects in these studies included healthy older adults and patients with hypertension and CHD. Five of these studies evaluated atherosclerosis in clinical subjects (CHD and hypertension), and one study was conducted in healthy elderly adults. In one of the studies (RCT)[56] conducted among 138 subjects with hypertension, subjects who were given TM along with other lifestyle modifications showed significant reduction in carotid intimal thickness (B-mode ultrasonography) compared to the control group. Other studies,[50,53,55,58] which used meditation as a part of lifestyle modification programs in patients with CHD and hypertension assessed coronary artery atherosclerosis by quantitative coronary angiography and ankle brachial indices. All of them showed statistically significant regression in atherosclerosis as compared to control group. Another study conducted in healthy elderly (>65 years), interventions with diet, exercise, and vitamin treatment with and without TM showed significant reduction in carotid intimal thickness in the meditation group compared to the nonmeditation group.[57]

Besides atherosclerosis, other mediating pathophysiological factors such as endothelial dysfunction and inducible myocardial ischemia have also been studied. Currently, only

three studies[43,59,60] have examined endothelial dysfunction with meditation intervention. Though there is improvement in the endothelial function, none of them were significantly different from control group. There are no recent studies which had evaluated the effect of meditation on inducible myocardial ischemia. However, two previous studies (conducted in the 1980s and 1990s)[49,61] have reported favorable outcomes (increased exercise duration, maximal workload, delay in onset of ST depression, and regional wall motion abnormality).

In a recent study by Kiran et al.,[62] CHD patients posted for coronary bypass artery surgery were randomized to Raja yoga meditation group or usual treatment to assess the effect of meditation on anxiety and serum cortisol. Patients in the Raja yoga meditation group had shown significant reduction in anxiety postoperatively (day 4) with a concomitant fall in serum cortisol compared to the control group.

Meditation and Congestive Heart Failure

Heart failure, sometimes called congestive heart failure (CHF), happens when the heart muscle becomes too weak or stiff to fill and pump the blood. Meditation might improve symptoms of cardiac failure independently or by working on the causes of CHF. Some of the studies have explored the role of meditation in CHF.

One study assessed 23 subjects admitted for heart failure symptoms with TM or health education in an RCT. Subjects in the TM group showed significant improvement in 6-minute walk test, depression scores, and quality of life over 6-month follow-up period. The number of hospitalizations was also significantly lesser in the meditation group.[63] In another RCT using body scan meditation as an intervention, patients with CHF showed improved quality of life scores, better exercise performance, and reduction in plasma norepinephrine.[64] Two more studies from the same group of researchers with movement-based meditation, tai chi, also reported significant improvement in 6-minute walk distance, improved quality of life, and reduction of brain natriuretic peptide (BNP) in patients with heart failure compared to control groups.[65,66]

A recent systematic review by Viveiros et al.[67] reported similar results from all the included studies, though the sample size was smaller in most of the studies. A recent pilot RCT using mindfulness-based stress reduction (MBSR) intervention among cardiac rehabilitation (CR) patients (which included CHF patients also) have also reported significant improvement in psychosocial outcomes and cardiovascular outcomes at 3 months that persisted at 9 months in a subset [who had Patient Health Questionnaire-9 (PHQ-9) scores ≥ 5].[68]

In a recent study,[69] 56 CHD patients (which also included CHF) registered for CR were randomized to CR, TM, or a combination of intervention, and myocardial flow reserve (MFR) was assessed by positron emission tomography (PET). Other CHD risk factors were also assessed as secondary outcomes. This study reported significant improvement in MFR in the groups which had TM or combination of TM and CR than the usual care. One of the important limitations of this study is that only 34 patients completed the posttest assessment.

Meditation and Arrhythmia

Autonomic nervous system plays a key role in the development of atrial and ventricular arrhythmia.[70,71] Intervention directed toward ANS modulation could be a viable treatment target for arrhythmias. For example, evidence shows that lifestyle modification programs can prevent the development of atrial fibrillation (AF)[72,73] and persistent forms of AF could regress to paroxysmal phenotype possibly leading to resolution of the disease.[74]

In this context, meditation which modulates the ANS[75,76] could be one of the adjunctive treatment options. Though conceptually it is convincing to propose meditation as a complementary therapy for arrhythmias, only one study has assessed arrhythmias as an outcome with meditation intervention. In a recent study conducted by Aditee et al. in 2020,[77] patients with CHF and implantable cardioverter defibrillator (ICD) were randomized to vipassana meditation or usual clinical care. Meditation intervention was given thrice in the first week, followed by once in 2 weeks. However, the patients were encouraged to do meditation at least once in a day. In this 7-year follow-up study, AF was the primary outcome measure, and ventricular arrhythmia, mortality, and heart failure hospitalization were secondary outcome measures. The study showed improved survival and reduced cumulative arrhythmias in the meditation group than the control group.

MEDITATION AND PLAUSIBLE MOLECULAR MECHANISMS FOR CARDIAC HEALTH

In general, acute/chronic stress is at the heart of many disorders, and relaxation response is at the core of the healing process. Broadly, the changes at the cellular and molecular levels caused either by stress or by mind–body therapies such as meditation (which causes relaxation response) are explained by modulation in the stress-related psychoneuroimmunology variables and related epigenetic markers. The studies discussed in the following section include subjects who are healthy or are suffering from CVD.

Cortisol is one of the commonly studied biomarkers of stress and has been widely evaluated in meditation studies as well. Several studies have reported reduction in cortisol levels following meditation intervention. In a recent meta-analysis by Koncz et al.,[78] 31 studies were analyzed for the effect of meditation programs on serum and salivary cortisol levels. The subjects included patients with various disorders, including cardiovascular disorders. The results showed that meditation intervention was significantly effective in reducing the serum cortisol level with a medium effect size. In the remaining studies which assessed salivary cortisol, the effect was small and significant for those who continue to live in stressful life situations.

Similar to elevated cortisol, reduced GABA is also implicated in stress-mediated biological effects, including

the cardiovascular system. Based on a close relationship between GABA and ANS activity, Streeter et al.[18] proposed that underactivity of GABA and parasympathetic nervous system and allostatic overload might be the pathway through which mind–body interventions such as Yoga/meditation act to bring back the homeostasis and normal physiology. This hypothesis is supported by increased GABA neurotransmission with vagus nerve stimulation in disorders such as epilepsy and depression (characterized by reduced GABA levels). Interestingly, mind–body interventions such as Yoga also found to enhance GABA levels in disorders such as depression.[79] Though the results might hold true for meditation as well, at present, there are no studies investigating the effect of meditation on GABA.

A recent systematic review by Djalilova et al.[80] assessed the impact of Yoga (meditation studies were also included) on inflammatory markers. The review included 15 studies in the final analysis, and most studies reported positive effect on inflammatory biomarkers following Yoga/meditation intervention. There was a dose–response relationship between the intervention and improvement in inflammatory biomarkers. Interleukin-6 (IL-6), C-reactive protein, and tumor necrosis factor were the markers evaluated in these studies. An earlier systematic review by Buric et al.[81] examined the effect of mind–body interventions, including meditation, on nuclear factor kappa B pathway. The review examined 18 studies with clinical and nonclinical populations. The results suggest that mind–body interventions, including meditation, are associated with a downregulation of nuclear factor kappa B pathway, which is opposite to the effects of chronic stress.

In the context of metabolic syndrome—an important risk factor for CVD, leptin is another adipocytokine influenced by stress. Leptin is an adipocytokine, structurally similar to IL-6, and its concentration is elevated in obesity and hypertension. Leptin's effect on food intake, energy expenditure, and regulation of adrenal and reproductive systems are centrally controlled by hypothalamus. Meditation and related practices that downregulate the HPA axis should possibly act on leptin as well and hence can facilitate cardioprotective effect by reduced risk of obesity and hypertension. In a cross-sectional study by Kiecolt-Glaser et al.,[82] blood leptin levels were significantly lower among expert Yoga practitioners than novices, and adiponectin (anti-inflammatory) was significantly higher among expert practitioners. Other studies have shown similar trends.[83,84]

Another molecule that is affected by stress and inflammatory cytokines is nitric oxide (NO). Impairment in NO levels is noted in many disorders, including CVD.[85] As meditation improves the inflammatory markers, it also impacts the serum NO levels. In a RCT by Prakhinkit et al.,[86] 45 elderly subjects were assessed for flow-mediated dilation (FMD) (using ultrasonography in brachial artery) and serum NO. Subjects in the Buddhist walking meditation group showed significant increase in the FMD and also serum NO.

Apart from reducing the inflammation, mind–body practices have been examined for their antioxidant effects as well. A recent meta-analysis (5 RCTs and 5 non-RCTs) studied the effect of tai chi (movement-based meditation) on oxidative stress reported increase in superoxide dismutase (SOD) [(mean difference (MD) = 34.97 U/mL, (95% CI 9.45–60.48)], catalase [MD = 15.63 U/mL, (95% CI 4.05–27.22)], and reduced levels of lipoperoxides [MD = –0.02 μmol/L, (95% CI –0.04 to –0.00)] suggestive of antioxidant effect.[87] Another study with Zen meditation also reported similar antioxidant effect through reduced lipid peroxidation assessed by malondialdehyde concentration.[88]

In recent years, interest in epigenetic changes induced by mind–body intervention has been growing rapidly. Epigenetics is the study of external molecular "switches" that turn genes on and off and changes phenotype without altering genotype. Acquired or inherited epigenetic changes are reversible. In this context, cellular senescence induced by stress and the impact of mind–body interventions on cellular senescence has been under investigation for the last two decades. Shortening of white blood cell (WBC) telomere length is considered as a marker of aging for conditions related to stress and chronic diseases. Telomere length shortens with age and is reported to be shortened with many diseases,[89] including CVD. A recent pilot study also reported shorter telomere length in young patients with MI who are nondiabetic and nonsmokers, suggestive of its potential utility for screening in young MI patients without conventional risk factors.[90]

A recent meta-analysis (cross-sectional studies) by Schutte et al.[91] evaluated 11 studies comparing telomere length in long-term meditators with controls. Long-term meditators were found to have significantly longer telomere length compared to control subjects. Across studies, there was a dose–response relationship between the hours of meditation and the effect on telomere length. However, a later systematic review in 2021[92] among healthy individuals showed mixed results. One RCT with loving kindness meditation showed beneficial effect on telomere length which was statistically significant, whereas the remaining studies showed beneficial effect which was not statistically significant.[93] One study with meditation intervention (alone or in combination with lifestyle modification) showed significant increase in telomere length following meditation intervention.[94] In another interesting study by Chandran et al.,[95] 220 genes directly associated with immune response, including 68 genes related to interferon signaling were upregulated following an intense 8 days meditation program. It is difficult to draw any definitive conclusions due to lack of systematic studies. The above pathways are interesting, but identifying the candidate genes and the biological pathways sensitive to meditation practice remains unexplored with robust research designs in clinical population.

A summary of all the studies is provided in **Table 1**.

CONCLUSION

Meditation has modest evidence in reducing stress and negative affect, which is at the core of majority of risk factors for CVD. It plays an adjunctive role in management of CVD risk factors such as hypertension, diabetes mellitus, obesity, and

TABLE 1: Studies on meditation and heart-related outcomes.

First author, year	Study design	Subject details	Intervention details	Findings
Patel C, 1975	Non-randomized controlled trial (non-RCT)	Hypertension subjects	• Psychophysical exercise including meditation ($n = 20$) • Usual treatment ($n = 20$) • 12 months follow-up study	Significant difference in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in intervention group than control group. Medication requirement was also lesser in intervention group
Bai Z, 2015	Meta-analysis	• 12 studies • Hypertension subjects	Transcendental meditation (TM)	Approximate reduction of systolic and diastolic BP of −4.26 mm Hg (95% CI = −6.06, −2.23) and −2.33 mm Hg (95% CI = −3.70, −0.97), respectively, in TM groups compared with control groups
Conversano C, 2021	Meta-analysis	• 6 studies • Hypertension subjects	Mindfulness-based stress reduction (MBSR)	• Comparison of MBSR versus control conditions on BP was associated with a statistically significant mean effect size favoring MBSR over control conditions • *DBP*: Mean difference = −2.029; 95% CI −3.676 to −0.383, $p = 0.016$ • *SBP*: Mean difference = −3.894; 95% CI −7.736 to 0.053, $p = 0.047$
Ooi SL, 2017	Overview of systematic review (SR) and meta-analysis	• 8 studies • Hypertension subjects	TM	Practicing TM may potentially reduce the SBP by ~4 mm Hg and DBP by ~2 mm Hg
Shi L, 2017	Meta-analysis	• 19 studies • Hypertension subjects	TM and non-TM types	Pooled SBP (ambulatory BP monitoring) effect estimate was 2.49 mm Hg [95% CI 7.51, 2.53] for TM intervention (statistically insignificant) and 3.77 mm Hg (95% CI 5.33, 2.21) for non-TM interventions, whereas the pooled DBP effect estimate was 4.26 mm Hg (95% CI 6.21, 2.31) for TM interventions and 2.18 mm Hg (95% CI 4.28, 0.09) for non-TM interventions
Paul-Labrador M, 2006	RCT	103 subjects with stable coronary heart disease (CHD)	• TM versus health education (HE) • 6 weeks intervention	TM group had beneficial changes [measured as mean ± standard deviation (SD)] in adjusted systolic blood pressure (−3.4 ± 2.0 vs. 2.8 ± 2.1 mm Hg; $p = 0.04$), insulin resistance (−0.75 ± 2.04 vs. 0.52 ± 2.84; $p = 0.01$), compared with the health education group
Khatri D, 2007	Single group pre-post design	101 subjects with metabolic syndrome	• *Yogasana* and meditation • 3 months duration	Significant difference in waist circumference, SBP, DBP, fasting blood sugar, HbA1C, serum triglyceride and serum high-density lipoprotein (HDL) following Yoga and meditation intervention
Innes KE, 2005	SR	• 70 studies • Multiple disorders including cardiovascular disorders (CVD) • CVD risk associated with insulin resistance syndrome (IRS) were assessed	*Yogasana* and meditation	Yoga and meditation may reduce many IRS-related risk factors for CVD, may improve clinical outcomes, and may aid in the management of CVD and other IRS-related conditions

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First author, year	Study design	Subject details	Intervention details	Findings
Ramamoorthi R, 2019	MA	• 14 studies • Prediabetic individuals	*Yogasana* and meditation	Compared to controls, Yoga intervention improved fasting blood glucose (FBG) [standard mean difference (SMD) –0.064 mg/dL (95% CI –0.201 to 0.074)]; low-density lipoprotein (LDL) [SMD –0.090 mg/dL (95% CI –0.270 to 0.090)]; triglycerides [SMD –0.148 mg/dL (95% CI –0.285 to –0.012)]; total cholesterol [SMD –0.058 mg/dL (95% CI –0.220 to 0.104)] and systolic blood pressure [SMD –0.058 mm Hg (95% CI –0.168 to 0.053)]
Ornish D, 1983	RCT	CHD subjects	• Stress management including *Yogasana* and meditation (n = 23) • Usual treatment (n = 23) • 3 weeks intervention	Experimental intervention group showed significant improvement in duration of exercise, total work performed, left ventricular ejection fraction, plasma cholesterol levels, and reduced angina episodes compared to control group
Ornish D, 1990	RCT	CHD subjects	• Lifestyle modification (low-fat diet, exercise, stopping smoking, stress management training including meditation) (n = 28) • Usual treatment (n = 20) • 1-year follow-up study	82% of experimental-group patients had an average change toward regression (assessed by quantitative coronary angiography) which was statistically significant compared to the control group
Linden W, 1996	MA	• 23 studies • CHD subjects	Psychosocial intervention including breathing-based relaxation for cardiac rehabilitation (CR)	• Psychosocially treated patients showed greater reductions in psychological distress, systolic blood pressure, heart rate, and cholesterol level (with effect size differences of 0.34, –0.24, –0.38, and –1.54, respectively) • Patients who did not receive psychosocial treatment showed greater mortality and cardiac recurrence rates during the first 2 years of follow-up with log-adjusted odds ratios of 1.70 for mortality [95% CI 1.09–2.64] and 1.84 for recurrence (CI 1.12–2.99)
Younge JO, 2015	MA	• 11 studies • CHD and heart failure subjects	TM, mindfulness meditation, and progressive muscular relaxation and stress management	Pool effect sizes were 0.45 (95% CI 0.20–0.72) for physical quality of life, 0.68 (95% CI 0.10–1.26) for mental quality of life, 0.61 (95% CI 0.23–0.99) for depression, 0.52 (95% CI 0.26–0.78) for anxiety, 0.48 (95% CI 0.27–0.69) for systolic blood pressure, and 0.36 (95% CI 0.15–0.57) for diastolic blood pressure
Gupta SK, 2011	Single group pre-post design	123 CHD subjects	• Brahmakumaris Raja yoga meditation-based lifestyle modification • 2 years follow-up study	Significant decrease in LDL and triglycerides and increase in HDL. Regression of coronary stenosis observed in the most compliant subjects
Schneider RH, 2012	RCT	CHD subjects	• TM (n = 99) • HE (n = 102) • 3 months follow-up study	TM program significantly reduced risk for mortality, myocardial infarction, and stroke in CHD patients compared to controls. These changes were associated with lower blood pressure and psychosocial stress factors

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First author, year	Study design	Subject details	Intervention details	Findings
Fields JZ, 2002	RCT	Healthy adults >65 years with and without CHD risk factors	• Vedic medicine-based approach (including TM): *n* = 20 • Usual approach (including physical exercise): *n* = 14 • Modern medicine-based approach: *n* = 9 • 3 months follow-up study	• Carotid intima-media thickness (IMT) decreased in a larger fraction in Vedic medicine group subjects (16 of 20) than in the modern (5 of 9) and usual care (7 of 14) groups combined (i.e., 12 of 23; odds ratio 3.7, *p* = 0.05) • Within group, reduction of IMT was significant for the Vedic medicine group along with other risk factors
Sivasankaran S, 2006	Single group pre-post design	Subjects with (*n* = 10) and without (*n* = 23) CHD	• *Yogasana* and meditation • 6 weeks intervention	• There were significant reductions in blood pressure, heart rate, and body mass index (BMI) following *Yogasana* and meditation intervention • In the subgroup analysis, subjects with CHD showed 69% improvement in endothelial-dependent vasodilatation following intervention
Vaccarino V, 2013	RCT	Subjects with metabolic syndrome risk factors	• *Mantra*-based meditation (*n* = 33) • HE (*n* = 35)	• Brachial artery flow-mediated dilation (FMD%), indicator of endothelial function improved in the meditation group than in the HE group, although not significant • Most metabolic syndrome risk factors showed beneficial trends in meditation group
Zamarra JW, 1996	Non-RCT	Subjects with CHD	• TM (*n* = 12) • Usual treatment (*n* = 9) • 8 months follow-up	TM reduced myocardial ischemia assessed by exercise tolerance test (exercise duration, maximal workload, ST depression onset, and rate pressure product were significantly different in TM group than controls)
Kiran U, 2017	RCT	Subjects with CHD posted for coronary artery bypass surgery	• Brahmakumaris Raja yoga meditation (BKRYM) (*n* = 73) • Psychoeducation (*n* = 74) • 7 days intervention	Anxiety levels and serum cortisol levels were significantly reduced in BKRYM group compared to control group from 2nd to 5th postoperative day
Jayadevappa R, 2007	RCT	Subjects with congestive heart failure (CHF)	• TM (*n* = 13) • HE (*n* = 10) • 6 months follow-up study	• TM group significantly improved on the 6-minute walk test than the control group after 6 months • Other quality of life measures also improved in the TM group
Curiati JA, 2005	RCT	Subjects with CHF	• Meditation (breathing, chanting, and body scan) (*n* = 10) • Usual treatment (*n* = 9) • 12 weeks intervention	Significant reduction in blood norepinephrine and VE/VCO_2 (ventilation per unit increase of carbon dioxide production) and improvement in quality of life in meditation group compared to control group
Yeh GY, 2004	RCT	Subjects with CHF	• Tai chi (*n* = 15) • Usual treatment (*n* = 15) • 12 weeks intervention	At 12 weeks, patients in the tai chi group showed improved quality-of-life scores (mean between-group difference in change, –25 points, $p < 0.001$), increased distance walked in 6 minutes (135 m, $p < 0.001$), and decreased serum B-type natriuretic peptide levels (–138 pg/mL, $p < 0.03$) compared with patients in the control group

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First author, year	Study design	Subject details	Intervention details	Findings
Viveiros J, 2019	SR	• 6 studies • Subjects with CHF	Meditation interventions	Compared with controls meditation practice significantly improved depression ($p < 0.05$), social support ($p < 0.05$), biophysical factors and quality of life ($p < 0.05$), in addition to reducing heart failure symptom burden
Nijjar PS, 2019	RCT	CR patients including CHF, CHD, valve replacement, and others	• MBSR ($n = 31$) • Usual treatment ($n = 16$) • 9 months follow-up study	At 3 months, compared to controls, MBSR patients showed improvements in depression ($p = 0.01$) and anxiety ($p = 0.04$) with a similar trend in health-related quality of life (HRQOL) ($p = 0.06$). The MBSR group showed greater improvement or less worsening of most CV risk factors, with an attenuation of treatment effects at 9 months. Participants with at patient health questionnaire-9 (PHQ-9) scores ≥5 at baseline showed greater improvement in psychosocial and CV outcomes that persisted at 9 months
Bokhari S, 2021	RCT	CHD patients eligible for CR	• TM alone or with CR ($n = 19$) • CR and usual care ($n = 18$)	Adding TM technique to standard CR or using TM alone improves the myocardial flow reserve (MFR) in African-American CHD patients. MFR was assessed by quantitative positron emission tomography (PET)
Aditee D, 2020	RCT	CHF patients with implantable cardioverter defibrillator (ICD)	• Vipassana meditation ($n = 16$) • Usual treatment ($n = 9$) • 8 years follow-up study	Comparing meditation versus control, survival was higher (88% vs. 67%); there were less cumulative sustained AF episodes (mean 0.9, IQR 0–1 vs. 2.5, IQR 2–4, $p = 0.045$), sustained VT occurred (25% vs. 55%), amiodarone use (none vs. 44%), and VT ablation in 6.6% versus 33% in the meditation group
Yadav R, 2021	Single group pre-post design	Prediabetic subjects	• *Yogasana*, pranayama, and meditation ($n = 59$) • 10 weeks intervention	10 weeks lead to intervention significant reduction in IL-6 levels and leptin levels and significant increase in adiponectin level. There was also a significant reduction in weight, DBP, and insulin resistance
Telles S, 2009	Single group pre-post design	Subjects with obesity	• *Yogasana, Pranayama*, and diet modification ($n = 47$) • 6 days residential intervention	Participants showed a significant decrease in BMI (1.6%), waist and hip circumferences, fat-free mass, total cholesterol (7.7% decrease), and fasting serum leptin levels (44.2% decrease)
Prakhinkit S, 2014	RCT	Elderly subjects (aged >60 years) with mild-to-moderate depression	• Traditional walking exercise (TWE) ($n = 15$) • Buddhist walking meditation (BWM) ($n = 15$) • Sedentary control (SC) ($n = 15$) • 12 weeks intervention	Buddhist walking meditation was effective in reducing depression, improving functional fitness, and vascular reactivity (FMD assessed by ultrasound Doppler in brachial artery) than the other two groups
Rosado-Pérez J, 2021	MA	Healthy adults	Tai chi intervention	Regular tai chi practice increases the levels of superoxide dismutase and catalase, as well as reduces the levels of lipoperoxides

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First author, year	Study design	Subject details	Intervention details	Findings
Kim DH, 2005	Non-RCT	Healthy adults	Zen meditation	Meditation group showed a significantly higher level of serum nitric oxide concentration and a significant reduction of serum malondialdehyde (MDA) (index of lipid peroxidation) than control group
Schutte NS, 2020	MA	11 studies	Various meditation types	• Telomere length in meditators is significantly longer than controls • Hours of meditation practice correlated with telomere length

dyslipidemia. Among the CVD, utility of meditation in CHD has been widely studied followed by CHF and arrhythmias, though the underlying mechanisms need to be studied in detail. A summary of meditation studies in CVD is given in **Table 1**.

Possible biological mechanisms for the effect of meditation on cardiac health could be improvement in sympathovagal tone, resetting of the cellular homeostasis through psychoneuro-immunology pathways including enhanced neurotransmission, balanced inflammatory response through better cytokine functioning, and epigenetic changes.

Despite the numerous positive findings, results need to be interpreted in the context of various limitations of the available evidence. Most of the available studies have the following shortcomings: (1) Small sample size, (2) focus mainly on short-term effect, (3) inherent complexity in defining an appropriate control group, (4) practical inability in doing a placebo-controlled trial (as in other behavioral intervention studies), (5) absence of multicentric trials, and (6) ambiguity in operational definition of meditation.

Future studies could focus more on the above issues with a focus on identifying the underlying mechanisms for the effect of meditation on cardiac health. As per the available evidence, considering the cost-effectiveness, availability/accessibility, and minimal side effect profile, meditation should be considered as an adjunct treatment for reducing the morbidity and mortality of CVD, including the prevention of risk factors.

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CHAPTER 33

Post-coronavirus Disease 2019 Long-term Cardiovascular Manifestations

SN Routray, Shishu Shankar Mishra, Dipak Ranjan Das

ABSTRACT

A substantial number of coronavirus disease 2019 (COVID-19) survivors develop cardiovascular manifestations in the long run. It has been observed that beyond 30 days of infection they are more prone to cardiac arrhythmia such as sinus bradycardia, sinus tachycardia, atrial flutter, atrial fibrillation, ventricular arrhythmias; inflammatory heart disease such as pericarditis and myocarditis; ischemic heart disease in the form of angina pectoris, myocardial infarction and ischemic cardiomyopathy and others such as nonischemic cardiomyopathy, heart failure, transient ischemic attack (TIA), stroke, superficial and deep vein thrombosis, and pulmonary thromboembolism. Mechanism of such manifestations is still not well understood; however, direct invasion of cardiac myocyte, endothelial dysfunction, autonomic dysfunction, complement activation and complement-mediated coagulopathy and microangiopathy, aberrant persistent hyperacute immune response and several others have been proposed. Management is symptom oriented; additional medical, psychological, and emotional support is essential.

INTRODUCTION

In the history of mankind for the first time a viral disease could become pandemic affecting all countries, irrespective of caste, creed, region, and ethnicity. The virus was unpredictably became fatal leading to significant morbidity and mortality. This virus is coronavirus disease 2019 (COVID-19) [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)], which started from Wuhan, China and spread rapidly all over world like a wild fire. The World Health Organization (WHO) declared officially this to be pandemic on April 11, 2020. Millions people got infected worldwide. Much of the focus was on respiratory involvement and related pulmonary complications. In many patients, acute and chronic cardiac involvement was also noticed in the form of: Myocardial injury, myocarditis, dysrhythmia, cardiomyopathy, venous thromboembolism (VTE), heart failure, shock, and cardiac arrest.

About 10% COVID patients progress to chronicity and designated as "Long COVID" **(Fig. 1)**.

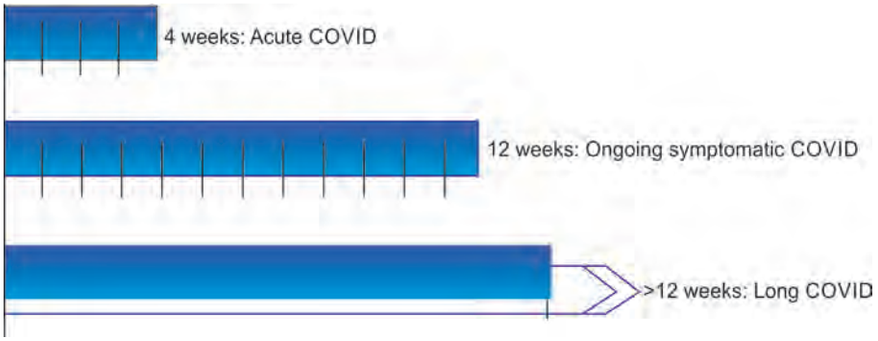

FIG. 1: Coronavirus disease (COVID) and duration of symptoms.

Coronavirus disease 2019 or the SARS-CoV-2 virus primarily affects the respiratory system causing acute respiratory symptoms. Many extra-respiratory manifestations involving multiple-organ systems possibly related to systemic inflammation and host immunological parameters have also been described. Recently it has been stated in various upcoming studies about the late onset manifestations of this illness and its detrimental effects on multi-organ systems leading to abnormal outcomes in patient and increasing healthcare concerns. A term "Long-COVID" or "Post-COVID" has been designated to categorize the patients for better diagnosis and care.

LONG-COVID OR POST-COVID

Long-COVID (or post-COVID) is described as a condition characterized by the persistence of variety of symptoms for more than 3 months (up to 12 weeks) **(Fig. 1)** after the onset of COVID-19 infection in the patients.[1] The symptoms may last for a longer duration, which is still a matter of debate. The symptomatology in this long-term COVID infection is heterogeneous and has a multiple-organ involvement including the cardiovascular system.[2] The WHO recently proclaimed that "Some people who had COVID-19, irrespective of having been hospitalized, continue to experience symptoms, including fatigue, cardiovascular, respiratory, and neurological symptoms".[1] The latest WHO update includes a new International Classification of Diseases (ICD) code for the post-COVID-19 condition (U09.9 post COVID-19 condition, unspecified).

Criteria for the diagnosis of long-COVID:[1]

- Persistence of symptoms more than 12 weeks of the onset of COVID-19
- Constitutional or cardiovascular symptoms
- Biomarkers-1-(coagulation)-fibrinogen, D-Dimer, platelets
  2-Myocyte damage-HsTn-I
  3-Systemic inflammation-CRP, leukocyte count
  4-Cytokines-interleukin (IL)-6
  5-Myocyte stress-B-type natriuretic peptide (BNP)/N-terminal pro B-type natriuretic peptide (NTproBP)
- New onset ECG changes and imaging findings-2D-TTE, CMR
- De novo events in low-risk subset of patients

POST-COVID-19 LONG-TERM CARDIOVASCULAR CLINICAL MANIFESTATIONS[3]

Palpitation

These are one of the most commonly reported symptoms by patients affected by long-COVID; they may be caused by simple sinus tachycardia, sinus bradycardia or supraventricular or ventricular arrhythmias.[4] These presentations may have no diagnostic specificity, but must be given some importance as they are a frequent cause for medical visits.

Chest Pain

It is another common symptom reported by patients with "Long-COVID". These pains may have ischemic or nonischemic origin but often do not lead to substantial findings useful for a correct interpretation,[5] and most evaluations are not conclusive.

Postural Tachycardia Syndrome

When orthostatic tachycardia and symptoms of orthostatic intolerance for at least 3 months are part of long-COVID syndrome, they may lead to a diagnosis of post-COVID-19 postural tachycardia syndrome (POTS). The diagnosis is made when there is an increase of >30 bpm in adults (>40 bpm in patients aged 12–19 years) within 10 minutes of assuming the upright posture in the absence of orthostatic hypotension with associated symptoms of orthostatic intolerance. A number of case reports have recently described patients who developed POTS after SARS-CoV-2 infection. Currently, little is known about the pathophysiology and the natural history of long-COVID POTS.[6]

Heart Failure

The exact prevalence of heart failure as a long-term complication of COVID-19 is found to be uncertain. In many of the studies the patients who were already suffering from heart failure due to various other causes had possible worsening of heart failure post-COVID-19, de novo cases have also been reported [both heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF)].[7]

The Venous Thrombotic Manifestations

The thromboembolic events studied in long-term COVID manifestations in the following year after recovering from acute COVID-19 included deep vein thrombosis (2.4%) and pulmonary thromboembolism (1.7%).[7] A follow-up strategy to look for the burden of residual risk, small vessel injury, and potential hemodynamic sequelae should be adopted as a practice considering state of lung perfusion.[8]

Arterial Thrombosis

Arterial thrombosis informs of acute coronary syndromes, and unexplained thrombotic/thromboembolic manifestations at the peripheral/splanchnic/cerebral levels have been described on occasional basis with manifestations of acute coronary syndromes in patients at low risk and without significant coronary artery disease on angiography.[9,10]

Arrhythmias

Supraventricular and ventricular arrhythmias along with conduction disturbances have been observed and reported among the long-term cardiovascular manifestations of COVID.[6]

Myocarditis, Pericarditis, and Myopericarditis

The diagnosis of myocarditis is controversial in acute as well as long-term COVID-19 mainly because of diagnostic dilemma and lack of certainty. In many recent studies, myocarditis is diagnosed either on the basis of isolated elevated troponin levels or on the basis of combination of elevated troponins and signs of myocardial edema on cardiac MRI.[11]

Cardiometabolic Conditions

Diabetes, both type 1 and type 2, is associated with severe acute COVID-19 and long-term cardiovascular manifestations of COVID. Interventions to target multiple risk factors, combined with the use of novel oral hypoglycemic agents that improve metabolic function and the key processes that are impaired in COVID-19, should be the preferred therapeutic options for the management of people with long-COVID.[12]

MECHANISM

The postulated potential mechanisms for the underlying cardiovascular consequences of acute COVID-19 infection includes a chronic inflammatory response induced by viral persistence in heart tissue, molecular mimicry that induces an autoimmune response to cardiac antigens, and persistent endothelial and microvascular dysfunction.[13] Numerous cardiometabolic risk factors such as obesity, smoking, hypertension, and diabetes mellitus are involved in the interaction between COVID-19 and cardiovascular diseases **(Fig. 2)**.

Prevention and management of these risk factors should be optimized.[14,15] Conversely, there is a possibility that fragments of the viral genome or viral antigens without infectious capacity may persist for long time.[16] A very recent study reported the possibility that the viral genome may be retro-transcribed and integrated into the human cellular DNA, thus becoming a driving factor and source of the synthesis of RNA and antigens of viral origin. Some studies and data suggest that this phenomenon may be the basis of persistently positive tests in patients recovered from COVID-19.[2,17,18] These molecules may be responsible for activating immune-inflammatory-procoagulant cascade, potentially explaining late onset of thrombotic events. The immunological/immune-mediated hypothesis could also be linked to this possibility. This hypothesis is supported both by the pathogenetic mechanisms of COVID-19, with cytokine storm induced by the inflammatory-immune reaction to the infection, and by early studies reporting an increase in autoantibodies titer of antinuclear antibodies (ANA).[19] The wide heterogeneity of the symptoms suggests that it is a multisystemic disorder. The hypothesis of a direct role of the virus and its possible persistence must be carefully considered. Some mechanisms are due to the damage to the cardiomyocytes from direct viral invasion and subsequent cell death, endothelial cell infiltration, and endothelial inflammation. The transcriptional alteration of various cell types in cardiac tissue, complement activation and complement-mediated coagulopathy and micro-angiopathy, downregulation of angiotensin-converting enzyme-2 (ACE2) and altered regulation of the renin–angiotensin–aldosterone system, autonomic dysfunction, escalated the levels of proinflammatory cytokines, and activation of TGF-β signaling pathway causative for subsequent fibrosis and scarring of cardiac structures.[2,17,18]

BIOMARKERS

The diagnosis of long-term cardiovascular manifestations of COVID-19 requires alertness, inquisitiveness, and up-to-date knowledge on the part of the physicians/cardiologists to make such diagnosis on the basis of descriptive reports. The diagnosis is mainly based on the biomarkers and the imaging evidences that have more clinical value if not present during the acute phase of COVID-19. Some of the most frequently tested biomarkers are: (i) Markers of systemic inflammation such as C-reactive protein, neutrophil counts, lymphocyte counts, and platelet counts; (ii) markers of immunological activity such as the cytokines (typically IL-6); (iii) markers of hypercoagulability such as elevated levels of fibrinogen, D-Dimer, or functional tests of platelet hyperactivity; (iv) markers of myocyte injury like plasma levels of HS troponin I; (v) markers of increased myocardial stress such as natriuretic peptides (BNP NTproBNP). Less frequently used are the alarms in [high-mobility group box 1 protein (HMGB1); heat shock proteins (HSP); IL-1a; IL-33; IL-37; S100; and defensins], investigated both in the acute phase and in long-COVID.[20]

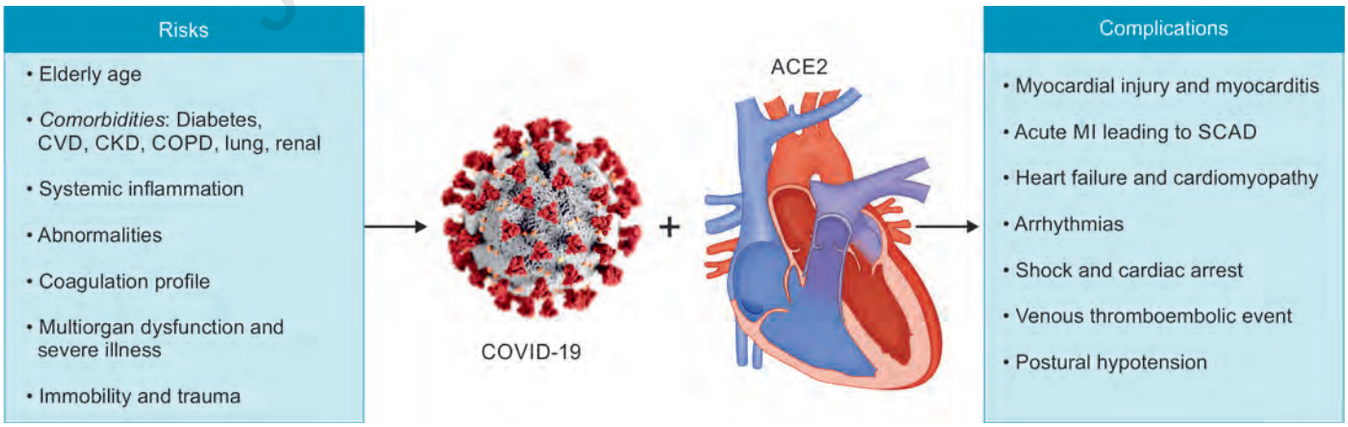

FIG. 2: Coronavirus disease 2019 (COVID-19) and the cardiovascular system.

(ACE2: angiotensin-converting enzyme 2; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; MI: myocardial infarction; SCAD: spontaneous coronary artery dissection)

Imaging studies, including cardiac magnetic resonance (CMR), are being done frequently but they provide information that is insufficient to ascertain the findings to long-COVID with certainty.

TREATMENT

The management mainly includes empirical treatment of the symptomatology to just control the subjective symptoms. This is because the diagnosis is mainly based on the patient symptoms with lack of measurable markers of the disease. Though various biomarkers and biochemical tests are instrumental and various invasive and noninvasive evaluations are performed; they may be of no diagnostic contribution at all, due to lack of evidence of organ or tissue damage. When symptoms are associated with evidence of organ involvement like increased levels of biomarkers (e.g., of myocyte damage), or ECG changes, or imaging findings, or acute events, the treatments are guided by the clinical phenotypes.[21]

CONCLUSION

Long-term cardiovascular manifestations of COVID are still not completely understood. They comprise many heterogeneous symptoms of unknown etiology and unexplainable direct causality of SARS-CoV-2 infection. Most of this uncertainty is attributable to the largely retrospective data published to date. There is a demanding need to study the post-COVID long-term cardiovascular manifestations, because many facts still remain unknown. Further follow-up studies and long-term data analysis will give insight to the problem of long-COVID syndrome.

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CHAPTER 34

Approach to Angiography in Cyanotic Congenital Heart Disease

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ABSTRACT

Cardiac catheterization and angiocardiography is the gold standard for the diagnosis of complex cyanotic congenital heart diseases (CCHDs). Their management is challenging, and exact anatomical and physiological diagnosis is mandatory for appropriate treatment. While superseded by noninvasive tools such as 2D/3D echocardiography, cardiac computed tomography, and magnetic resonance imaging, angiography continues to be relevant for diagnosis and as a gateway to therapeutic measures. In this chapter, we will discuss the basics of angiography in CCHD, indications, tips and tricks, and angiography in preoperative and postoperative scenarios.

INTRODUCTION

The diagnosis and management of cyanotic congenital heart diseases (CCHD) are challenging. These young patients require multiple staged surgeries and interventions from childhood to adulthood, either corrective or for palliation. Over the years, the tools for diagnosis have grown and noninvasive multimodality imaging—segmental transthoracic echocardiography (TTE), cardiac computed tomography (CT), and magnetic resonance imaging (MRI)—have taken the center stage. Good quality TTE can help diagnose most of the CCHDs. This has led to angiocardiography, the gold standard, taking a backseat. But its continued relevance cannot be ignored. It remains safe in experienced hands. This chapter focuses on the importance of cardiac catheterization and angiography, techniques, and equipment used with relevant case examples.

All the video files can be accessed on the link https://t.ly/kCLK or by using the QR code provided in **Figure 1**.

CLASSIFICATION OF CYANOTIC CONGENITAL HEART DISEASES

Cyanotic congenital heart diseases have cyanosis due to the presence of a right-to-left shunt, at the level of either the interatrial septum (IAS) or the interventricular septum (IVS). They are classified based on the pulmonary blood flow (PBF) **(Table 1)**.[1] This classification is a simplistic take on a spectrum of CCHDs. These diseases have varying presentations and are complicated by patients with palliated or corrected defects, often with residual lesions.

- Reduced PBF—the group of diseases with pulmonary stenosis (PS) or obstructions at the level of the right ventricular outflow tract (RVOT)
- Increased PBF—the group of diseases with pulmonary arterial hypertension (PAH)

FIG. 1: QR code for chapter videos.

TABLE 1: Classification of cyanotic congenital heart diseases.

With PS		
With VSD (TOF physiologies)		**Without VSD**
• Classical TOF • DORV + VSD + PS • D and L TGA + VSD + PS • Tricuspid atresia + PS • Unbalanced AVCD + PS • Single ventricle + PS		• Critical PS • Ebstein's anomaly • PA/IVS
Without PS, with PAH		
Admixture lesions	**Transposition, with parallel circulation**	**Erstwhile left-to-right shunts with PVOD**
• TAPVC • Common atrium • Single ventricle • DORV + VSD • AVCD • Tricuspid atresia + VSD • Common arterial trunk	TGA	• Large left-to-right shunts with PVOD • Eisenmenger physiology
Structurally normal heart with cyanosis (miscellaneous)		
• Pulmonary AV fistula • PA–LA fistula • PA–PV fistula • Abernathy malformations • Unroofed coronary sinus to the LA		

(AV: atrioventricular; AVCD: atrioventricular canal defect; D and L: dextro and levo; DORV: double outlet right ventricle; LA: left atrium; PA: pulmonary artery; PAH: pulmonary arterial hypertension; PA/IVS: pulmonary atresia with intact ventricular septum; PS: pulmonary stenosis; PV: pulmonary vein; PVOD: pulmonary vascular occlusive disease; TAPVC: total anomalous pulmonary venous connection; TGA: transposition of great arteries; TOF: tetralogy of Fallot; VSD: ventricular septal defect)

CARDIAC CATHETERIZATION AND ANGIOGRAPHY: ADVANTAGES

In the current era, where most of the diagnosis and management plan are made noninvasively, angiogram has its uses:[2]

- Angiogram allows for simultaneous pressure and hemodynamic assessment.
- It can generate a complete anatomical and physiological profile of the cyanotic lesion.
- Compared to CT and MRI, angiography offers improved temporal, axial, and spatial resolution and is invaluable in evaluating smaller structures in patients with high heart rate.
- Exact course of the vascular structures, flow of blood, drainage, and takeoff sites can be delineated clearly.
- It offers more clarity to doubtful noninvasive findings.
- In chronically underfilled structures, the opacification is less with CT or MRI. Angiography is invaluable to improve anatomical delineation.
- In postoperative patients, cardiac catheterization and angiography are better than noninvasive imaging.
- Additional therapeutic management can be offered after cardiac catheterization.

PREPROCEDURAL PLANNING

Prior to cardiac catheterization, it is essential to have the following information in hand in addition to the usual preprocedural investigations. Catheterization in patients with CCHDs is done after sedation. The staff performing and assisting procedures in these patients need additional training, show restraint, and have heightened awareness during cardiac catheterization in this vulnerable population.

- Complete diagnosis obtained from noninvasive imaging
- A review of prior surgeries, catheterization procedures, and interventions
- Postoperative anatomy—obtained from the surgical notes
- Routes of access to the right and left heart, and alternative access sites
- Readiness to perform therapeutic procedures, should the need arise

CARDIAC CATHETERIZATION: BASIC PRINCIPLES

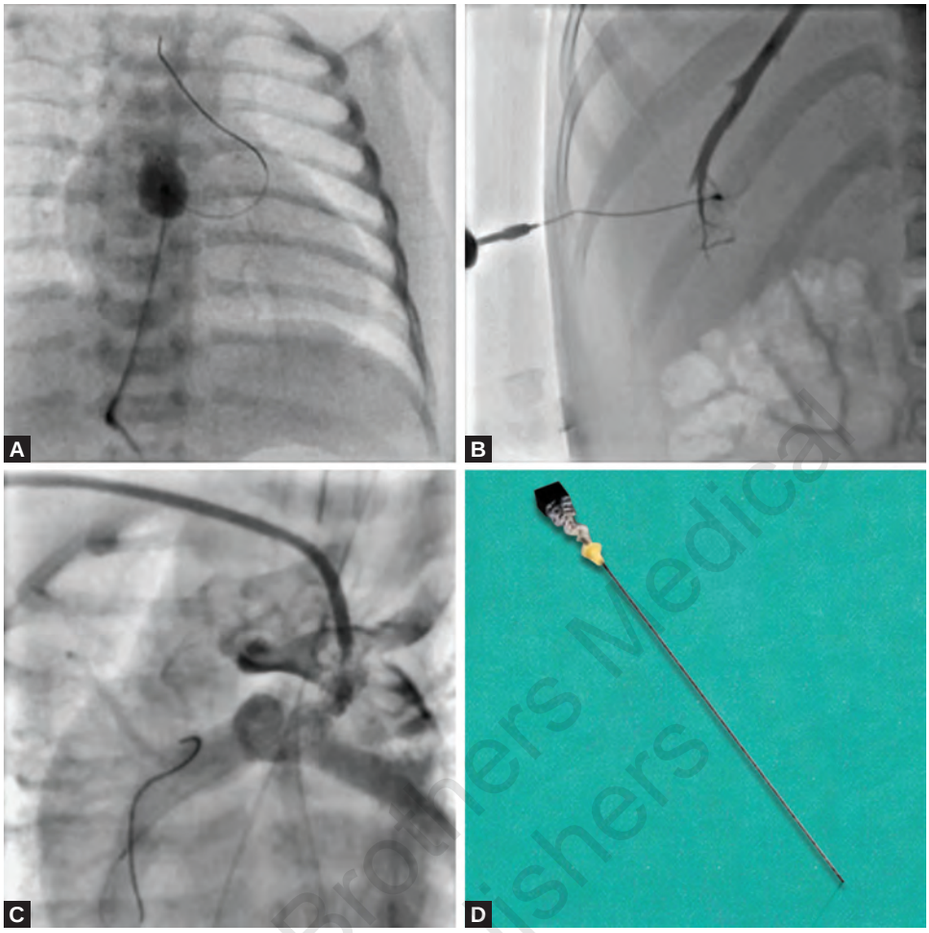
The core tenets of cardiac catheterization apply to patients with CCHDs. We will look at some important principles specific to catheterizing a patient with CCHD.

Vascular Access

Classically, vascular access to the right heart is through the femoral veins (FVs) or the internal jugular vein (IJV). In patients with altered anatomy, caval thrombosis, postoperative states, or heterotaxy syndrome with interrupted inferior vena cava (IVC), access to the right heart is not possible via the conventional veins. The hepatic veins drain into the right atrium (RA) and thus offer a direct route to the right heart.[3] Percutaneous access to the hepatic veins is often achieved with a slender 22G Chiba needle under continuous ultrasound (US) guidance. Sheaths up to 6F can be safely introduced into the hepatic veins through the liver parenchyma, and catheterization and angiocardiography are completed **(Figs. 2A to D)**. Hemostasis can be achieved when the tract is closed post procedure with gel foam or coils.

Another alternative route to access the right heart is the umbilical venous (UV) route. The UVs are patent until 72 hours after childbirth. The UV supports up to 5F sheaths. Although diagnostic cardiac catheterization is seldom done in newborns, the UV route is useful to perform balloon atrial septostomy (BAS) and for the insertion of a temporary pacemaker (TPI) lead. The course of a catheter inserted to the UV is: UV → portal vein → ductus venosus → IVC → RA.[4]

The left heart is accessed via the femoral arteries (FAs). In cases where it is not possible, axillary access is an excellent, safe alternative. This is especially useful for therapeutic



FIGS. 2A TO D: Various alternative access routes: (A) Umbilical access showing balloon atrial septostomy being done; (B) Transhepatic access with a Chiba needle; (C) Right axillary access for ductal stenting; (D) Chiba needle.

procedures—complex ductal stenting in cases of duct-dependent circulation—or for coarctoplasty in infants with poor FA pulses **(Figs. 2A to D)**.

Contrast Administration

For excellent anatomic delineation, good contrast injection is essential. Here are a few key important takeaways:

- Opacification is determined by contrast volume, flow rate, pressure of injection in pounds per square inch (PSI), and the contrast medium viscosity.
- Contrast should be injected rapidly into the vascular structures, with the entire bolus injected in less than 2 seconds.
- For aorta and cardiac chamber opacification, it is recommended to use 1–1.5 mL/kg of contrast and 0.5–1 mL/kg for opacification of pulmonary arteries, its branches, and venous structures.
- Total contrast volume should be ideally kept <5 mL/kg/study.
- Power injectors should be ideally used. Hand injections may paradoxically use more contrast due to poor opacification.
- Flow rate per second is more important than the volume used, and it is proportional to the French size used. Flow rate/French size = (French size of the catheter × 2) + 2
- 800 PSI for left-sided structures and 600 PSI for right-sided structures usually offer good opacification.
- Viscosity of the contrast medium is inversely proportional to temperature. So warm contrast flows better through the catheters.
- Injecting downstream opacifies vascular structures better.
- Catheter selection is important. Larger bore catheters allow for a high flow rate and opacify the structure better.
- Select angiographic views based on desired information. Avoid indiscriminate angiograms. Biplane angiography suites are ideal to reduce contrast use, at the expense of more radiation.

Use of contrast medium in cyanotic patients has its own risks. Cyanosis provokes erythrocytosis and increases the viscosity of blood, making the milieu more thrombotic. The risk of contrast-induced acute kidney injury (CI-AKI) is increased in patients with CCHD. Preprocedural fluids and the use of iso-osmolar contrast agents can mitigate the risk to an extent. Additionally, in a sedated patient with CCHD, hypoventilation

and ventilation–perfusion (V/Q) mismatch can cause and worsen acidosis.

Catheters

There are numerous diagnostic catheters used in the pediatric cardiac catheterization laboratory. It is essential to understand the nature and specifications of commonly used ones. Many catheters of historical renown are no longer in common use, and catheters designed for adult coronary use are often used in pediatric cardiology. An ideal angiographic catheter should be stable in vivo, have less to no whip, withstand high PSI pressure injections, and have multiple proximal side holes for adequate contrast dispersion. An end-hole catheter without side holes may cause myocardial staining and perforation of cardiac chambers during contrast injection. **Table 2** summarizes the currently used diagnostic catheters.

Catheter Manipulation

Catheters should be advanced into the cardiac chambers and vessels over a deflectable guidewire. Balloon-tipped catheters, after inflation with CO_2, float into the pulmonary arteries (PAs) easily through the venous system.

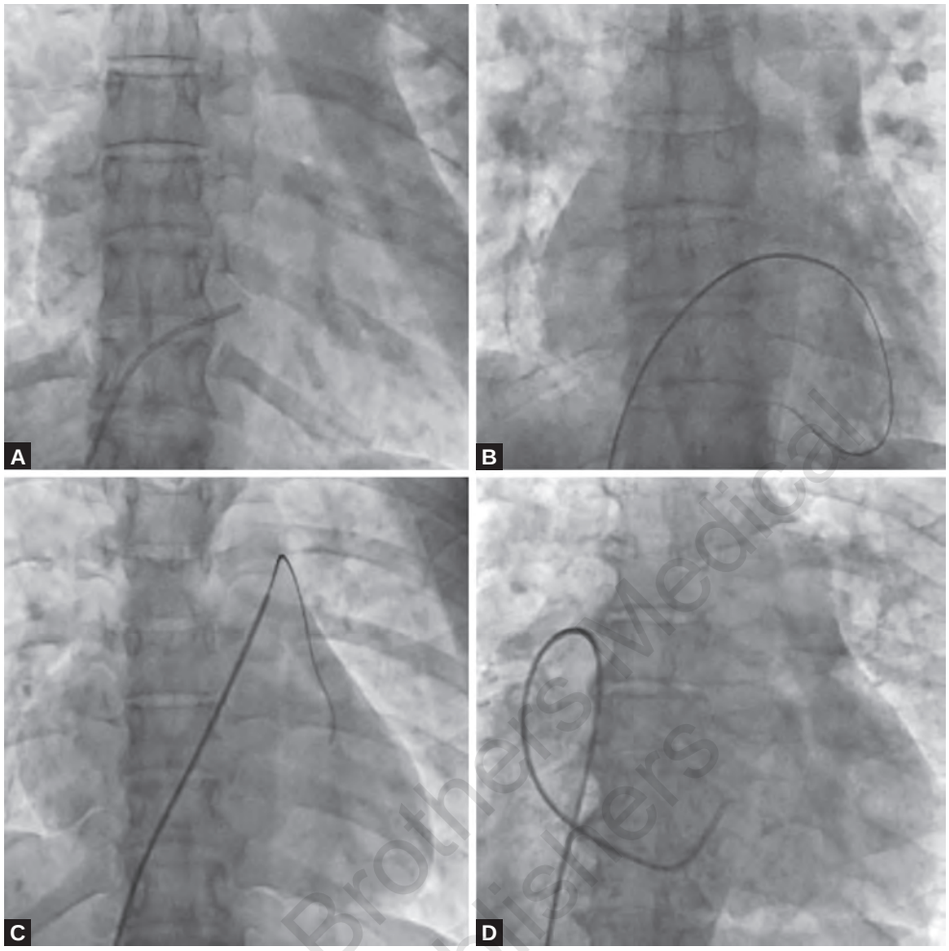
Entry into right ventricle (RV) and PA from the FVs can be accomplished by a few methods:[2]

- The catheter over a soft-tipped guidewire is introduced into the RA and the tip is aimed toward the anteriorly placed tricuspid valve (TV) by clockwise catheter torque. The guidewire is first advanced into the RV, followed by the catheter. This passage may be difficult in case of:
  - Large RA
  - Severe tricuspid regurgitation (TR) or tricuspid stenosis (TS)
  - RV hypoplasia
- The right atrial appendage (RAA) is anterior, and the superior vena cava (SVC) is posteriorly related to the RA. Forming a reverse loop with the guidewire and catheter in RA, avoiding the thin-walled RAA will prolapse the catheter into the RV and direct it toward the PA.
- Once in the RV, the catheter tip will be across the spine in the anterior–posterior (AP) projection. Clockwise torque will make the catheter tip face the RV outflow, and the

TABLE 2: Diagnostic catheters.

Selective, preformed curve, torque-controlled catheters	
Judkins right catheter	Commonly used in coronary catheterization, it is used extensively to enter the vascular structures—branches, RVOT → PA, APCs
Multi-purpose catheter	Has distal ends at obtuse angles and is used to enter vascular branches, perform selective angiograms, and measure pressure. Has end and side holes
Simmons (Sim) catheter	Originally designed for cerebral and renal angiography, it is a catheter that "looks down." In the pediatric catheterization laboratory, it is used to engage APCs, postsurgically placed shunts, and cannulate any vascular structure with a down-going, angulated takeoff from the aorta
Cobra catheter	A complex catheter with wall-seeking ability, it is used to cannulate down-going branches of the aorta and APCs
IMA catheter	Resembles the Judkins right catheter and is useful for selective angiography
Angiographic catheters	
NIH	The prototypic right heart angiographic catheter, with six side holes and no end hole
Pigtail catheter and angled pigtail catheter	• Used for ventricular angiography. Ideally designed with multiple side holes for even contrast dispersion and catheter stability during power injection. Distal end hole allows for insertion over a guidewire • Marked pigtail can help in measuring the vascular structures
Cut pigtail catheter	A modified pigtail which is manually cut at the distal end to accommodate vascular entry in difficult to cannulate, angulated structures
Balloon floatation catheters	
Standard Berman angiographic catheter	Balloon at the distal end with side holes proximal to it. No end hole and thus does not accommodate a guidewire. Floated to the right heart with CO_2 insufflation, or to the left heart across IAS or IVS, it is excellent for: • RV and PA angiography • Antegrade balloon occlusion aortography in TGA for coronary visualization • Occlusion of fenestration in a fenestrated Fontan circuit to measure pressure changes
Reverse Berman catheter	Distal end has multiple side holes with the balloon proximal. Contrast gets injected distally to the balloon. Used in pulmonary venous wedge angiogram

(APCs: aortopulmonary collaterals; IAS: interatrial septum; IMA: internal mammary artery; IVS: interventricular septum; PA: pulmonary artery; RV: right ventricle; RVOT: right ventricular outflow tract; TGA: transposition of great vessels)



FIGS. 3A TO D: Right ventricle entry.

guidewire and catheter can be easily advanced into the PAs **(Figs. 3A to D)**.

- Patients with CCHDs are prone to atrial and ventricular arrhythmias. They can be provoked during aggressive catheter manipulation in the RA and RV.

The left atrium can be easily entered with a multipurpose catheter in the presence of an atrial septal defect (ASD) and the pulmonary veins (PVs) can be accessed.

Angiographic Projections

Angiography should produce crisp images with no overlap or foreshortening. Due to the limited amount of contrast that can be used per study, selecting angiographic views is an important part of preprocedural planning. Good noninvasive imaging and understanding of anatomy will help the operator choose optimal projections—saving time, reducing radiation, and optimizing contrast volumes. There is no ideal angiographic projection as anatomy in CCHD is remarkably diverse and exotic. **Table 3** collates the optimal views used during angiography in patients with CCHD.[5] A major caveat that there is no "one size fits all" must be kept in mind and adjustments must be made on the fly during the procedure.

ANGIOGRAPHY IN CYANOTIC CONGENITAL HEART DISEASES

Angiography is an important adjunct to diagnose and plan the management of complex CCHDs. Additionally, it is useful in follow-up and management of postoperative patients, especially when transesophageal echocardiogram (TEE) does not define the anatomy. We will discuss the utility with the following examples. The readers are welcome to go through the video files at the link https://t.ly/kCLK.

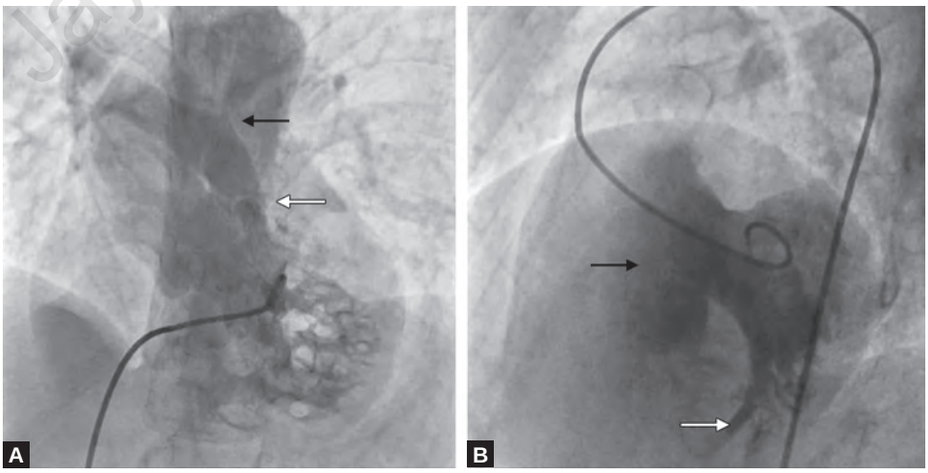
Tetralogy of Fallot

Classic tetralogy of Fallot (TOF) **(Figs. 4 to 6)** and TOF physiologies [with a ventricular septal defect (VSD) and PS] are the most common CCHDs. Classical TOF is a conotruncal anomaly with anterior displacement of the conal septum, which results in four overlapping components that cause the unique physiology of reduced PBF–RVOT obstruction with hypoplastic PAs, malaligned VSD, aortic override, and right ventricular hypertrophy. There could be other abnormalities such as additional VSDs, coronary artery abnormalities, and a right aortic arch. As TEE and CT are often enough to diagnose and plan

TABLE 3: Angiographic projections.

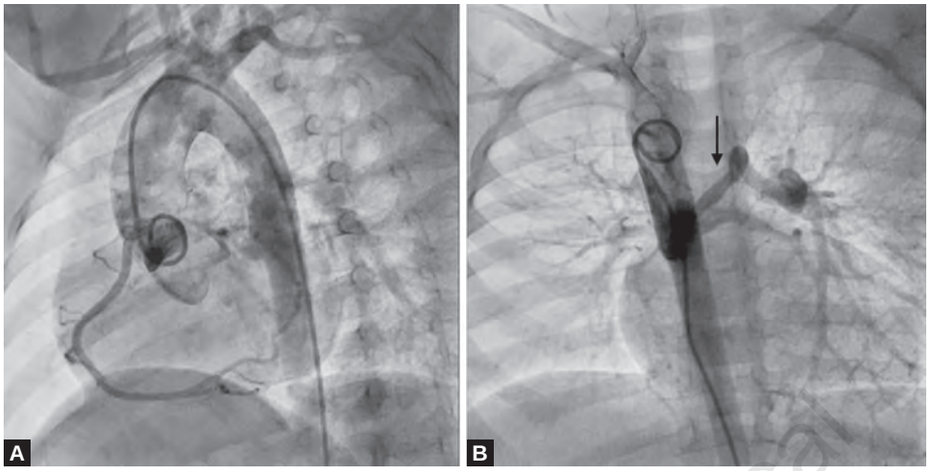
Chamber	Projection
RV	• AP • AP cranial 30° • Left lateral 90°
RVOT	• LAO 15 cranial 30°–40° • RAO • Left lateral 90°
PAs	Angiographic imaging of pulmonary arteries is fraught with difficulties due to foreshortening. So, modifications must be made in each individual case
• MPA	AP cranial 30°
• LPA	• LAO 60° cranial 20° • Left lateral 90°
• RPA	Shallow RAO cranial 10°–15°
Peripheral PAs	AP
IAS and ASD	• LAO 30°, cranial 30° • Steep LAO
LV	• RAO, LAO • *Long axis oblique view*: LAO 70° cranial 30° • *Hepatoclavicular view*: LAO 45° cranial 45°
PVs	• AP in levophase after injection in the MPA/LPA/RPA • Left lateral 90°
Ascending aorta and coronaries	AP caudal 45°
Arch of aorta	Steep RAO or LAO
Descending aorta	• Left lateral 90° • AP
APCs	AP
Conduits from RV	AP cranial 30°

(AP: anterior–posterior; APCs: aortopulmonary collaterals; ASD: atrial septal defect; IAS: interatrial septum; LAO: left anterior oblique; LPA: left pulmonary artery; LV: left ventricle; MPA: main pulmonary artery; PA: pulmonary artery; PVs: pulmonary veins; RAO: right anterior oblique; RPA: right pulmonary artery; RV: right ventricle; RVOT: right ventricular outflow tract)

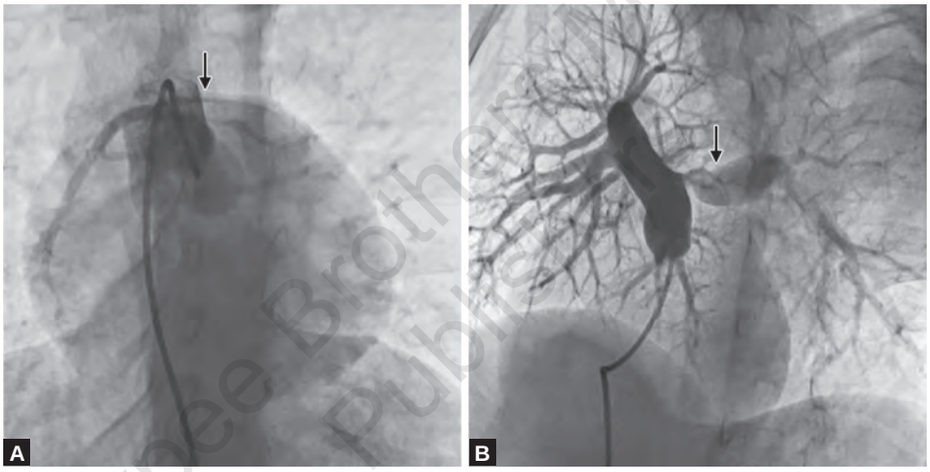


FIGS. 4A AND B: TOF: (A) Right ventricular angiogram showing a trabeculated RV, infundibular and pulmonary valve narrowing (white arrow). Bilateral branch PAs are visible with an LPA ostial stenosis (black arrow). (B) Retrograde LV angiogram showing two VSDs. Black arrow—subaortic VSD, and white arrow—apical VSD.

(LPA: left pulmonary artery; LV: left ventricle; PAs: pulmonary arteries; RV: right ventricle; TOF: tetralogy of Fallot; VSD: ventricular septal defect)



FIGS. 5A AND B: TOF: (A) Aortic root angiogram; (B) Descending aortic angiogram showing collaterals (black arrow) to the lung.
(TOF: tetralogy of Fallot)



FIGS. 6A AND B: TOF: (A) Root angiogram showing a coronary branch crossing the RVOT (black arrow); (B) RVOT angiogram showing a narrow LPA origin stenosis.
(LPA: left pulmonary artery; RVOT: right ventricular outflow tract; TOF: tetralogy of Fallot)

management, the role of catheterization and angiogram is to complete the evaluation by providing the missing information. In our center, catheterization for diagnosis is rarely done.

After FA and venous access, a total of four to five angiograms is enough to provide all necessary information in TOF **(Table 4)**. Alternatively, with just the femoral arterial access, the RV can be entered from the aorta retrogradely through the override and the VSD.

- *Additional VSDs*: Due to the equalization of pressures in the LV and the RV, additional small-to-moderate-sized VSDs in the mid muscular septum and the apical septum cannot be detected by TEE. LV angiography defines them, so they can be addressed during surgery. Residual VSDs detected after complete repair are important causes for weaning failure and hemodynamic instability **(Figs. 3A to D)**.
- Pressure difference across the VSD can be measured to rule out a restrictive VSD.
- *PA anatomy*: While TEE and CT can define the PA anatomy, a conventional angiogram provides more clarity to:
  - Presence or absence of native PAs, their anatomy and flow across the RVOT, and the branch pulmonary arteries
  - Imaging of left PA (LPA) and right PA (RPA) origin stenosis
  - Quantification of hypoplasia of the PAs using various indices[6-8] described in **Table 4**. Surgical management depends on the adequacy of the PAs.
  - Distal arborization of the PAs in the lung segment. Lung segments not supplied by the PAs usually have supply from aortopulmonary collaterals (APCs).
- *Coronary anatomy*: The prevalence of coronary anomalies in TOF is 4–6%.[9] In patients with coronary anomalies, 72% of the anomalous arteries cross the RVOT. Defining the course of such arteries is essential for a safe, successful surgery to

TABLE 4: Angiography in tetralogy of Fallot (TOF).

Angiographic views	Indices to assess adequacy of PAs (applies to TOF and PA/VSD)
• RV angiogram in AP projection with a slight cranial tilt to image the RVOT and PA • LV angiogram in long-axis oblique view to assess additional VSDs • Aortic root angiogram in AP view to define the coronary anatomy • Aortic arch angiogram to demonstrate APCs from the subclavian arteries and confirm arch sidedness • Descending aortic angiogram to demonstrate APCs to the lung	• McGoon ratio • Diameter of the LPA + RPA/diameter of the DA at the level of diaphragm ○ Normal = 2–2.5 ○ VSD can be closed at corrective surgery if ratio > 1 ○ If less, VSD should be fenestrated at the time of surgery to avoid RV dysfunction. Fenestration can be later addressed once the PAs grow post operation • Nakata index ○ Cross section area of RPA and LPA/BSA ○ Normal ≥ 330 mm^2/m^2 • *Z score*: Using web-based tools (www.parameterz.com), Z-scores can be calculated for the PAs to assess their adequacy

Note: Diameters of the RPA and LPA must be measured just before the level of their first branch.

(AP: anterior–posterior; APCs: aortopulmonary collaterals; BSA: body surface area; DA: descending aorta; LPA: left pulmonary artery; LV: left ventricle; PA: pulmonary artery; RPA: right pulmonary artery; RV: right ventricle; RVOT: right ventricular outflow tract; VSD: ventricular septal defect)

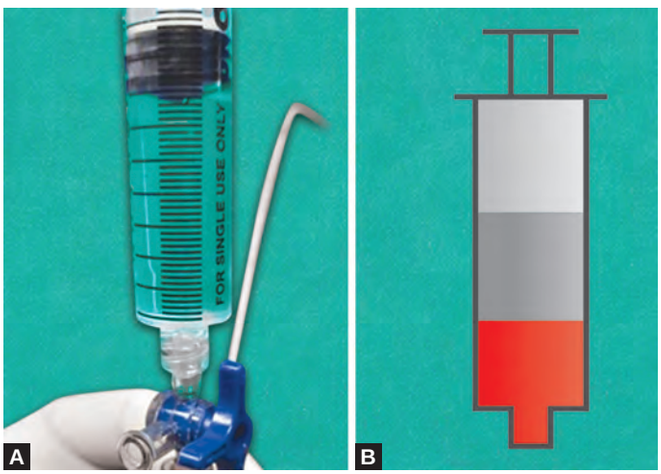
avoid damaging these vessels during RVOT muscle bundle resection. Aortic root angiogram defines the abnormal course **(Figs. 6A and B)**.

- *APCs*: Detection of APCs and interventional closure is a common reason for catheterization and angiography in a case of TOF.[10] APCs are usually seen in cases of pulmonary atresia with VSD, TOF with severely reduced antegrade PBF, or in adult TOF. The APCs can arise from the descending aorta, innominate, subclavian arteries, and the ascending aorta. If the patient has a patent ductus arteriosus (PDA) supplying the PAs, the APCs are usually absent. Angiography in the AP projection at the level of arch and descending aorta is key to detecting the number, size, and significance of the APCs. APCs cause persistent pulmonary venous returns and result in a bloody surgical field after cardiopulmonary bypass at the time of corrective repair, causing difficulties. Post procedure, after establishing good antegrade PA flows, the persisting APC flow to the lung increases PBF, resulting in failure to wean from the ventilator. So, all significant APCs should be coil-embolized either peri/post procedure or ligated intraoperatively **(Figs. 5A and B)**.

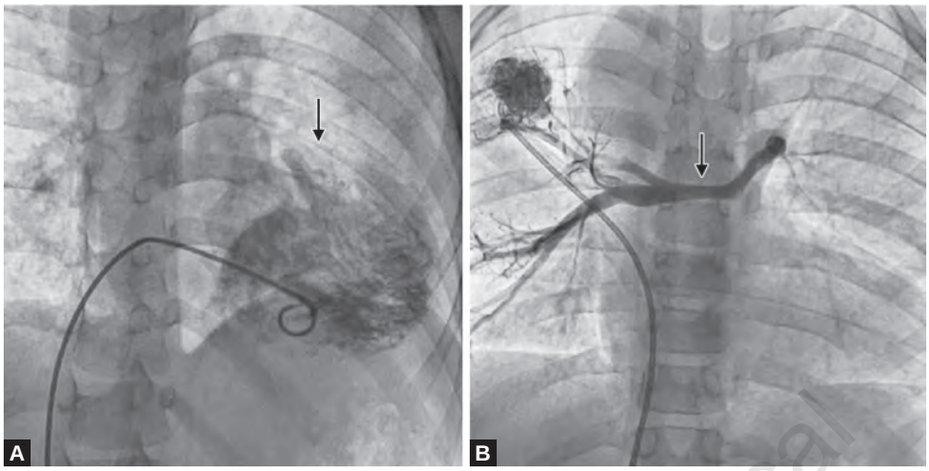
Pulmonary Atresia with Ventricular Septal Defect (Figs. 7 and 8)

Pulmonary atresia with ventricular septal defect (PA/VSD) is a rare CCHD with a challenging management course. The clinical presentation is akin to a patient with classical TOF, and the pulmonary flow is maintained by APCs or a PDA. The RVOT is blind and atretic, with no connection between the RV and the PAs. TEE and cardiac CT are often enough to establish a diagnosis, but additional imaging is often mandatory.

- The surgical management in PA/VSD depends on the adequacy of the central pulmonary arteries. Confluent PAs will allow for unifocalization and complete repair. RV angiogram will reveal a blind RVOT with no opacification of the PAs. The PAs are visualized by performing a pulmonary venous wedge angiogram **(Figs. 6A and B)**. The principle behind this is that a retrograde injection of contrast into the PVs will retrogradely fill and opacify the branch PAs and the confluence.
  - The PV is assessed from the LA in the presence of an ASD. If the IAS is intact, a catheter can be advanced retrogradely from the aorta → LV → LA across the mitral valve → PV.
  - An end-hole catheter is wedged in the PV.
  - The PVs are filled gradually and gently with contrast and flushed with saline. The contrast and saline are drawn and layered in the same syringe to flush the contrast rapidly **(Figs. 7A and B)**.
  - Continuous angiography is performed, and the retrograde filling of pulmonary arteries is appreciated. Confluent PAs will demonstrate the "sea gull sign" **(Figs. 8A and B)**.
- In many cases of PA/VSD, a PDA will be supplying the PAs. PDA is usually vertical and arises from the undersurface of the arch, rather than at the usual location. A unilateral PDA is associated with confluent PAs and a bilateral PDA is associated with nonconfluent PAs, complicating the further management of these patients. Aortic root angiogram will reveal the location and nature of the PDA.
- As described for patients with classical TOF, multiple APCs should be defined as they are the only supply for

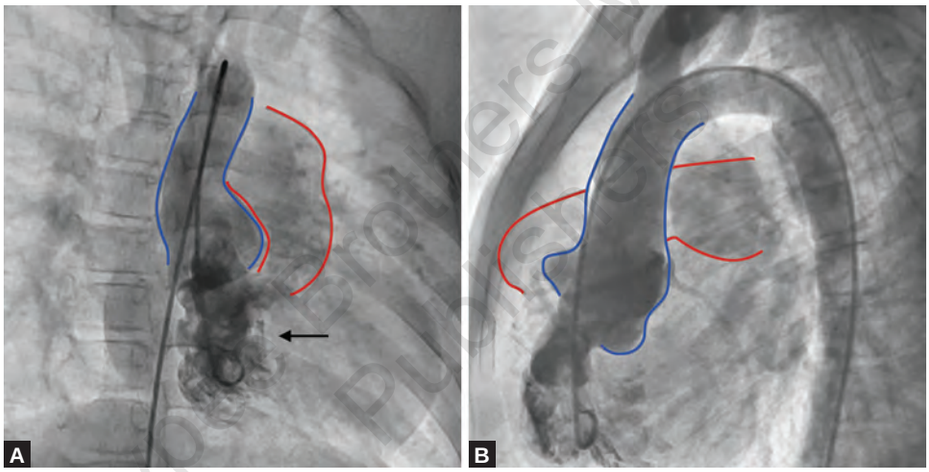


FIGS. 7A AND B: Pulmonary venous wedge angiogram: (A and B) Syringe filled for venous wedge angiogram. The blood (red), contrast (grey), and saline (light grey) must be layered, and the syringe is held perpendicularly and injected.



FIGS. 8A AND B: Pulmonary atresia with VSD: (A) Trabeculated RV with a bling RVOT (black arrow); (B) Pulmonary venous wedge angiogram showing the filling of the PAs. The PAs are confluent.

(PAs: pulmonary arteries; RV: right ventricle; RVOT: right ventricular outflow tract; VSD: ventricular septal defect)



FIGS. 9A AND B: DORV: (A) Retrograde pigtail catheter in the aorta → trabeculated RV. RV gives origin to aorta and the PA. Aorta is highlighted in blue and PA is highlighted in red. (B) Lateral view of the same. PA is anterior to the aorta.

(DORV: double outlet right ventricle; PA: pulmonary artery; RV: right ventricle)

the lung and need to be unifocalized to a surgically placed RV–PA conduit at the time of surgery. APCs can arise from anywhere in the aorta, head and neck vessels, or rarely from the coronary arteries.

- With catheterization, it is important to fully quantify the sources of blood flow to all segments of the lung, as it is essential for surgical management.

Double Outlet Right Ventricle

Double outlet right ventricle (DORV) **(Figs. 9A and B)** is of several types. Simplistically, it is a disease complex with abnormal ventriculo-arterial connection, where both the great arteries arise from the morphological RV. The oxygenated blood must exit the LV through a VSD to enter the aorta. This gives rise to the important concept of blood streaming. If the VSD is subaortic, blood preferentially streams to the aorta whereas a subpulmonary VSD will stream the blood preferentially to the PAs, causing a transposition physiology. Noninvasive diagnostic modalities are more than sufficient to diagnose DORV and plan management. Cardiac catheterization and angiography in DORV is useful in a few cases. A classification is presented in **Table 5**.[11] More than angiography, hemodynamic assessment [pulmonary vascular resistance (PVR), interventricular gradient to rule out restrictive VSD] is important in cases of DORV to plan surgery.

L and D Transposition of Great Arteries

Angiography is not routinely performed to diagnose these conditions. Catheterization in D-transposition of great arteries (D-TGA) is restricted to interventions—BAS to improve

atrial mixing or prior to a PDA stent for LV training **(Figs. 10 to 12)**.

Total Anomalous Pulmonary Venous Connection

Noninvasive modalities have superseded traditional angiography in these patients. In adult unobstructed total anomalous pulmonary venous connections (TAPVCs; **Figs. 13 and 14**), catheterization is performed to assess PVR for operability and rarely to diagnose. Levophase injections in the PAs will reveal the drainage patterns **(Fig. 13A)**. In a rare case, a 2-day-old infant with obstructed TAPVC (hemodynamic vice with an adequate interatrial communication) and hypoxic encephalopathy and sepsis, catheterization, and intervention—stenting of the vertical vein at the site of the vice was performed to improve hemodynamics as the child was waiting for corrective surgery. This offers a not often seen angiographic view of TAPVC **(Figs. 14A and B)**.

Cyanotic Heart Disease at the Level of Great Arteries

This includes truncus arteriosus (TA) and abnormal aortic origin of (right or left) pulmonary artery (AOPA). Noninvasive imaging is sufficient for diagnosis. But a few important uses remain for angiography.

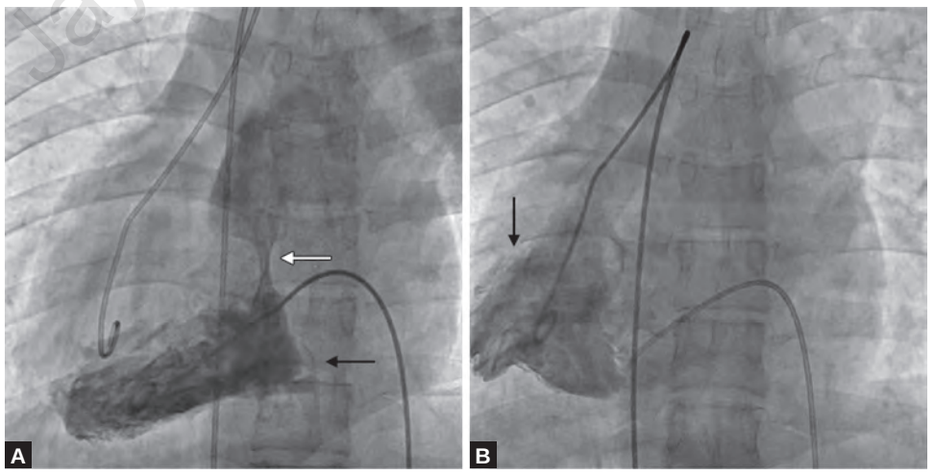
- In TA, angiography can be used to demonstrate the truncal root, origin of the PAs, and their orientation, coronary pattern, and truncal regurgitation.
- Injection in the ascending truncal root will also demonstrate any arch interruptions.
- One-sixth of TA patients have unilateral absence of PAs. In such cases, the source of blood supply to the lung must be delineated. The operator should look for APCs or PDA supplying the PA or perform a pulmonary venous wedge angiogram to demonstrate the pulmonary blood supply.[12]

Aortic origin of pulmonary artery is a rare anomaly that by the time identified is inevitably inoperable. Here, one PA, usually

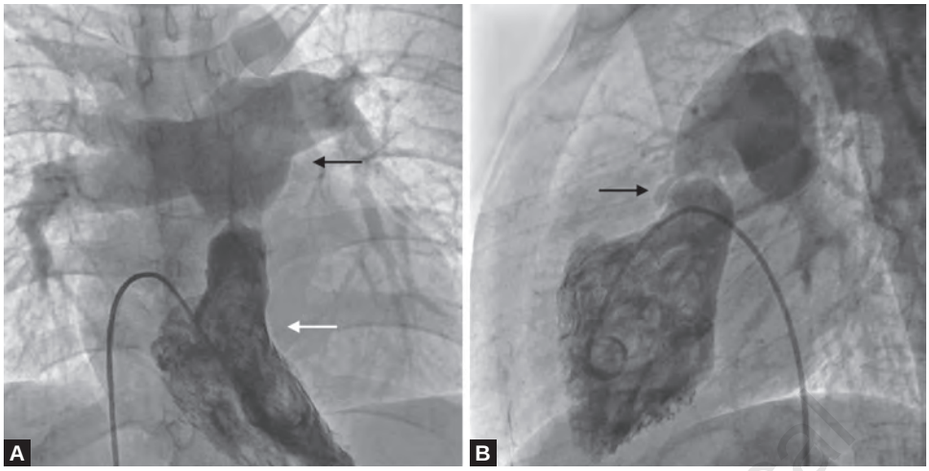
TABLE 5: Angiography in double outlet right ventricle.

Types of DORV and angiocardiography	
Types	**Catheterization and angiogram**
DORV with VSD and PS (TOF type)	Same as TOF
Transposition type of DORV (DORV with subpulmonary VSD)	LV angiogram will selectively fill the PAs (unfavorable streaming)
DORV with VSD (subaortic VSD)	• LV angiogram can delineate the size and location of the VSD, demonstrate the aorta filling (favorable streaming), and demonstrate the VSD position in relation to the origins of the great arteries (routability of the VSD to the aorta) • RV angiogram will show the arrangement of the great vessels
DORV with noncommitted VSD (remote, nonroutable VSD)	LV angiogram can be done to assess for routability of the VSD to the aorta

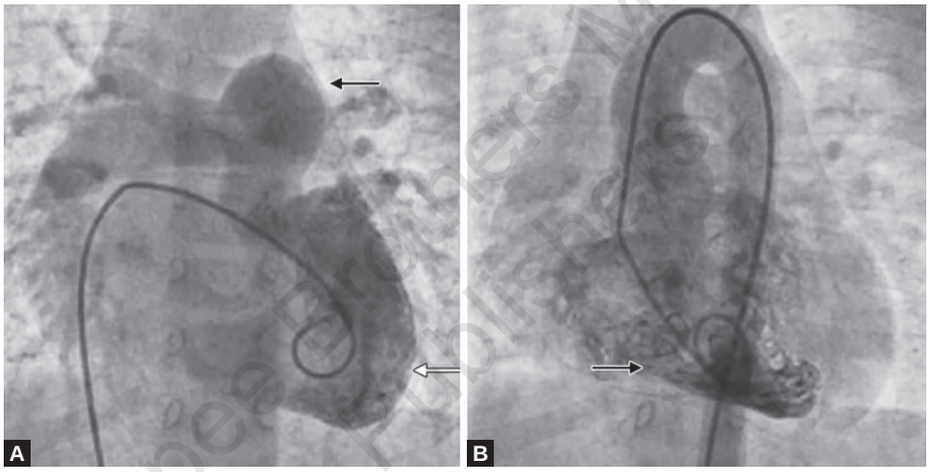
(DORV: double outlet right ventricle; LV: left ventricle; PA: pulmonary artery; PS: pulmonary stenosis; RV: right ventricle; TOF: tetralogy of Fallot; VSD: ventricular septal defect)



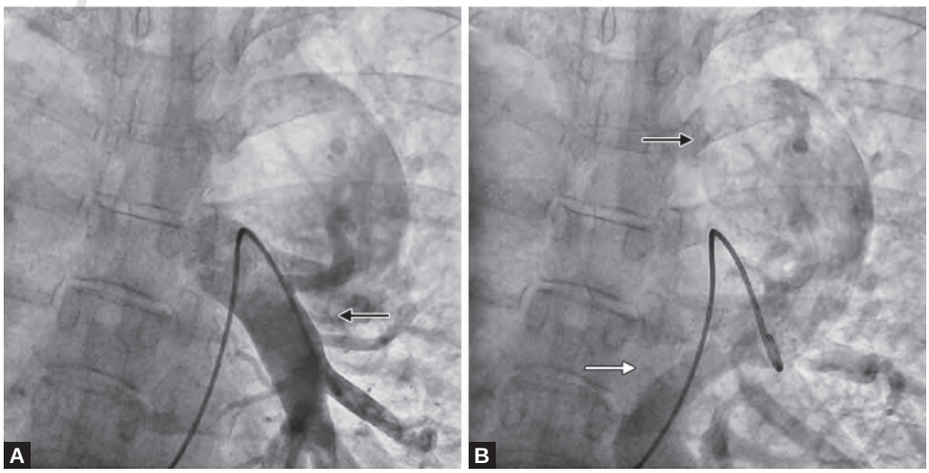
FIGS. 10A AND B: CTGA: (A) Retrograde aortic pigtail is in the subaortic ventricle. Contrast delivered via the antegrade venous pigtail is in the smooth-walled morphological LV, which is the subpulmonary ventricle. There is LVOT obstruction (white arrow) amounting to pulmonary stenosis. (B) Injection into the retrograde aortic pigtail shows a trabeculated morphological RV (black arrow), which is the systemic ventricle.
(CTGA: corrected transposition of great arteries; LV: left ventricle; LVOT: left ventricular outflow tract; RV: right ventricle)



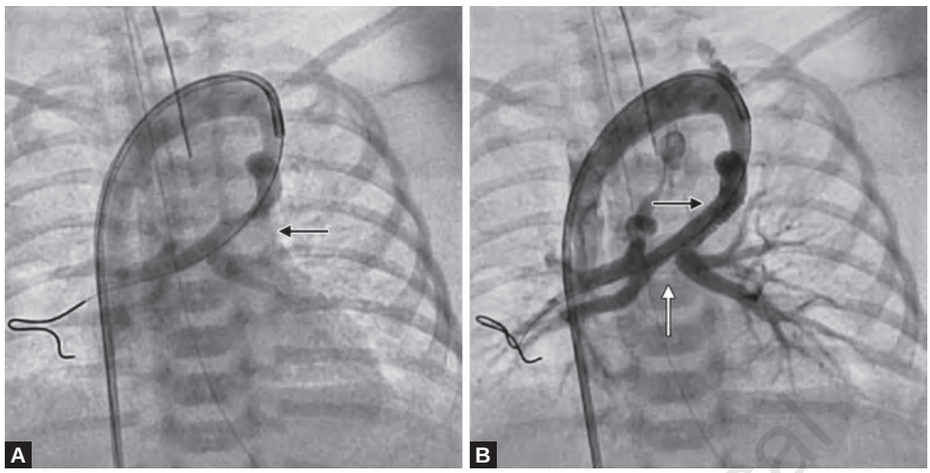
FIGS. 11A AND B: CTGA: (A) Retrograde venous catheter into the smooth-walled morphological subpulmonary left ventricle. Injection revealed a pulmonary valve stenosis with a poststenotic dilatation (black arrow). (B) Lateral view.
(CTGA: corrected transposition of great arteries)



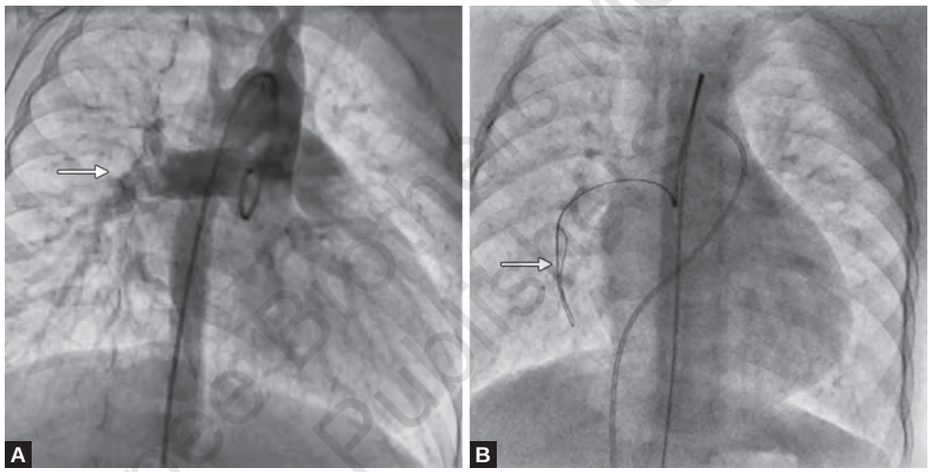
FIGS. 12A AND B: D-TGA: (A) Smooth-walled LV is connected to the PA (black arrow); (B) Trabeculated RV is connected to the aorta.
(D-TGA: D-transposition of the great arteries; LV: left ventricle; PA: pulmonary artery; RV: right ventricle)



FIGS. 13A AND B: TAPVC: (A) LPA injection; (B) Levophase showing the dilated vertical vein connecting the SVC (white and black arrows).
(LPA: left pulmonary artery; SVC: superior vena cava; TAPVC: total anomalous pulmonary venous connection)



FIGS. 14A AND B: TAPVC: (A) Antegrade venous catheter IVC → RA → innominate vein → vertical vein → common chamber of the PVs; (B) Stent in place at the narrowest obstructed part of the vertical vein.
(IVC: inferior vena cava; PVs: pulmonary veins; RA: right atrium; TAPVC: total anomalous pulmonary venous connection)



FIGS. 15A AND B: AORPA: (A) Aortic injection fills the RPA; (B) A 0.025″ wire is placed retrogradely from the aorta into the RPA (white arrow) to show the anomalous origin. This patient had intractable pulmonary hypertension.
(AORPA: aortic origin of right pulmonary artery; RPA: right pulmonary artery)

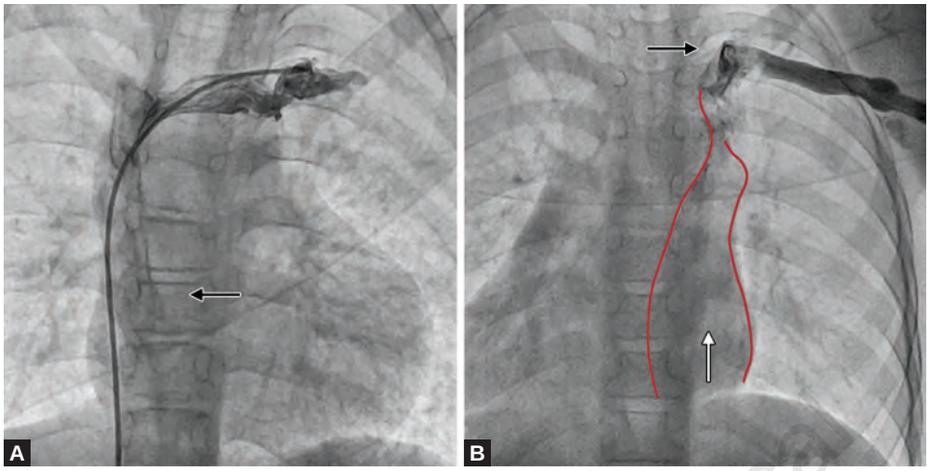
the RPA, arises from the aorta. The right lung is then exposed to systemic pressures and develops pulmonary vascular occlusive disease (PVOD). Due to neurohormonal feedback mechanisms, the left lung, even though supplied by the normally arising LPA (from the RV), also develops PVOD and elevated PVR. Cardiac catheterization is essential to determine operability by measuring the PVR. Angiograms are shown in **Figures 15A and B**.

Cyanosis in a Structurally Normal Heart

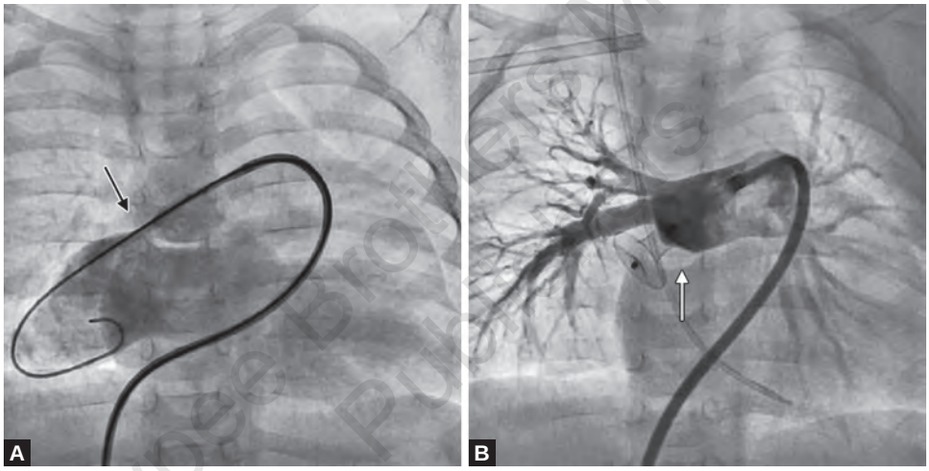
Cyanosis in a structurally normal heart is a miscellaneous group that includes CCHDs that cause cyanosis because of abnormal systemic vein drainage, due to either abnormal communication between systemic and PVs or cardiac chambers. Noninvasive imaging is often sufficient for diagnosis, and agitated bubble contrast echo given in the left forearm will pick up abnormal communications. CT often is sufficient to further plan and manage. Cardiac catheterization and angiography is relevant, prior to therapeutic management.

Left Superior Vena Cava

The persistent left SVC (LSVC) is an embryological remnant that persists in a few patients due to the failure of involution of the left superior and left common cardinal veins. It is a frequent association in any CCHDs and acyanotic obstructive lesions of the left heart. It drains via the coronary sinus into the RA, and very rarely causes any effect. Sometimes, the LSVC can cause cyanosis when it drains into the LA directly or indirectly due to fenestrations and unroofing of the coronary sinus. While LSVC is the most common of the anomalies of systemic venous drainage, right SVC (RSVC) drainage to LA, IVC to LA, and totally anomalous systemic venous connections (TASVCs) are



FIGS. 16A AND B: LSVC: (A) LSVC draining to the RA; (B) LSVC draining to LA (white arrow) via an unroofed CS. Injection done via the left brachial vein.
(CS: coronary sinus; LA: left atrium; LSVC: left superior vena cava; RA: right atrium)



FIGS. 17A AND B: PALAF: (A) Fistula from PA → LA. Injection in the PA pacifies the LA and LV. (B) Device closure done.
(LA: left atrium; LV: left ventricle; PA: pulmonary artery; PALAF: pulmonary artery to left atrial fistula)

also described and can cause cyanosis. **Figures 16A and B** show LSVC's draining to RA and LA.

Pulmonary Artery to Cardiac Shunts

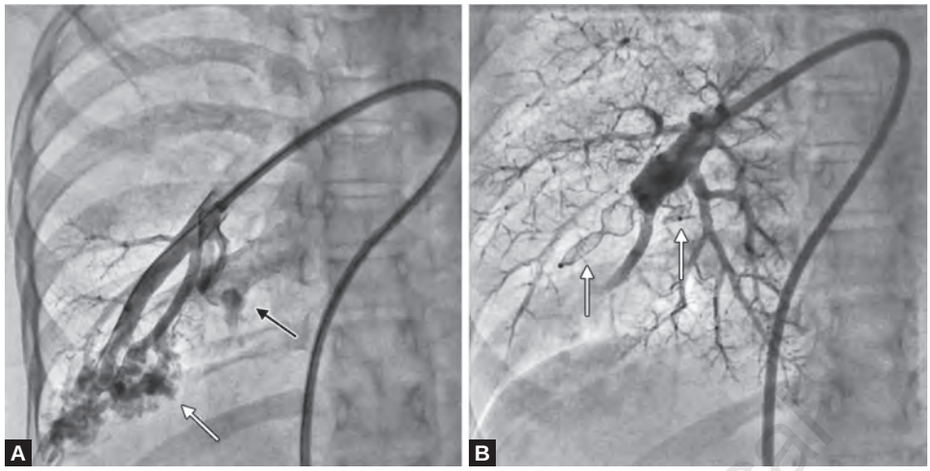
Pulmonary artery to cardiac shunts include, but are not limited to, PA to LA fistula (PALAF) and PA to PV fistula (PAPVF). They present with cyanosis, continuous murmur in a structurally normal heart. Cyanosis is a consequence of abnormal arteriovenous connections. Careful TEE may reveal abnormal connections and bubble contrast echo can identify the defect. Catheterization and angiography is an adjunct to diagnosis and is indicated prior to therapeutic closure. An example is shown in **Figures 17A and B**.

Pulmonary Arteriovenous Malformations

Pulmonary arteriovenous malformations (PAVMs) bypass the normal capillary drainage of the lung, resulting in unoxygenated blood from the pulmonary arteries shunting into the PVs **(Figs. 18A and B)**. This right-to-left shunt with a structurally normal heart causes cyanosis, and is a major cause for cyanosis in structurally normal hearts. The PAVMs come into clinical light when they cause complications—brain abscess or paradoxical embolism. TEE is usually normal and bubble contrast echo is diagnostic. The various types are given in **Table 6**.

Pulmonary angiography is indicated prior to therapeutic interventions. Simple and complex PAVMs, to an extent, are closed with coils or devices. Any PAVM above 3 mm is indicated for closure, regardless of the symptoms. Diffuse PAVMs often need surgery.

Angiograms are done in the individual PAs or the subsegmental PAs. After contrast injection, levophase is obtained. Normal levophase takes a few cardiac cycles to opacify the PVs. In case of a PAVM, the angiogram will highlight the feeding vessels, tortuous sac, and the draining PVs in just one cardiac cycle.



FIGS. 18A AND B: PAVM: (A) RPA injection shows numerous PAVMs; (B) Device closure done.
(PAVM: pulmonary arteriovenous malformations; RPA: right pulmonary artery)

TABLE 6: Types of pulmonary arteriovenous malformation (PAVMs).

Simple	Single branch of pulmonary artery supplies the PAVM
Complex	Two or three arteries create a plexiform lesion, usually in the lower lobes of the lungs
Diffuse	Involves several segmental pulmonary arteries, creates a tortuous mass of PAVMs. Usually in bilateral lungs because of hereditary disorders

Abernethy Malformations

The congenital extrahepatic portosystemic shunt (CEPS) (or Abernethy malformations) is a rare condition wherein the portal blood is shunted into the systemic circulation, bypassing the liver whether partially or completely.[13] It is because of the presence of abnormal vascular channels—either intra- or extrahepatic connections between the portal and the systemic systems. The portal blood contains blood rich in vasoactive substances, normally detoxified by the liver. The liver is bypassed, and these substances enter the pulmonary system. This results in the development of PAVMs, and they subsequently cause cyanosis. These children will have structurally normal hearts. With clinical suspicion, these can be identified by TEE and abdominal US. Several types exist, and type 2 CEPS is amenable to interventional closure where angiography is indicated. **Figures 19A and B** describe the types and a case example of type 2 CEPS.

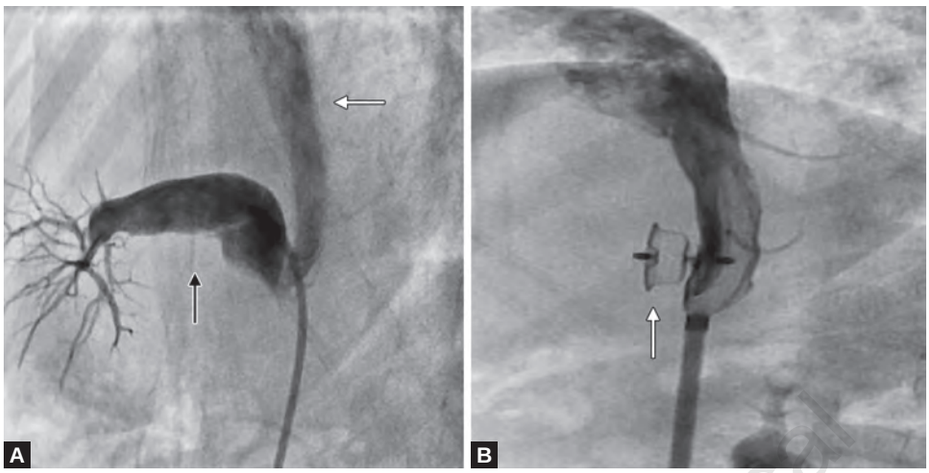
ANGIOGRAPHY IN POSTOPERATIVE CYANOTIC CONGENITAL HEART DISEASES

Cardiac catheterization and angiography is indicated in postoperative patients, for both diagnosis and therapeutic interventions. Postoperative states can have residuals (obligatory or due to the nature of the preoperative disease) or sequelae (situations that arise after the surgery and are inevitable) as defined by Perloff.[14] We will discuss a few scenarios.

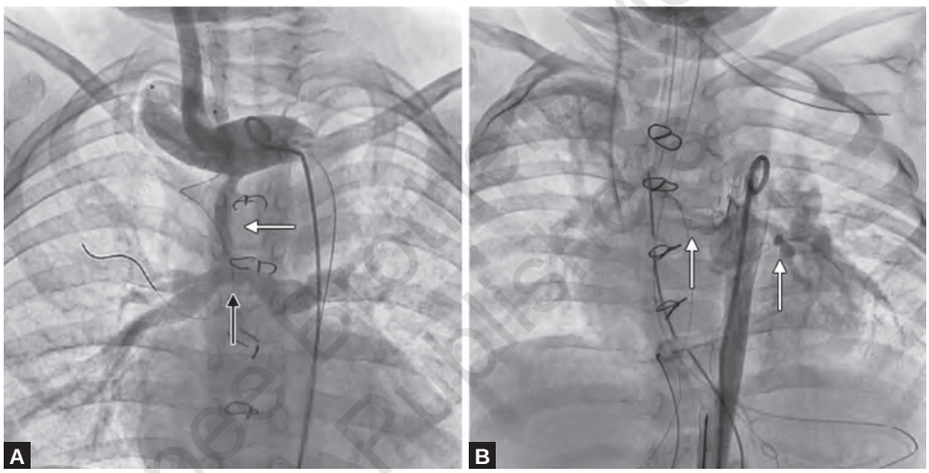
In postoperative patients, the cardiac anatomy and position in the thoracic cavity are altered and TEE may not provide all the information needed.

Angiography in Postoperative Tetralogy of Fallot (Figs. 20 to 25)

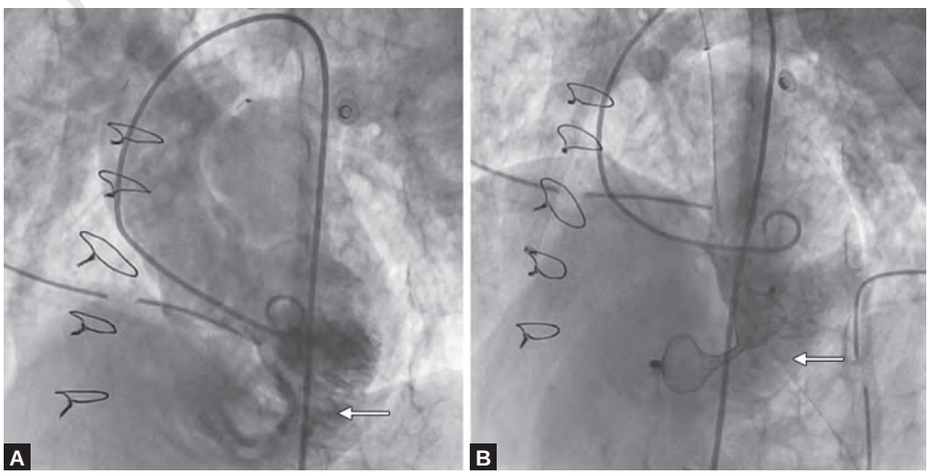
- The commonly performed systemic artery to PA shunts are the modified Blalock–Taussig—Thomas (BTT), Sano (RV–PA), and the central shunts (Waterson, Potts). These are palliative and are placed to improve PBF in patients who are not fit or need time for complete correction. They can develop dysfunction—shunt obstruction, stenosis either at the shunt or at the level of attachment at the PAs, leading to poor lung development and inadequate palliation. Acute thrombosis of the shunts after surgical placement is catastrophic. Angiography can identify these and help in therapeutic management **(Figs. 20A and B)**.
- Complete correction of TOF is not the end of the road for these children but instead the beginning of a long course with multiple future procedures.
- Immediate postoperative issues include residual VSDs causing difficulty in weaning and APCs causing increased PBF. Residual VSDs are documented on TTE, but cardiac catheterization and angiography is needed to quantify the severity. Ratio of pulmonary blood flow (Qp) to systemic blood flow (Qs) is more than 1.5, they need to be closed whether with a device or surgically. APCs need coil closure **(Figs. 21 and 22)**.
- Delayed complications in post TOF include severe progressive pulmonary regurgitation (PR) and right ventricular outflow tract obstruction (RVOTO), causing RV dysfunction and worsening TR. Angiography is essential to document PR and plan transcatheter valve replacement **(Figs. 22A and B)**.



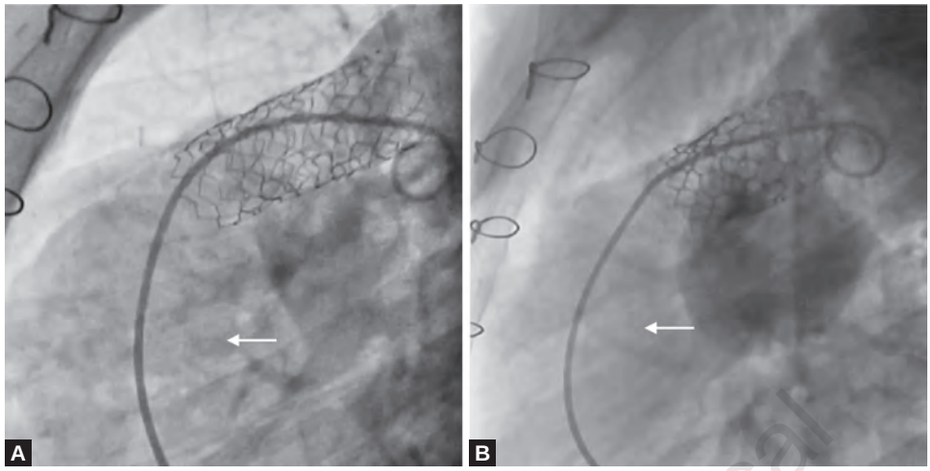
FIGS. 19A AND B: Abernethy malformation: (A) IVC injection shows an abnormal communication between the portal vein and IVC; (B) Device closure done.
(IVC: inferior vena cava)



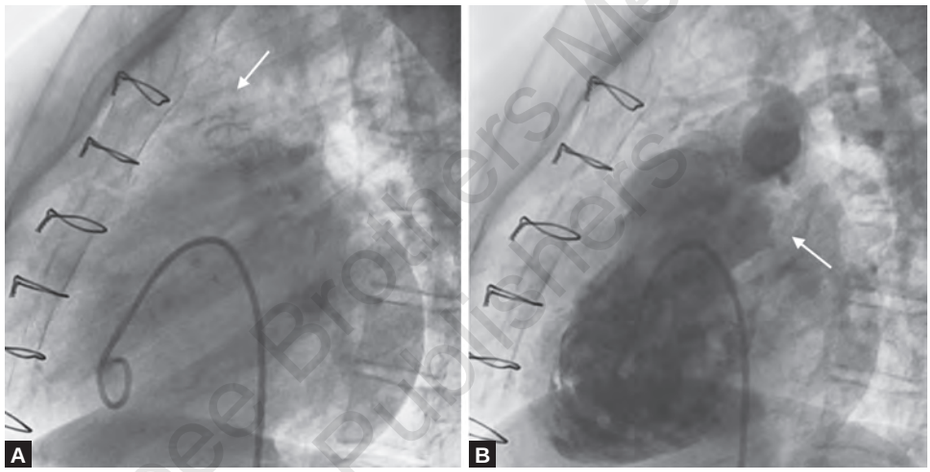
FIGS. 20A AND B: Post TOF: (A) BTT shunt; (B) Post TOF repair collaterals. These caused desaturation and were closed with coils.
(BTT: Blalock–Thomas–Taussig shunt; TOF: tetralogy of Fallot)



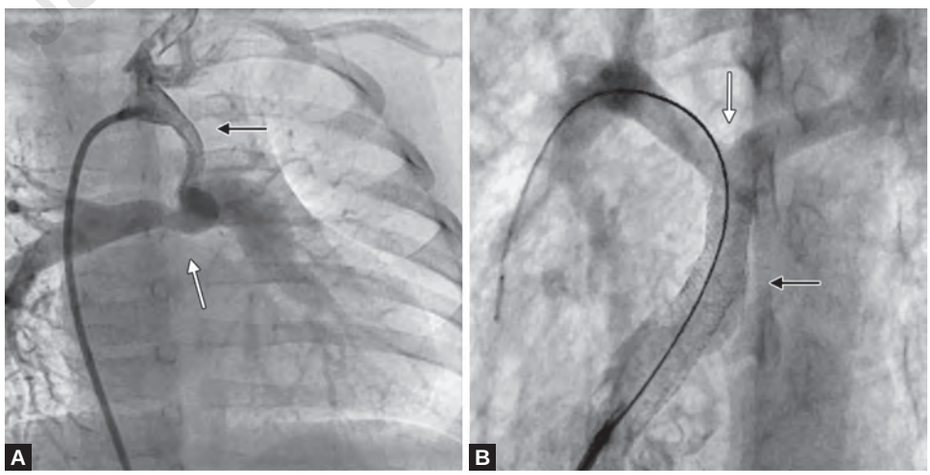
FIGS. 21A AND B: Post TOF: (A) Postoperative apical VSD (white arrow); (B) Device closure done.
(TOF: tetralogy of Fallot; VSD: ventricular septal defect)



FIGS. 22A AND B: Post TOF: (A) Severe PR after TOF surgery with TAP; (B) TPVR done with complete resolution of PR.
(PR: pulmonary regurgitation; TAP: transannular patch; TOF: tetralogy of Fallot; TPVR: transcatheter pulmonary valve replacement)



FIGS. 23A AND B: Post TOF: (A) RVOT conduit calcification; (B) RVOT conduit shows aneurysmal dilatation.
(RVOT: right ventricular outflow tract; TOF: tetralogy of Fallot)



FIGS. 24A AND B: Post-TOF physiology transcatheter palliation: (A) Ductal stent; (B) RVOT stent.
(RVOT: right ventricular outflow tract; TOF: tetralogy of Fallot)

- In rare cases, the RVOT or the surgically placed conduit may develop aneurysm **(Figs. 23A and B)**. Aneurysmally enlarged RVOT can cause cranial displacement of the LPA and functional LPA stenosis.
- Palliative transcatheter options for TOF include RVOT or PDA stenting **(Figs. 24A and B)**. Angiography is essential during pre- and postprocedure. Postprocedure complications range from RVOT stent migration, PA occlusion, or PDA stent thrombosis. These can be identified with angiography. These are shown in **Figure 25**.

Postoperative Angiography Following Arterial Switch Operation

The Jatene arterial switch operation (ASO) is the procedure of choice to completely correct infants with D-TGA **(Figs. 26 and 27)**. Postoperative complications include the following:

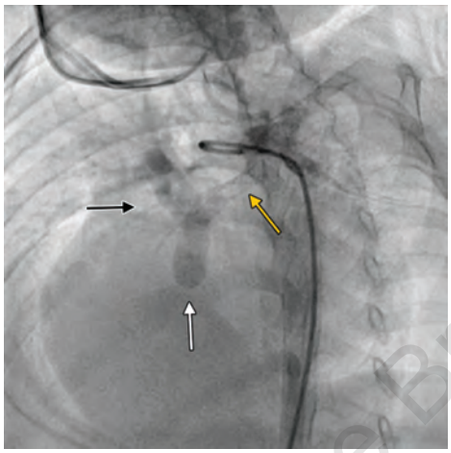


FIG. 25: Post-TOF physiology transcatheter palliation with ductal stent shows LPA cut off. Yellow arrow—ductal stent, black arrow—RPA, white arrow—blind RVOT due to pulmonary atresia.

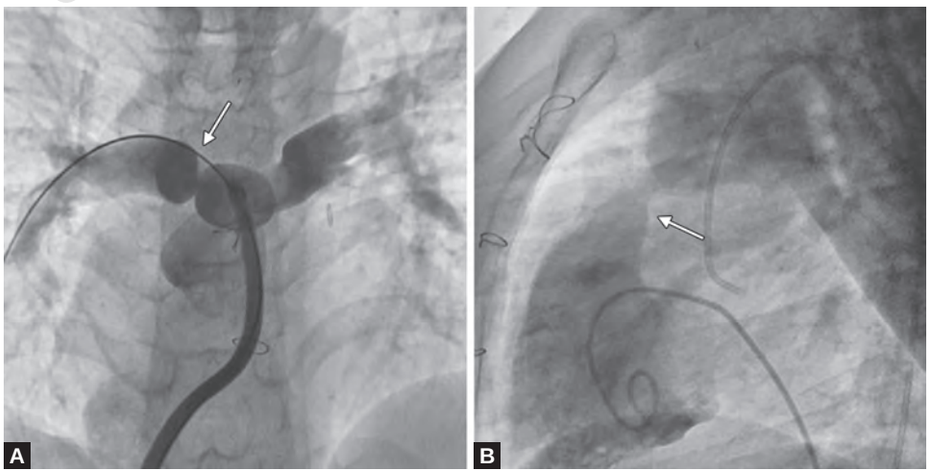
(LPA: left pulmonary artery; RPA: right pulmonary artery; RVOT: right ventricular outflow tract; TOF: tetralogy of Fallot)

- Neo PS—at the valvular, supravalvular, and the peripheral levels
- Aortic root dilatation, aneurysm formation
- Neo aortic regurgitation
- Coronary artery stenosis during coronary button translocation; can lead to ischemia and LV dysfunction

Postoperative Single Ventricular Pathway (Figs. 28 to 30)

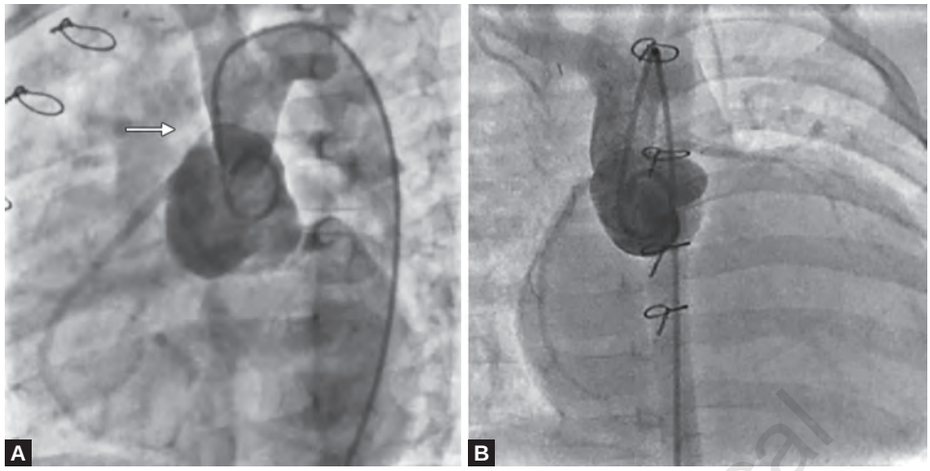
Various complex CCHDs are palliated successfully with the single ventricle pathway—the total cavopulmonary connection (TCPC) or the Fontan operation with various modifications over the years. While classically described for CCHDs with systemic LVs such as tricuspid atresia, with improvement in surgical outcomes, other CCHDs such as systemic RVs (hypoplastic left heart syndrome), unrouteable DORVs, unbalanced atrioventricular defects (AVCDs), and severe Ebstein's syndrome are palliated with TCPC. The Fontan pathway needs multiple stages, and angiography and cardiac catheterization is essential to manage interstage problems and assess hemodynamics between stages.

- The first stage of the TCPC is a modified bidirectional Glenn shunt, fashioned between the SVC and the PA. It is usually done at around 6 months to 1 year of life. It maintains forward PBF, owing to a low resistance in the pulmonary circuit. It does not cause volume overload to the ventricles. The antegrade pulmonary flow via the native RVOT is either banded or left behind, resulting in a pulsatile Glenn. The pulsatile forward flow also carries with it the hepatic factors that help with pulmonary growth and avoid the development of PAVMs.
- When the child on a Glenn graduates to a Fontan completion (IVC and hepatic venous blood routed to the PAs bypassing the heart), a few hemodynamic principles must be adhered to—collectively called the "Choussat criteria" **(Table 7)**.[11,15] This information is obtained from a pre-Fontan cardiac catheterization.

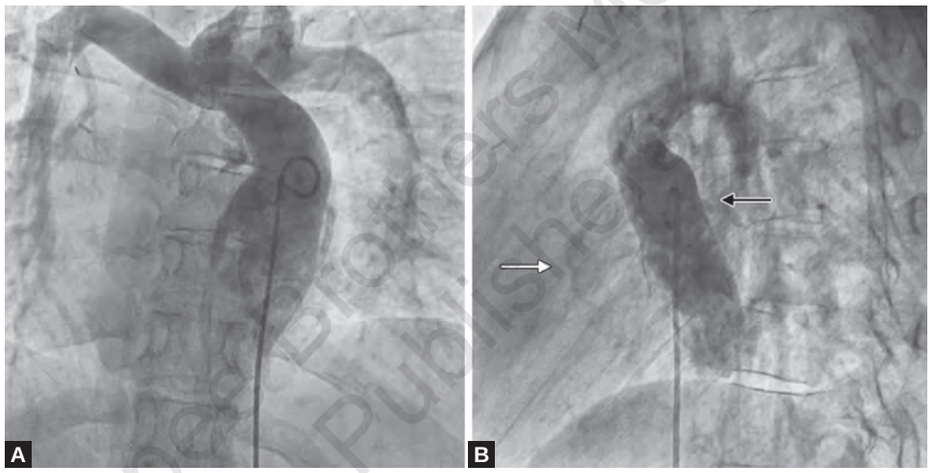


FIGS. 26A AND B: Post ASO: (A) RPA stenosis; (B) RVOT (subpulmonary stenosis).

(ASO: arterial switch operation; RPA: right pulmonary artery; RVOT: right ventricular outflow tract)



FIGS. 27A AND B: Post ASO: (A) Supra-aortic stenosis; (B) Demonstration of coronary arteries in this child post ASO with LV dysfunction.
(ASO: arterial switch operation; LV: left ventricle)



FIGS. 28A AND B: Post-Fontan completion: (A) Fontan circuit; (B) Fenestrated Fontan (white arrow—fenestration).

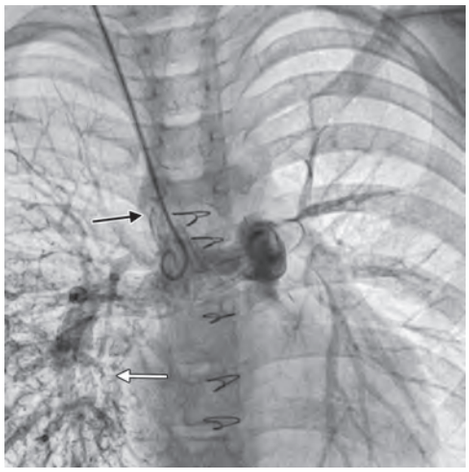
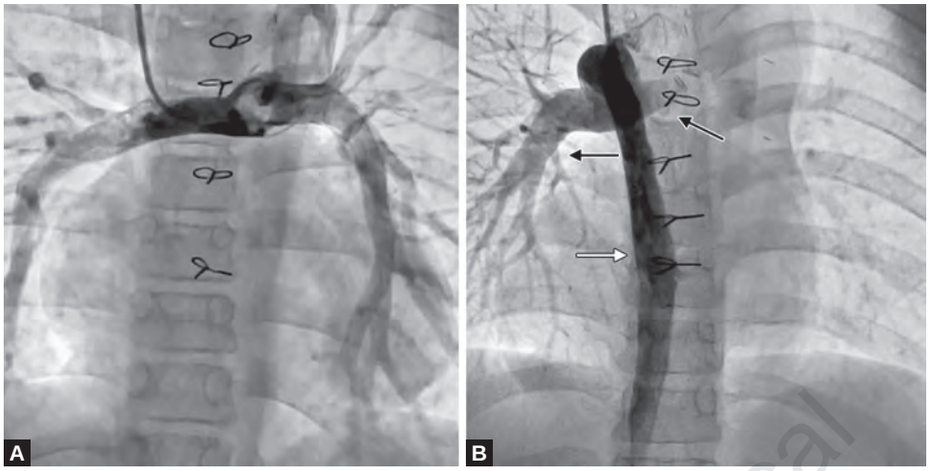


FIG. 29: Post-Glenn shunt showing diffuse right pulmonary arteriovenous malformation.



FIGS. 30A AND B: Post Glenn: (A) Bidirectional functional Glenn shunt; (B) Post Glenn with reopening of the azygos vein (white arrow).

TABLE 7: Choussat criteria: Modified as absolute and relative commandments.

Absolute contraindications	
Severe ventricular dysfunction (systolic or diastolic)	
Severe pulmonary hypertension, increased PVR	
Pulmonary vein stenosis	
Relative contraindications (can be corrected)	
Age	Age <4 years is the norm, with early diagnosis and palliation
Arrhythmias	Epicardial pacemakers
Competent mitral valve	Valve repair
Surgical distortion/dilatation of pulmonary arteries	PA angioplasty
RA volume	In extracardiac Fontan, RA size is not important
Aortic arch obstruction	Aortic arch balloon dilatation/arch stenting

(PA: pulmonary artery; PVR: pulmonary vascular resistance; RA: right atrium)

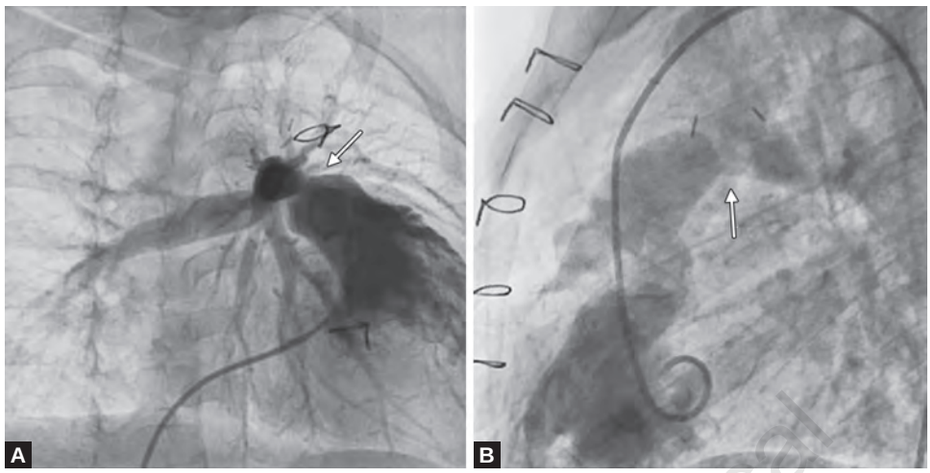
- Post TCPC, many common issues can be identified by catheterization and angiography:
  - Stenosis and thrombosis across the conduits
  - Pulmonary hypoplasia and branch PS
  - PAVMs
- In a fenestrated Fontan, a fenestration is created between the Fontan circuit and the RA, which allows for the systemic venous blood to decompress to the RA, reducing the systemic congestion. This results in arterial desaturation and paradoxical embolism but offers for better hemodynamics immediate post procedure. Such fenestrations may have to be closed later and angiography identifies them and allows for device closure.
- In addition, post TCPC one should look for the presence of venovenous collaterals (VVCs) that tend to arise due to systemic venous hypertension. VVCs lead to arterial desaturation and promote paradoxical embolism. Often difficult to image noninvasively, angiography delineates them well and allows for therapeutic closure.
- **Figure 29** shows the right pulmonary diffuse arteriovenous malformation (AVM). This occurs when the hepatic factors do not enter the lung. Lack of hepatic factors promotes the development of diffuse AVMs.

Postoperative Surgeries: Miscellaneous (Figs. 31A and B)

Pulmonary artery banding (PAB) is done in conditions where there is torrentially increased PBF to protect the pulmonary system from PVOD. It is also performed to train the LV in cases of D-TGA prior to ASO, or to occlude the antegrade PBF during a Glenn shunt. The PAB can cause erosion of the band or migration and occlusion of the branch pulmonary arteries. In some cases, the PAB may not be tight enough and it allows antegrade pulmonary flows. In such cases, cardiac angiography is indicated to document the flows and plan device closure.

CONCLUSION

This brief review of an important, vast topic serves to highlight the lasting importance of conventional angiography in the



FIGS. 31A AND B: Post PAB: (A) White arrow shows the pulmonary artery band; (B) Lateral view.
(PAB: pulmonary artery band)

current era of noninvasive imaging. It helps in the diagnosis and offers a therapeutic gateway to patients with CCHDs—be it unrepaired, repaired, or palliated. Physicians caring for these patients need to be aware of the complex anatomy and must be well versed in both noninvasive and invasive modalities for definitive diagnosis and management.

The readers are again reminded to consult the videos and angiograms posted on the website https://t.ly/kCLK.

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CHAPTER 35

Antiplatelets in High Bleeding Risk Patients

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ABSTRACT

The antiplatelet medications are a cornerstone of modern medicine. They have been very helpful in managing patients with coronary/peripheral/cerebral vascular diseases including acute coronary syndrome, ischemic cerebrovascular accidents, etc. The issue that concerns an individual with their use is the risk of bleeding associated in using them, especially in high bleeding risk (HBR) patients. This chapter focuses on various scores developed and used to assess the risk of bleeding as well as grading the severity of bleeding in an individual on antiplatelets. Further, a discussion on the choice of class of antiplatelet, the number of antiplatelet agents, and their duration of use has been done. The discussion about bleeding in HBR individuals on antiplatelet therapy has been carried out in view of the recent American College of Cardiology (ACC) and European Society of Cardiology (ESC) guidelines. Efficacy of abbreviated regimen of dual antiplatelets with newer stents has been discussed in the light of recent trials.

INTRODUCTION

Ever since the advent of antiplatelets, there has always been a concern about the risks involved in using them, especially regarding that of the increased risk of bleeding. Many trials have been conducted to investigate into this issue, which has enlightened us regarding the proper dosing and duration of the antiplatelet agents available. This chapter is focused on the subset of patients who are on these drugs and are on high bleeding risk (HBR).

ANTIPLATELET AGENTS

A brief classification of antiplatelets is as follows:

- *Cyclooxygenase inhibitors*: Acetylsalicylic acid (ASA) and aspirin, Triflusal
- *Adenosine diphosphate (ADP) P2Y12 inhibitor*: Clopidogrel, prasugrel, ticagrelor, and cangrelor
- *Glycoprotein (GP) IIb/IIIa inhibitors*: Abciximab, eptifibatide, and tirofiban
- *Prostacyclin and analogs*: Prostaglandin (PG) I2, iloprost, and treprostinil
- *Phosphodiesterase inhibitors*: Dipyridamole and cilostazol
- *Protease activated receptor-1 (PAR-1) inhibitors*: Vorapaxar and atopaxar

ASSESSING HIGH BLEEDING RISK

While considering bleeding in a patient on antiplatelets, one is concerned with mainly three issues:

1. The risk profile of the patient on antiplatelets, i.e., what amount of risk of bleeding the patient has with antiplatelet therapy?
2. The severity of bleeding
3. Antiplatelets and their bleeding risk

Severity of Bleeding Caused by Antiplatelet Agents

The severity of bleeding was assessed by various scores, which were used in different studies. Some of the frequently used scores include TIMI (thrombolysis in myocardial infarction)[1] bleeding, GUSTO (global use of strategies to open occluded arteries),[2] and the BARC (Bleeding Academic Research Consortium)[3] definitions.

TIMI Bleeding Definitions

- *Major bleeding*: Intracranial hemorrhage (ICH)
  - ≥5 g/dL decrease in the hemoglobin concentration
  - ≥15% absolute decrease in hematocrit
- *Minor bleeding*: Observed blood loss

- ≥3 g/dL decrease in the hemoglobin concentration
- ≥10% absolute decrease in hematocrit

No observed blood loss:

- ≥4 g/dL decrease in the hemoglobin concentration
- ≥12% absolute decrease in hematocrit

- *Minimal bleeding*: Any clinically overt sign of hemorrhage associated with <3 g/dL decrease in hemoglobin concentration or <9% decrease in the hematocrit.

GUSTO Bleeding Definitions

- *Severe or life-threatening*: ICH—bleeding that causes hemodynamic compromise and requires intervention
- *Moderate*: Bleeding that requires blood transfusion but does not lead to hemodynamic instability
- *Mild*: Bleeding that does not meet the criteria for severe or moderate bleeding

BARC Definition

As different scores were used in different studies to define patients on HBR, it was difficult to compare the data from one study to the other. This led to the formation of a consortium, which thoroughly discussed the issue and came up with the BARC[3] definition **(Table 1)** for bleeding in 2011.

For validation of the BARC bleeding criteria analysis of data in TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction) trial[4] was done and its results were published in 2016, which showed increased incidence of severe bleeding. The vorapaxar group also had higher TIMI major bleeding[1] [4.0% vs. 2.5%; hazard ratio (HR) 1.53; 95% confidence interval (CI) 1.24–1.90; $p < 0.001$] and rates of GUSTO severe bleeding[2] (2.9% vs. 1.6%; HR, 1.66; 95% CI 1.27–2.16; $p < 0.001$). The study included the analysis of 12,944 patients with acute coronary syndrome (ACS) and non-ST-elevation myocardial infarction (STEMI) who were given vorapaxar versus placebo. The results showed the relationship between BARC-classified bleeding and mortality and compared its prognostic value with two already validated scales—GUSTO and TIMI.

TABLE 1: Bleeding Academic Research Consortium (BARC) bleeding definitions.

Class I	Bleeding that is not actionable	• BARC minor bleeding is class I, II, and III A • Validation: Diminished quality of life, prolonged hospitalization, and increased costs
Class II	Any overt, actionable sign of bleeding	
Class III A	Overt bleeding with hemoglobin drop of 3–5 g/dL or any transfusion	
Class III B	Overt bleeding with hemoglobin drop of ≥5 g/dL, bleeding requiring pressors, surgical intervention, or due to tamponade	• BARC major bleeding is classes III B, III C, IV, and V • Validation: Bleeding independently associated with 1-year mortality
Class III C	Intraocular or intracranial bleed	
Class IV	Coronary artery bypass graft (CABG)-related bleeding: Transfusion of ≥5 units of blood, repeat sternotomy, and chest tube output ≥2 L within 24 hours	
Class V	Fatal bleeding	

Risk Profile of the Patient on Antiplatelets, i.e., What Amount of Risk of Bleeding the Patient has with Antiplatelet Therapy?

A few scores have been proposed for identifying the HBR patients. Many trials have been conducted to assess the bleeding risk or risk-to-benefit ratio but initially, each trial used different scores to do the same. Some important scores to assess ischemic/bleeding risk used were DAPT (dual antiplatelet therapy) score[5] (for ischemic risk), PRECISE-DAPT (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy) score,[6] and PARIS (Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients)[7] score. All of them used variables to calculate scores, which were validated using analysis of bleeding pattern and patient characteristics in various studies.

DAPT Score

Risk profile assessment by DAPT score **(Table 2)**[4] was made after patients had received 12 months of DAPT (clopidogrel or ticagrelor with aspirin) and this score decides the benefit versus risk of continuing DAPT from 12th month onward up to 30 months.

The range of the score is from –2 to 10. Score of 2 or >2 defines high ischemic risk and <2 defines low ischemic risk. This means that a score of 2 or >2 favored prolonged DAPT use after drug eluting stent (DES), while a score of <2 showed poor benefit-to-risk ratio for using DAPT.

PRECISE-DAPT Score

The PRECISE-DAPT score[5] is used for grading the risk of bleeding in patients on antiplatelets **(Fig. 1)**. It includes various

TABLE 2: DAPT score.

Variable	Points
Age:	
• ≥75 years	–2
• 65–75 years	–1
• ≤64 years	0
Diabetes mellitus	1
Current cigarette smoker	1
Prior PCI or MI	1
MI at presentation	1
Stent diameter <3 mm	1
Congestive heart failure or ejection fraction <30%	2
Vein-graft PCI	2

(DAPT: dual antiplatelet therapy; MI: myocardial infarction; PCI: percutaneous coronary intervention)

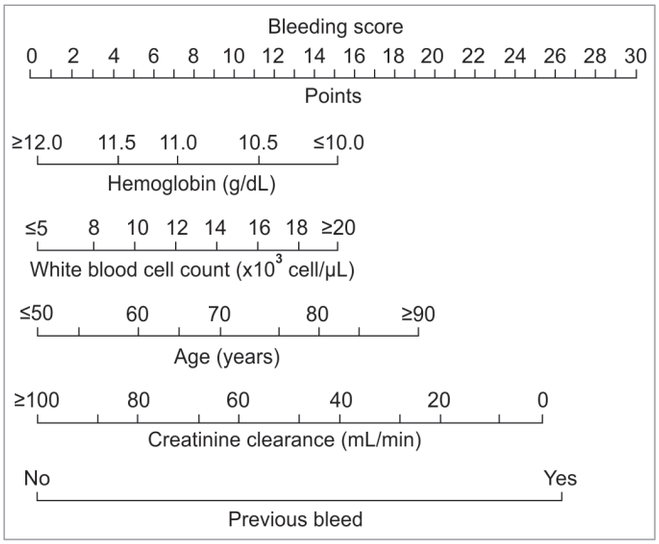

FIG. 1: PRECISE-DAPT score.

parameters: Hemoglobin, white blood cell count, age (in years), creatinine clearance, and previous bleeding event. The risk was graded as follows: Low bleeding risk (PRECISE-DAPT < 17), intermediate bleeding risk (17–24), and HBR (≥25) score groups.

PARIS Score

The PARIS bleeding score **(Table 3)**[3] predicts the out-of-hospital bleeding risk after percutaneous coronary intervention (PCI). It has the range of scores for bleeding from 0 to 14, and patients are categorized at low (0–3), intermediate (4–7), and high (8 or more) bleeding risk.

Academic Research Consortium-high Bleeding Risk

This definition specifically categorized the BARC 3 or 5 bleeding as Academic Research Consortium-high Bleeding Risk (ARC-HBR).

The risk was defined based on 14 major and 6 minor criteria. An individual was considered as HBR if one patient had at least one major or two minor criteria.

The major criterion for ARC-HBR includes clinical diagnoses, which confer BARC 3 or 5 bleeding risk ≥ 4% at 1 year or a risk of ICH of ≥1% at 1 year.

Major criteria include:

- Long-term oral anticoagulation
- Severe or end-stage chronic kidney disease (CKD) [estimated glomerular filtration rate (eGFR) <30 mL/min]
- Hemoglobin < 11 g/dL
- Spontaneous bleeding requiring hospitalization and transfusion in the past 6 months
- Moderate-to-severe baseline thrombocytopenia (platelet count $<100 \times 10^9$/L)
- Chronic bleeding diathesis
- Liver cirrhosis with portal hypertension

TABLE 3: PARIS bleeding score.

Parameter	Score
Diabetes mellitus	
None	0
Noninsulin-dependent	+1
Insulin-dependent	+3
Acute coronary syndrome	
No	0
Yes, Tn-negative	+1
Yes, Tn-positive	+2
Current smoking	
Yes	+1
No	0
CrCl <60 mL/min	
Present	+2
Absent	0
Prior PCI	
Yes	+2
No	0
Prior CABG	
Yes	+2
No	0

(CABG: coronary artery bypass graft; CrCl: creatinine clearance; PARIS: Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients; PCI: percutaneous coronary intervention)

- Active cancer in the past 12 months
- Previous spontaneous ICH (at any time)
- Previous traumatic ICH within the past 12 months
- Presence of known brain arteriovenous malformations
- Moderate-to-severe ischemic stroke within the past 6 months
- Nondeferrable major surgery on dual antiplatelet therapy
- Recent major surgery or trauma within 30 days before PCI

The minor criterion for ARC-HBR is defined as any criterion that, in isolation, is considered to confer increased bleeding risk, with a BARC 3 or 5 bleeding rate of <4% at 1 year.

Minor criteria include:

- Age >75 years
- Moderate CKD (eGFR 30–59 mL/min)
- Hemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women
- Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months, not meeting major criterion
- Long-term use of oral nonsteroidal anti-inflammatory drugs or steroids
- Any ischemic stroke at any time, not meeting major criterion

Patients satisfying at least one major or two minor criteria were defined as HBR. So, this definition, unlike other

definitions, divided the patients under two groups, i.e., the patient fell into either HBR category or non-HBR category.

Antiplatelets and their Bleeding Risk

An important bleeding risk profile of frequently used antiplatelet agents as evaluated by various studies with their results is discussed in brief in the following text.

Aspirin

- A systematic review and meta-analysis were conducted by Zheng SL et al.[8] in which 13 trials randomizing 164,225 participants with 1,050,511 participant-years of follow-up were included. The median age of trial participants was 62 years (range, 53–74); 77,501 (47%) were men; 30,361 (19%) had diabetes; and the median baseline risk of the primary cardiovascular outcome was 10.2% (range, 2.6–30.9%). There was an increased risk of major bleeding events compared with no aspirin (23.1 per 10,000 participant-years with aspirin and 16.4 per 10,000 participant-years with no aspirin) [HR 1.43 (95% CI 1.30–1.56); absolute risk increase, 0.47% (95% CI 0.34–0.62%); number needed to harm, 210]
- De Berardis et al.[9] conducted a population-based cohort study in which hospitalizations for major gastrointestinal bleeding or cerebral hemorrhage occurring after the initiation of aspirin therapy was assessed. Patients treated with aspirin were 186,425 individuals and followed up for median 5.7 years. Results showed the overall incidence rate of hemorrhagic events to be 5.58 (95% CI 5.39–5.77) per 1,000 person-years for aspirin use and 3.60 (95% CI 3.48–3.72) per 1,000 person-years for those without aspirin use [incidence rate ratio (IRR) 1.55; 95% CI 1.48–1.63]. The use of aspirin was associated with a greater risk of major bleeding in most of the subgroups investigated but not in individuals with diabetes (IRR 1.09; 95% CI 0.97–1.22). Irrespective of aspirin use, diabetes was independently associated with an increased risk of major bleeding episodes (IRR 1.36; 95% CI 1.28–1.44).

Adenosine Diphosphate P2Y12 Inhibitors

- Bhatt et al.[10] conducted the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial. The patients were either those who had a clinically evident disease or those who had multiple risk factors. The rate of the primary safety end point (severe bleeding according to the GUSTO definition) was higher but not statistically significant in the clopidogrel group (1.7%) than in the placebo group (1.3%) [RR 1.25; 95% CI 0.97–1.61; $p = 0.09$].
- Zocca et al.[11] conducted the prospective observational CHANGE DAPT study, which compared clopidogrel versus ticagrelor-based DAPT regimens in consecutive patients with ACS, treated with PCI with contemporary DES. Among HBR patients, the rate of major bleeding was significantly higher with ticagrelor [1.7% vs. 5.0%; HR-adjusted 3.70 (95% CI 1.18–11.67), $p = 0.03$], while there was no significant difference in the ischemic endpoint [6.6% vs. 8.0%, HR-adjusted 1.23 (95% CI 0.63–2.42), $p = 0.54$].
- Marcucci et al. studied the risk of bleeding in patients with ACS treated with clopidogrel versus ticagrelor. The data was analyzed from the START-ANTIPLATELET registry.[12] The dual antiplatelet treatment most prescribed was aspirin plus ticagrelor (47.9%) and aspirin plus clopidogrel (32.1%). At a mean follow-up of 335 ± 131 days, both ticagrelor and prasugrel are associated with a statistically significant reduced total mortality and cardiovascular mortality. Both prasugrel and ticagrelor do not show a significant increased incidence of major and minor bleeding with respect to clopidogrel.
- A meta-analysis was done by Jia et al.[13] to compare prasugrel with clopidogrel. The analysis included six studies, which showed that clopidogrel and prasugrel had similar risks of all causes of death (pooled RR 0.83; 95% CI 0.64–1.06, $p = 0.14$, $I^2 = 55\%$), MI (pooled RR 0.86; 95% CI 0.71–1.04, $p = 0.12$), and stroke (pooled RR 0.88; 95% CI 0.70–1.10, $p = 0.25$), but prasugrel was associated with significantly higher risk of major bleeding (pooled RR 1.19; 95% CI 0.99–1.44, $p = 0.06$, $I^2 = 0\%$).
- Schüpke et al. conducted ISAR-REACT 5[14] study, comparing ticagrelor and prasugrel in ACS patients. The comparison of the ticagrelor group and the prasugrel group was: Death (4.5% vs. 3.7%), myocardial infarction (4.8% vs. 3.0%), and stroke (1.1% vs. 1.0%). Stent thrombosis (definite or probable) occurred in 1.3% of patients assigned to ticagrelor and 1.0% of patients assigned to prasugrel. The study showed major bleeding (as per BARC scale), which was seen in 5.4% of patients in the ticagrelor group and in 4.8% of patients in the prasugrel group (HR 1.12; 95% CI 0.83–1.51; $p = 0.46$).

GP IIb/IIIa Inhibitors

- Lenderink et al.[15] published a study in 7,800 patients, which showed that 1,507 patients (19.3%) had bleeding during hospitalization or within 7 days according to the TIMI classification in patients with ACS who were given abciximab infusion. Major bleeding was seen in only 98 patients (1.2%) including 8 with ICHs. Only 2% patients in the study underwent revascularization.
- In the EPIC trial[16] in high-risk angioplasty, 14% of patients who received bolus of abciximab followed by an infusion had a TIMI major bleeding versus 7% in the placebo group ($p = 0.001$).
- The PURSUIT trial[17] showed increased risk of bleeding in patients where eptifibatide infusion was given to manage ACS versus placebo, in addition to standard therapy. Using TIMI scale, major bleeding occurred in 10.6% in eptifibatide group versus 9.1% in placebo group ($p = 0.02$).
- In the PRISM-PLUS study,[18] tirofiban infusion was given in unstable angina and non-Q wave MI. According to TIMI criteria, the incidence of major bleeding occurred 0.8% in the heparin group versus 1.4% in the heparin plus tirofiban infusion group ($p = 0.23$).

Various scenarios regarding management of specifically HBR subset of patients:

Scenario 1: Patient with ACS or non-ACS who undergoes PCI with stenting along with guideline-directed medical therapy (GDMT)

With the introduction of the first generation of DES, it was thought that 3–6 months of DAPT was sufficient but increased risk of thrombosis leads to an increase in the duration to be 12 months. Advancements in the types of DES studies showed that it required lesser DAPT duration, which decreased the risk of bleeding. Recent American College of Cardiology (ACC) guidelines with focused update on DAPT 2016,[19] European Society of Cardiology (ESC) guidelines for management of STEMI 2017,[20] and ESC guidelines on non-ST elevation-acute coronary syndrome (NSTE–ACS) 2020[21] on DAPT suggest their use for shorter duration in patients with HBR. The recent (ESC 2020) guidelines have used ARC-HBR criteria to identify the patients at HBR.

Some recent studies have been published in which the effect of antiplatelets has been assessed in HBR individuals:

- *EVOLVE short DAPT study*: In EVOLVE short DAPT study,[22] a 3-month DAPT was given after bioabsorbable polymer-coated everolimus-eluting stent (SYNERGY) in HBR patients (BARC 3, 5 along with BARC 2). The population studied in this trial was 1,487 non-ACS patients who did not have complex lesions. This study showed that among HBR patients, the 3-month DAPT group showed favorable ischemic outcomes. The adjusted rate of death/myocardial infarction between 3 and 15 months was 5.6% among patients receiving a 3-month DAPT versus 5.7% patients in the 12-month DAPT control (propensity adjusted difference = –0.12%; 97.5% upper bound = 1.63%, which was less than the prespecified margin of 2.52; *p* noninferiority = 0.0016). The second coprimary endpoint of study, stent-related definite/probable ST between 3 and 15 months was 0.2% in the 3-month DAPT group with a one-sided 97.5% upper bound of 0.63%, which was lower than the prespecified performance goal of 1.0% ($p = 0.0005$). BARC 2, 3, or 5 bleeding between 3 and 15 months was 6.26% in the 3-month DAPT group versus 4.17% in the control group that received a 12-month DAPT ($p = 0.98$).
- *MASTER DAPT trial*: In MASTER DAPT trial,[23] patients with HBR post PCI who used biodegradable-polymer sirolimus-eluting coronary stent were randomized into two groups. Case group was given DAPT for 1 month followed by 11 months of single antiplatelet therapy and the control arm patients received DAPT for at least 3 months. Outcomes of the study as given in **Table 4** suggest that 1-month DAPT was not inferior to its continuation for two more months as per the occurrence of net adverse clinical events and major adverse cardiac or cerebral events, and short duration 1-month DAPT was associated with a lower incidence of major bleeding (BARC 3–5).
- *Onyx ONE clear trial, Onyx ONE US/Japan, and Onyx ONE randomized controlled trial (RCT)*: Patients with HBR characteristics were studied, who underwent PCI with resolute Onyx stent and received DAPT for 1 month followed by 11 months of single antiplatelet therapy. Results obtained in three studies are as shown in **Table 5**. Among HBR patients undergoing PCI with resolute Onyx zotarolimus-eluting stents who were event free before DAPT discontinuation at 1 month, favorable safety and effectiveness through 1 year were demonstrated among patients treated in the United States and Japan, thereby extending the results of the recent Onyx ONE RCT. 2-year outcomes: The primary safety endpoint of Onyx ONE RCT showed cardiac death/myocardial infarction/stent thrombosis for resolute Onyx versus BioFreedom was 21.2% versus 20.7% ($p = 0.78$) and all-cause death was 15.6% versus 12.1% ($p = 0.03$).
- *LEADERS FREE trial*: LEADERS FREE trial **(Table 6)**[25] concluded that the patients with HBR characteristics who received antiplatelet therapy after PCI with a polymer-free umirolimus-coated stent (Biolimus A9) were superior to a bare-metal stent (BMS) with respect to the primary safety and efficacy endpoints when used with a 1-month course of DAPT. In this trial, there was a comparison of DES with a very similar BMS. Post PCI, all patients were given DAPT (aspirin plus one P2Y12 inhibitor) for 1 month followed by single antiplatelet, preferably aspirin.

Scenario 2: Patients on anticoagulants for atrial fibrillation (AFib)/venous thromboembolism with antiplatelet therapy:

Trials were conducted to compare the safety and efficacy of DAPT with an anticoagulant, i.e., triple therapy **(Table 7)** included WOEST[26] [What is the Optimal antiplatElet and anticoagulant therapy in patients with OAC and coronary StenTing], PIONEER AF-PCI[27] (rivaroxaban and a dose-adjusted oral vitamin K antagonist (VKA) treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention), RE-DUAL PCI[28] (Evaluation Of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin In Patients With AFib that Undergo a PCI With Stenting), AUGUSTUS[29] (Antithrombotic Therapy After Acute Coronary Syndrome or PCI in Atrial Fibrillation), and ENTRUST AF[30] (Edoxaban-Based Antithrombotic Regimen in Patients With AFib).

TABLE 4: Results of MASTER DAPT trial.

Trial/study (sample size)	Drug protocol (case arm)	Drug protocol (control arm)	Net adverse events case versus control	Death from all cause case versus control	Cardiovascular cause of death case versus control	Stent thrombosis (definite + probable) case versus control	Bleeding (criteria used) case versus control
MASTER DAPT (4,434)	1 month-DAPT followed by 11-month single antiplatelet	At least 3-month DAPT	165 (7.5%) vs. 172 (7.7%)	3.3% vs. 3.6%	1.7% vs. 2.0%	0.6% vs. 0.4%	2.3% vs. 2.5% (BARC 3–5)

(BARC: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy)

Based on these trials, there was an update from ACC in 2020—ACC Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients with Atrial Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary Intervention or With Atherosclerotic Cardiovascular Disease.[31] It divided patients in different groups and recommended the following:

- *Patient with AFib on anticoagulation (AC) therapy who now needs PCI*:
  - To hold or stop anticoagulation therapy and initiate unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or bivalirudin, if needed. Post procedure, restart AC with direct oral anticoagulants (DOAC) or VKA along with clopidogrel for 12 months.
- *Patient on antiplatelet therapy with a new diagnosis of AF*: In this scenario, it depends on the primary reason for which the antiplatelet was started.
  - Hold antiplatelet therapy if the reason to start it was primary prevention of atherosclerotic cardiovascular disease (ASCVD).
  - Patient with stable ischemic heart disease (SIHD) or ACS taking antiplatelet therapy for recent PCI (<12 months), it is advisable to continue clopidogrel and add AC therapy (DOAC is preferred).
- *Patient with prior venous thromboembolism (VTE) being considered for PCI*:
  - If AC course is not complete, hold or stop AC therapy and initiate UFH, LMWH, or bivalirudin, if needed. Post procedure, restart AC with DOAC or VKA along with clopidogrel for 12 months.
- *Patient on antiplatelet therapy with new VTE*: In this scenario, it depends on the primary reason for which the antiplatelet was started.
  - Hold antiplatelet therapy if the reason to start it was primary prevention of ASCVD.
  - For a patient with SIHD or ACS taking antiplatelet therapy for recent PCI (<12 months), it is advisable to continue clopidogrel and add AC therapy (DOAC is preferred).

TABLE 5: Results of Onyx ONE clear trial, Onyx ONE US/Japan, and Onyx ONE RCT.

	Onyx ONE clear trial (%)	Onyx ONE US/Japan (%)	Onyx ONE RCT[24] (%)
Cardiac death or MI	7	7.1	6.9
MACE	11.7	12.3	11.3
Bleeding:			
• BARC 1–5	13.1	18.7	9.4
• BARC 2–5	11.7	16.8	8.4
• BARC 3–5	4.0	6.6	2.3

(BARC: Bleeding Academic Research Consortium; MACE: major adverse cardiovascular events; MI: myocardial infarction; RCT: randomized controlled trial)

TABLE 6: Results of LEADERS FREE trial.

	Drug-coated stent (%)	Bare-metal stent (%)	*p* value
Cardiac death, MI, stent thrombosis	9.4	12.9	0.005
All-cause mortality	8	9	0.39
Stent thrombosis	2	2.2	0.75
Bleeding:			
• BARC 1–5	18.1	19.1	0.56
• BARC 2–5	13.9	14.7	0.68
• BARC 3–5	7.2	7.3	0.96

(BARC: Bleeding Academic Research Consortium; MI: myocardial infarction)

TABLE 7: Event rate for primary ischemic/thrombotic endpoint (HR; 95% CI) versus TIMI major bleeding (HR; 95% CI) in WOEST, PIONEER AF PCI, RE-DUAL PCI, AUGUSTUS, ENTRUST AF.

	WOEST	PIONEER AF-PCI	RE-DUAL PCI	AUGUSTUS	ENTRUST AF
Treatment arms	Group 1: VKA (INR per indication), P2Y12 inhibitors vs. Group 2: VKA (INR 2.0), aspirin P2Y12 inhibitors	Group 1: Rivaroxaban (15 mg daily), P2Y12 inhibitors vs. Group 2: Rivaroxaban (2.5 mg twice daily), aspirin, P2Y12 inhibitors vs. Group 3: VKA (INR 2–3), aspirin, P2Y12 inhibitors	Group 1: Dabigatran (110 mg twice daily), P2Y12 inhibitors vs. Group 2: Dabigatran (150 mg twice daily), P2Y12 inhibitors vs. Group 3: VKA (INR 2–3), aspirin (1–3 months), P2Y12 inhibitors (WTT)	Group 1: Apixaban (5 mg twice daily), P2Y12 inhibitors vs. Group 2: Apixaban (5 mg twice daily), aspirin, P2Y12 inhibitors vs. Group 3: VKA (INR 2–3), P2Y12 inhibitors vs. Group 4: VKA (INR 2–3), aspirin, P2Y12 inhibitors	Group 1: Edoxaban (60 mg daily), P2Y12 inhibitors vs. Group 2: VKA (INR 2–3), aspirin (1–12 months) P2Y12 inhibitors
Primary ischemic/thrombotic endpoint	Group 1 vs. 2: 11.1% vs. 17.6%; (0.60, 0.38–0.94)	• Group 1 vs. 3: 6.5% vs. 6.0%; (1.08, 0.69–1.68) • Group 2 vs. 3: 5.6% vs. 6.0%; (0.93, 0.59–1.48)	• Group 1 vs. 3: 15.2% vs. 13.4%; (1.13, 0.90–1.43) • Group 2 vs. 3: 11.8% vs. 12.8%; (0.89, 0.67–1.19)	• Apixaban vs. VKA 6.7% vs. 7.1%; (0.93, 0.75–1.16) • Aspirin vs. placebo 6.5% vs. 7.3%; (0.89, 0.71–1.11)	Group 1 vs. 2: 7% vs. 6%; (1.06; 0.71–1.69)
TIMI major bleeding	Group 1 vs. 2: 3.2% vs. 5.6%; (0.56, 0.25–1.27)	• Group 1 vs. 3: 2.1% vs. 3.3%; (0.66, 0.33–1.31) • Group 2 vs. 3: 1.9 vs. 3.3%; (0.57, 0.28–1.16)	• Group 1 vs. 3: 1.4% vs. 3.8%; (0.37, 0.20–0.68) • Group 2 vs. 3: 2.1% vs. 3.9%; (0.51, 0.28–0.93)	• Apixaban vs. VKA 1.7% vs. 2.1%; (0.78, 0.51–1.20) • Aspirin vs. placebo 2.4% vs. 1.3%; (1.93, 1.23–3.03)	Group 1 vs. 2: 2.0% vs. 3.2%; (0.62; 0.33–1.19)

(AUGUSTUS: Antithrombotic Therapy After Acute Coronary Syndrome or PCI in AFib; ENTRUST AF: Edoxaban-Based Antithrombotic Regimen in Patients With AFib; INR: international normalized ratio; RE-DUAL PCI: Evaluation Of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin In Patients With AFib that Undergo a PCI With Stenting; TIMI: thrombosis in myocardial infarction; VKA: vitamin K antagonist; WOEST: What is the Optimal antiplatElet and anticoagulant therapy in patients with OAC and coronary StenTing; WTT: warfarin triple therapy)

Scenario 3: Patient with cerebrovascular accidents (CVAs) on antiplatelets:

S2TOP-BLEED[32] [i.e., male *S*ex, *S*moking, *T*ype of antiplatelet agents, *O*utcome on modified Rankin Scale (mRS), *P*rior stroke, high *B*lood pressure, *L*ower body-mass index (BMI), *E*lderly, Asian *E*thnicity, and *D*iabetes] score was developed after investigating retrospectively the patients who had transient ischemic attack (TIA) or ischemic stroke. Data from six randomized clinical trials (CAPRIE, ESPS-2, MATCH, CHARISMA, ESPRIT, and PRoFESS) were used to assess the bleeding risk associated with antiplatelets. This score was used to assess 3-year bleeding risk in patients on antiplatelets and the risk was predicted age-wise **(Tables 8 and 9)**.

After calculating the total score, the 3-year risk in percentage is seen from the **Table 9**.

TABLE 8: S2TOP-BLEED score for assessing major bleeding risk.

Factor	Points
Sex	
• Female • Male	0 2
Smoking	
• No • Current	0 1
Type of the antiplatelet agent	
• Clopidogrel • Aspirin (± dipyridamole) • Aspirin + clopidogrel	0 1 5
Outcome on mRS	
• mRS 0–2 • mRS 3–5	0 2
Prior stroke	
• No • Yes	0 1
Blood pressure (hypertension)	
• No • Yes	0 1
Low BMI	
• <20 • 20–25 • >25	2 1 0
Ethnicity	
• Non-Asian • Asian	0 1
Diabetes	
• No • Yes	0 1

(BMI: body-mass index; mRS: modified Rankin scale)

TABLE 9: Predicting risk in percentage (%) as per age group.

	45–54	55–64	65–74	75–84	≥85
0	2	2	2	4	
1	2	2	3	4	6
2	2	2	3	5	7
3	2	3	4	6	8
4	2	3	4	6	10
5	3	4	5	7	11
6	3	4	6	8	13
7	4	5	6	10	14
8	4	6	7	11	17
9	5	6	8	13	18
10	6	7	10	14	>20
11	6	8	11	17	>20
12	7	10	13	18	>20
13	8	11	14	>20	

Note: Cells containing <5 patients were removed in original study.[33]

DISCUSSION

There has been an evolution in the way one treats patients who require antiplatelets, especially in the subgroup where there is HBR. HBR was defined by different scores, which included PRECISE-DAPT score[6] of ≥25 and PARIS score[7] of ≥8. Later, to stop the confusion and the problem faced to compare results of one study to the other as they used different scores to define HBR, BARC[3] definition was developed. In BARC definition III B, III C, IV, and V were included in HBR.

Using the above definitions many trials were done, which led to the abbreviated regimen of DAPT in HBR patients. The ACC 2016 guidelines[19] suggested at least 6 months of DAPT for HBR patients undergoing PCI with DES if the indication was SIHD but if the indication was ACS, then 12-month treatment was recommended (COR–I). In 2017, ESC guidelines[20] for management of STEMI patients was published, which also recommended 6 months of DAPT in HBR patients (COR–II a). Followed by this, there was DAPT-focused update in 2017,[33] which recommended reduced duration of DAPT to 3 months for HBR non-ACS patients undergoing PCI with DES. In 2020 another update for NSTEMI ACS[21] was published, which recommended 3 months of DAPT for those undergoing PCI as was seen in EVOLVE DAPT[22] trial in which everolimus-eluting stent (SYNERGY) showed favorable outcome with 3 months of DAPT. Newer generation stents were evaluated in recent trials for abbreviated DAPT, such as biodegradable polymer sirolimus-eluting stent in MASTER DAPT trial,[23] resolute Onyx in Onyx RCT,[24] and polymer-free Biolimus A9 stent in LEADERS FREE trial,[25] and they have shown that even 1-month DAPT can produce favorable outcome in patients with HBR characteristics as well as reduce the risk of bleeding in them.

CONCLUSION

Antiplatelets, whether used as a single agent or as DAPT, pose an increased risk of bleeding, especially in the HBR population. Methods to control bleeding in them are to use abbreviated (1 or 3 months of DAPT) regimen than the longer 6 or 12 months' regimen. It has also been seen that newer DESs may help to reduce stent-related complications even in short-term DAPT. Bleeding risk assessment for each individual must be done before starting antiplatelets so that proper dosing and duration of antiplatelets can be prescribed.

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SECTION 3

PREVENTIVE CARDIOLOGY

CHAPTER 36: **Revisiting Secondary Prevention in Coronary Artery Disease**
Prem Ratan Degawat, Sumit Kumar, Rajeev Gupta

CHAPTER 37: **Genetic Risk Scores for Premature Coronary Artery Disease in India**
Rajeev Gupta

CHAPTER 38: **Exercise and Cardiovascular Health**
Chetan P Shah, Charan Reddy KV

CHAPTER 39: **Lipid Profile: Clinical Interpretation and Management Strategies**
SS Iyengar, Saikat Kanjilal

CHAPTER 40: **Lipoprotein(a): Atherogenic Risk and Management Challenges**
JPS Sawhney, Kushal Madan, Ashwani Mehta

CHAPTER 41: **Prevention of Atherosclerosis in Childhood and Adolescents**
Sunil Modi, Ranjan Modi, Shaan Khetrapal

CHAPTER 42: **Management of Dyslipidemia in Statin Intolerance**
Manu Gupta, Rajeev Gupta, Nitesh Arora, Anuj Gupta

CHAPTER 43: **Coronary Artery Calcification in Risk Stratification of Coronary Artery Disease**
Kajal Ganguly, Mainak Mukhopadhyay, Subhasis Roy Chowdhury, Arijit Ghosh

CHAPTER 44: **Atherogenic Risk of Low Density Lipoprotein and Management Strategies**
Kannan Kumaresan, Prabhakar Dorairaj

CHAPTER 45: **Primary Prevention of Cardiovascular Disease: The Current Approach**
G Rajendiran, Puneeth Kumar

CHAPTER 46: **Use of Biomarkers: Troponin and B-type Natriuretic Peptide—in Cardiovascular Risk Stratification and Disease Prevention**
Mini G Varughese, Vijay Nambi

CHAPTER 47: **Reducing Cardiometabolic Risk Through Diet and Exercise: The Power of Lifestyle Change**
Roshani Sanghani

CHAPTER 36

Revisiting Secondary Prevention in Coronary Artery Disease

Prem Ratan Degawat, Sumit Kumar, Rajeev Gupta

ABSTRACT

Secondary prevention in coronary heart disease (CHD) is the prevention of occurrence of recurrent coronary events after clinical diagnosis. A high level of adherence to secondary prevention interventions, especially aggressive lifestyle changes and pharmacotherapy, can lead to significant decline in recurrent coronary events. Both international and Indian studies have reported low adherence to such therapies. Evidence-based useful interventions include regular physical activity, yoga, intake of healthy diet, smoking and tobacco use cessation, and weight management. Pharmacotherapeutic interventions that are useful are antiplatelet therapy (short-term dual and long-term single), target-oriented lipid-lowering therapy with statins (ezetimibe, bempedoic acid, or PCSK9 inhibitors in statin nonresponsive or intolerant), β-blockers (medium to long-term), and angiotensin-converting enzyme (ACE) inhibitors [angiotensin receptor blockers (ARBs) in ACE inhibitor intolerant] in patients with impaired left ventricular function. Hypertension and diabetes management with control to targets is important. Novel strategies include use of anticoagulants, anti-inflammatory drugs, and triglyceride lowering for residual risk. Physician and patient level interventions using multifaceted educational, socioeconomic, and technological innovations are important to promote lifelong adherence to these strategies.

INTRODUCTION

Coronary heart disease (CHD) is the most common type of cardiovascular disease and is the leading cause of death worldwide.[1] Mortality due to CHD has decreased in developed countries, but India and many other developing countries are still experiencing a significant increase in CHD morbidity and death rates.[2] Many studies have reported that Indians are more susceptible to coronary artery disease (CAD) and have a higher case-fatality rate than the Western populations.[3,4]

Advances in medical care and prevention have improved survival after the initial event, but people with established CHD are at a high risk of subsequent cardiovascular events such as myocardial infarction (MI), stroke, and cardiovascular death. Despite advances in pharmacological treatments and invasive procedures, the quality of post-CHD management with better risk factor control and other pharmacological strategies and socioeconomic determinants of health remain independent predictors for fatality in patients with CAD.[5,6] Secondary prevention in CHD is the prevention of occurrence of recurrent coronary events after clinical diagnosis.[7] In this chapter, we shall focus on the status of secondary prevention in India and highlight the existing and emerging pharmacological therapies that can prevent recurrent coronary events. We also suggest interventions to promote adherence to these lifelong therapies.

STATUS OF SECONDARY PREVENTION IN INDIA

There is substantial evidence showing that secondary prevention through comprehensive risk factor modification has beneficial effects in patients with CAD, such as a decrease in mortality, reduction in recurrent cardiac events, and better quality of life.[7,8] It has been suggested that adherence to four cardioprotective medicines—antiplatelet drugs, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and lipid-lowering statins—can reduce 2-year mortality after acute coronary syndrome (ACS) from 10 to about 2% **(Fig. 1)**.[9]

Guidelines from the American College of Cardiology/American Heart Association (ACC/AHA),[7,8,10,11] European Society of Cardiology (ESC),[12,13] and almost all global CHD management guidelines have recommended aggressive

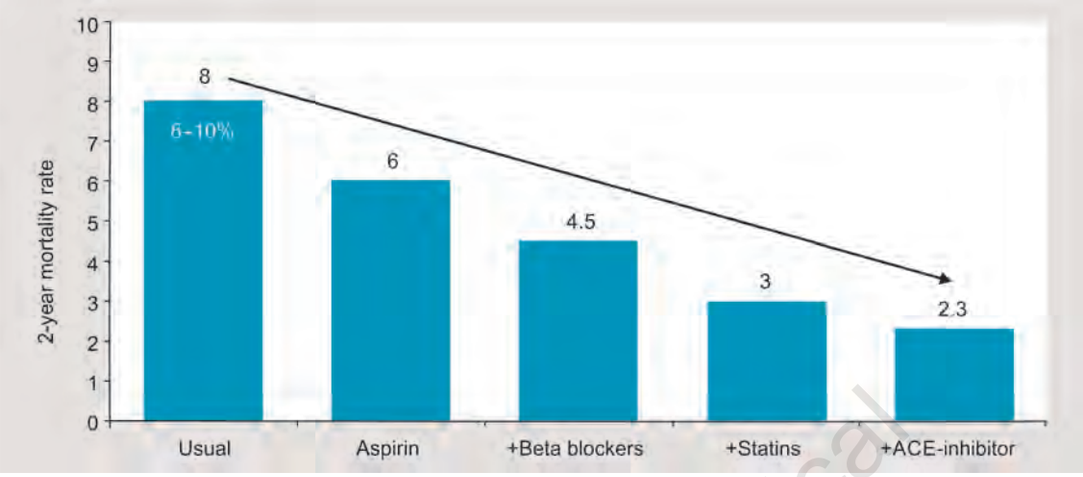

FIG. 1: Influence of cardioprotective therapies in reducing 2-year cardiovascular mortality in patients with known CHD.[9]
(ACE: angiotensin-converting enzyme; CHD: coronary heart disease)

risk factor management with adherence to healthy lifestyle and cardioprotective therapies in all patients who have been diagnosed with ACS or have chronic coronary syndromes (CCS).[14,15]

Status of secondary prevention is poor worldwide, and multiple factors, predominantly social determinants of health such as rural location, poverty, illiteracy, and low affordability and availability of supportive therapies, are important.[6] In a low-resource setting such as India, with poor focus on primary care, secondary prevention of CAD is a difficult task. Delays in diagnosis, poor quality treatment, and poor adherence to primary and secondary prevention strategies are all symptoms of resource constraints.[5]

The WHO-PREMISE study in 10 countries reported low adherence to drug therapies, particularly ACE inhibitors and statins, in developing compared to the more developed countries.[16] EUROASPIRE studies were performed in multiple European countries, and initial surveys reported low adherence to healthy lifestyles and drug therapies. It was also reported that countries with a lower human development index had significantly less adherence to healthy lifestyles (smoking cessation, physical acidity, and healthy diet) and secondary preventive cardiac medicines (antiplatelets, β-blockers, ACE inhibitors, and statins).[17,18] In high-income countries, it has been reported that lower socioeconomic status (SES) patients have less access to cardiac rehabilitation and lower adherence to healthy lifestyles and secondary prevention drug therapies.[19]

In Prospective Urban Rural Epidemiology (PURE) study, we reported a very low uptake of all the cardioprotective therapies in patients with known ischemic heart disease (IHD) and stroke in developing countries compared to more developed countries.[20] In the South Asian cohort of PURE study, we reported that low SES patients (low educational status or low wealth index) with IHD or stroke had the lowest consumption of various evidence-based therapies at 4–5 years after diagnosis.[21] A nationwide prescription audit[22] and a Rajasthan state prescription audit[23] reported lower secondary prevention therapies in primary care clinics compared to IHD patients in secondary and tertiary care **(Fig. 2)**. A prescription audit among stable IHD patients in a nationally representative sample in China reported that low SES was independently associated with lower treatment rates for aspirin, clopidogrel, β-blockers, and statins.[24]

SECONDARY PREVENTION INTERVENTIONS

The main focus of secondary prevention is to prevent recurrent coronary events before symptoms appear and to prolong life. It includes lifestyle management and therapeutic management. Lifestyle management focuses on tobacco (smoking and smokeless) cessation, increased physical activity, weight management, and healthy dietary modification, while therapeutic management focuses on standard and emerging cardioprotective medical therapies and percutaneous coronary interventions (PCI), and surgical coronary revascularization. The class of recommendations and level of evidence of use of various interventions are shown in **Table 1**.[25]

Physical Activity

Regular physical activity in any form is an important aspect of secondary prevention of CHD because it enhances exercise capacity, ameliorates comorbid risk factors, and improves quality of life.[26] Exercise-based cardiac rehabilitation has been shown that it lowers all-cause and cardiac lethality when compared to standard therapies.[26-28] All patients should be actively involved in 30–60 minutes of moderate-intensity physical activity, such as biking or brisk walking. Ancillary physical activity lowers total cholesterol, triglyceride levels, and systolic blood pressure (BP). Exercise-based cardiac rehabilitation program can be started soon after an ACS or revascularization procedure.[29] Before starting an intensive exercise routine, physicians should assess their patients' cardiovascular status by taking a physical activity history or performing an exercise test.

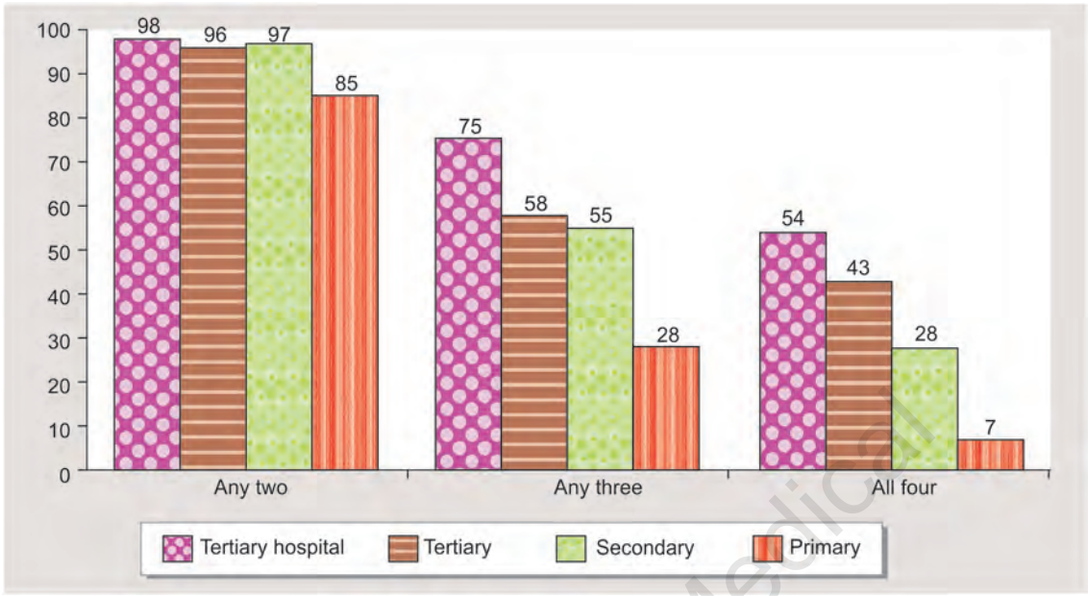

FIG. 2: Cardioprotective secondary prevention medicines [aspirin, β-blockers, statins, and angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blocker (ARB)] in primary, secondary, and tertiary care in Rajasthan. Use of any two, three, or all four of these drugs is the highest in tertiary care hospitals and lowest in primary care.

Source: Sharma KK, Gupta R, Agrawal A, Roy S, Kasliwal A, Bana A, et al. Low use of statins and other coronary secondary prevention therapies in primary and secondary care in India. Vasc Health Risk Manag. 2009;5:1007-14.

TABLE 1: Summary of secondary prevention guidelines and class of recommendation.[25]

Lifestyle interventions	Therapeutic agents
• Physical activity (Class I) • Healthy diet (Classes I–II) ○ No trans fats (Class I) ○ Reduce saturated fats (Class IIA) ○ Increased MUFA, PUFA (Class IIA) ○ Fruits, vegetables, nuts (Class IB) • Smoking/tobacco cessation (Class I) • Alcohol moderation (Class II) • Weight management (Class II) • Cardiac rehabilitation (Class I)	• Antiplatelets (Class I) ○ Long-term dual (Class IA) versus single (Class IB) • Statins (Class I) • β-blockers, medium term (Class I) • ACE inhibitors (Class I) or angiotensin receptor blockers (Class IIA) • *Other drugs classes*: Nitrates, calcium channel blockers, metabolic modulators, other vasodilators (Class II, III)

(MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids)

Dietary Modification: Healthy Diet

Dietary restrictions vary depending on the type of CAD risk factors. Adults who are at risk for high blood lipids should eat more fruits, leafy greens, whole grains, eggs, fish, and low-fat dairy products (healthy diet) while avoiding sugary drinks, sweets, and red meat.[26] It is also suggested that saturated fat calories be limited to 5–6% of total daily calories.[30] Adults with high BP problems should follow the same dietary restrictions but with low sodium levels. Dietary sodium restriction has also been recommended to reduce the risk of CAD in the general population.[29] Sodium (in the form of salt) causes water retention, which results in high BP **(Table 2)**.

Smoking/Tobacco Cessation

One of the most cost-effective interventions in secondary prevention is smoking and tobacco-use cessation.[26] All the guidelines recommend absolute tobacco cessation for CAD secondary prevention. Policy interventions are important, and worldwide implementation of WHO Framework Convention for Tobacco Control (FCTC) can lead to avoidance of millions of CAD events and can result in saving lakhs of lives.[31] At the individual level, tobacco cessation can be achieved by patient education, nicotine replacement therapies, bupropion, psychotherapy, and family support. Avoiding second-hand smoke is equally important.

Alcohol

A controversial issue in secondary prevention relates to alcohol use.[11] Light to moderate alcohol consumption has been linked to a reduced risk of CAD, but the evidence is controversial. It is not recommended by any of the guidelines either for primary or secondary prevention.[8,26]

Weight Management

Obesity has been associated with an increased risk of CAD death rates as well as an adverse influence on cardiac function and comorbid lifestyle factors. Maintaining an average weight with a body mass index (BMI) of 23–27 kg/m^2 and a waist circumference of <80 cm for women and <90 cm for men is suggested. The BMI should be measured at each counseling session, according to the AHA, and then objective reviews and reliable counseling on weight loss programs should be provided. Balance of physical activities and dietary changes is required for long-term weight control, and modest weight loss is associated with changes in cardiac risk factors.[11]

TABLE 2: Recommendation for healthy food in various guidelines.

Mediterranean Diet (PREDIMED)	Lancet-EAT Commission Anthropocene Diet	American Heart Association	European Society of Cardiology
• *Recommended*: Olive oil, tree nuts or peanuts, fresh fruits, fatty fish, legumes, white meat, wine • *Discouraged*: Soda drinks, commercial bakery goods, sweets, pastries, spread fats, red and processed meats	• Diversity of plant-based foods • Low animal source • Balanced intake of unsaturated and saturated fats • Reduced amounts of refined grains, highly processed foods, added sugars	• Greater intake of vegetables, fruits, legumes, nuts, whole grains, fish • Low intake of refined grains, highly processed foods, added sugars	• Recommendations for whole-grain products, oily fish, unsalted nuts • High intake of fruits and vegetables, >200 g each • Low intake of refined grains, highly processed foods, added sugars

TABLE 3: Reducing cardiovascular risk for secondary prevention.

Biological factors	Biomarker	Intervention/s	Trial evidence	Prevention guidelines
Thrombotic risk	None	Aspirin, P2Y12 inhibitors, rivaroxaban, and other novel oral anticoagulants	++++	Yes
Cholesterol and residual cholesterol risk	LDL-C ≥ 70 mg/dL	LDL-C reduction (ezetimibe, bempedoic acid, PCSK9 inhibition, monoclonal antibodies, small RNA molecules)	++++	Yes
Triglyceride risk	Triglyceride ≥ 150 mg/dL	High-dose purified omega-3 fatty acids (icosapent ethyl)	+++	Yes
Lp(a) risk	Lp(a) ≥ 50 mg/dL	Monoclonal antibodies—APO(a)-LRX, pelacarsen, etc.	– –	No
Vascular risk	Blood pressure <130/80 mm Hg	β-blockers, RAAS blockers	++++	Yes
Diabetes risk	HbA1c ≥ 6.5%	SGLT-2 inhibitors, GLP-1 agonists	+++	Yes
Inflammatory risk	hsCRP ≥ 2 mg/dL	Aspirin, colchicine, monoclonal antibodies (e.g., canakinumab)	++	No

[APO(a): apolipoprotein A; GLP-1: glucagon-like peptide 1; HbA1c: glycated hemoglobin A1C; hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; Lp(a): lipoprotein(a); RNA: ribonucleic acid; SGLT-2: sodium-glucose cotransporter-2; RAAS: renin–angiotensin–aldosterone system]

Cardiac Rehabilitation

Enrollment in a formal cardiac rehabilitation program is useful to learn the lessons for secondary prevention and better motivation.[32] Studies in India have reported that there is low availability, affordability, and awareness of cardiac rehabilitation facilities.[33] Comprehensive cardiac rehabilitation facility needs physicians, technicians, nurses, and other health workers and could be expensive to maintain. Studies in the USA have shown that the intervention is cost-effective.[32] No similar studies exist in India. A low-cost cardiac rehabilitation program has been developed using home-based follow-up following a hospital training protocol.[34] Outcome studies are needed.

PHARMACOTHERAPY

There has been a recent surge in understanding of approaches to long-term management of CAD.[35] Multiple approaches have been found to be useful and include multiple pillars of intervention.[36] We hereby suggest six pillars of risk mitigation and interventions that focus on low-density lipoprotein cholesterol (LDL-C) and residual cholesterol risk, triglyceride risk, thrombotic risk, vascular risk, hyperglycemia and diabetes risk, and inflammatory risk. The targets and therapeutic approaches to achieve targets are shown in **Table 3**. A combination of these drug therapies is required to achieve improved outcomes in secondary prevention. Despite the use of all these pharmacological approaches and drugs, there remains a substantial residual risk and more studies are required to identify interventions to overcome this risk.

Antiplatelet Therapy

Antiplatelet therapy is an essential part of medical regimen in ACS as well as for secondary prevention after stabilization. Multiple randomized trials have clearly shown that dual antiplatelet therapy (DAPT) that includes aspirin and P2Y12 inhibitors should be taken for at least 12 months following ACS. It has also been shown in clinical trials that third-generation P2Y12 inhibitors (ticagrelor and prasugrel) show additional benefit in terms of decreased ischemic events compared to clopidogrel with an added cost of a slight increase in bleeding; however, the net outcomes are favorable for these drugs.

In all the current guidelines, DAPT has typically been recommended for 12 months following ACSs with ticagrelor and prasugrel generally preferred over clopidogrel.[37-39] The choice of drug as the third-generation antiplatelet has been tested in a few trials. The ISAR-REACT (Intracoronary

Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) 5 trial[40] was a randomized, open-label comparison of prasugrel versus ticagrelor and reported higher rate of the composite primary endpoint (death, MI, or stroke) at 1 year in patients randomized to ticagrelor [9.3 vs. 6.9%; hazard ratio (HR) 1.36; 95% confidence interval (CI) 1.09–1.70] with no significant difference in major bleeding. The 2020 ESC guidelines suggest a Class IIa (level of evidence B) recommendation for prasugrel over ticagrelor in patients with non-ST elevation ACS who undergo PCI and are eligible for prasugrel (no prior stroke or transient ischemic attack).[39] As for the consideration of single antiplatelet therapy following ACS, the TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial and a meta-analysis of 32,000 patients found equivalent risk of major adverse cardiovascular event (MACE) with early discontinuation of aspirin within 12 months.[41,42] Thus, randomized clinical trials and meta-analyses support DAPT following an acute coronary event for at least 12 months and in those with a high risk of bleeding, DAPT for 1 month followed by ticagrelor (or prasugrel) as a single antiplatelet drug can be recommended.

Anticoagulation Therapy

Approximately 8–10% of patients undergoing PCI have atrial fibrillation and other indications for an oral anticoagulant.[43] Several trials have evaluated different strategies and a meta-analysis of these trials reported lower rates of bleeding with a direct oral anticoagulant (DOAC)-based dual antithrombotic therapy than vitamin K agonist triple antithrombotic therapy, but with numerically greater rates of MI and stent thrombosis without statistical significance.[43] Two large randomized trials that compared a DOAC (apixaban or edoxaban) and vitamin K agonist in this setting found lower rates of bleeding with the DOACs.[43,44] The 2020 ESC non-ST elevation-ACS guidelines[45] recommend 1 week of triple antithrombotic therapy (or until hospital discharge) as a default strategy followed by dual antithrombotic therapy with a DOAC plus P2Y12 inhibitor (typically clopidogrel) until 1 year, at which point DOAC monotherapy can be considered.[33]

Lipid Lowering

Low-density Lipoprotein Cholesterol Management

Various studies have shown that reducing the level of circulating atherogenic lipoproteins has a major effect on the risk of adverse cardiovascular events. A target LDL-C level lower than 70 mg/dL with an optional target of 55 mg/dL in high-risk secondary prevention has been suggested by European guidelines.[46] Meta-analyses of multiple statin trials show a dose-dependent relative reduction in cardiovascular events with LDL-C lowering. The Cholesterol Treatment Trialists' (CTT) collaborators performed a series of meta-analysis of cholesterol lowering (statins) from 2005 to 2020. In the first report which evaluated 14 trials with 90,056 participants, there was significant benefit in primary prevention.[47] In a follow-up study with 18,686 patients with diabetes in these 14 randomized trials, there was a significant 21% proportional reduction in major vascular events per1 mmol/L (38 mg/dL) reduction in LDL-C in people with diabetes [odds ratio (OR) 0.79; 95% CI 0.72–0.86] which was similar in those without diabetes (OR 0.79; CI 0.76–0.82) with greater reduction in MI and coronary deaths (OR 0.78; CI 0.69–0.87).[48] In another meta-analysis by CTT collaborators in 2015 among 174,000 participants in 27 randomized trials, lowering of LDL-C by 1 mmol/L reduced major vascular events by 20% (OR 0.80; CI 0.74–0.82).[49] Wang et al. performed a meta-analysis of benefit of lipid lowering in 2020 among 327,037 participants in 27 trials of LDL lowering and reported that reducing LDL-C by 1 mmol/L led to reduced major vascular events by 17% (OR 0.83; CI 0.79–0.88).[50] Statins are universally recommended for secondary prevention by all the international and national guidelines. High-intensity statin therapy (atorvastatin 40–80 mg/day or rosuvastatin 20–40 mg/dL) must be given to all the patients to achieve targets **(Table 4)**.[46,51,52]

TABLE 4: Statin therapy (mg/day) for secondary prevention.

Statin	Low intensity <30% LDL lowering	Moderate intensity 30–49% LDL lowering	High intensity >50% LDL lowering
Lovastatin	20 mg	–	–
Pravastatin	10–20 mg	40–80 mg	–
Simvastatin	10 mg	20–40 mg	–
Atorvastatin	–	10–20 mg	40–80 mg
Rosuvastatin	–	5–10 mg	20–40 mg
Pitavastatin	–	1–4 mg	–

(LDL: low-density lipoprotein)

If LDL-C remains above 70 mg/dL (55 mg/dL in very high-risk patients) despite the use of a maximally tolerated statin, ezetimibe should be added.[46,51,52] Oral bempedoic acid has also emerged as a choice second-line drug in combination with a high-dose statin.[53] Two monoclonal antibodies against PCSK9, evolocumab, and alirocumab reduce LDL-C by 50–70% and have shown major reductions in cardiovascular events in high-risk patients, including within 12 months of ACSs.[54-56] The EVOPACS (EVOlocumab for Early Reduction of LDL-C Levels in Patients with Acute Coronary Syndromes) trial[57] has investigated the safety and feasibility of evolocumab use in ACS patients. Inclisiran, a small molecule-based PCSK9 inhibitor, has also shown efficacy in reducing LDL-C and effectiveness in reducing cardiovascular outcomes in CAD.[58] PCSK9 inhibition is equally efficient in those with and without diabetes, with a 27% relative risk reduction in cardiovascular death, MI, stroke, and hospitalization for unstable angina or revascularization. All these drugs have been approved for use in CAD for LDL-C reduction and outcome benefits. Guidelines recommend their use when LDL-C remains >70 mg/dL despite maximal dose statin plus ezetimibe, or if patients are statin intolerant and ezetimibe alone is ineffective in patients with established CAD.[46,51]

Triglyceride Lowering

Epidemiological studies have reported that raised serum triglycerides are significant and independent CAD risk factor, but the association is weaker than for hypercholesterolemia.[58,59] Meta-analyses suggest that targeting triglycerides may reduce CAD in specific subgroups with high triglycerides and low HDL-C.[60,61] Other meta-analyses have also shown similar results.[61-63] REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial), using high dose purified eicosapentaenoic acid (icosapent ethyl), is the first trial to report significant benefits of triglyceride reduction combined with nontriglyceride mechanisms on cardiovascular outcomes.[63] This drug is now available in India and can be used in secondary prevention and high-risk primary prevention.

Lipoprotein(a) Management

Raised lipoprotein(a) [Lp(a)] is now recognized as an important CAD risk factor in epidemiological studies, Mendelian randomized studies, and genetic studies.[64,65] However, there is no randomized intervention study showing that reducing Lp(a) decreases CAD risk. At present, there is no justification for screening the general population for Lp(a), but it may be considered in patients at moderate risk to refine risk evaluation or in subjects with a family history of premature CAD.[35,46,65]

Cardiovascular Protective Agents

Cardioprotective agents work by decreasing left ventricular ejection fraction, restricting left ventricular hypertrophy, lowering myocardial oxygen demand (which is elevated in patients with CAD due to atherosclerosis), and vascular protection. These drugs include β-blockers, ACE inhibitors/angiotensin receptor blockers (ARBs), calcium channel blockers, and nitrates.

β-blockers

β-blockers are first-line cardioprotective agents for patients with CAD.[8] These drugs reduce heart rate, increase diastolic filling time, and lower cardiac contractility by restricting β1 and β2 adrenergic receptors. This significant inotropic and chronotropic effect reduces myocardial oxygen demand. Meta-analyses of multiple trials involving more than 24,000 patients who received β-blockers in the convalescent phase of ST-elevation MI (STEMI) have shown a 23% reduction in long-term mortality.[7] When β-blockers are administered early (<6 hours) in the acute phase of infarction and continued in the chronic phase of treatment, some of the benefits may result from a reduction in infarct size. Patients with a relative contraindication to β-blockers (e.g., bradyarrhythmias, atrioventricular blocks) should undergo a monitored trial of therapy in the hospital. Studies have suggested that β-blocker therapy be continued for at least 2–3 years after an acute coronary event. Long-term use is indicated in patients with stable angina, recurrent unstable angina, and congestive heart failure.[14,15]

Inhibitors of the Renin–angiotensin–aldosterone System

Inhibition of the renin–angiotensin–aldosterone system (RAAS) is essential to prevent cardiac remodeling in post-ACSs [STEMI or non-ST-elevation MI (NSTEMI)] patients. Based on the results of the HOPE (Heart Outcomes Prevention Evaluation) and EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease) trials, the treatment with an ACE inhibitor (ramipril, perindopril) for all STEMI patients with ejection fraction < 40%, renal dysfunction, or diabetes regardless of ejection fraction should be given if no contraindication exists.[45] The VALIANT (Valsartan in Acute Myocardial Infarction) trial results suggest that valsartan may be used as an alternative to an ACE inhibitor (in ACE inhibitor–intolerant patients) for the long-term management of patients with left ventricular dysfunction after STEMI.[66]

Diabetes Management

Proper management of type 2 diabetes mellitus (T2DM) is crucial to prevent complications in secondary prevention of CAD. Two classes of drugs, sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, have shown long-term benefit in secondary prevention.[67] Results of meta-analyses of randomized controlled trials suggest that while GLP-1 receptor agonists are more useful for primary prevention, SGLT-2 inhibitors are better in secondary prevention, especially in patients with impaired left ventricular function.[68,69] Braunwald concluded that SGLT-2 inhibitors are responsible for paradigm shifts in care of patients at high risk of heart failure–CAD secondary prevention, or having heart failure.[70] SGLT-2 inhibition improves cardiovascular outcomes in patients with heart failure over a wide range of ejection fractions, regardless of whether the patients have T2DM. These drugs are also recommended as part of secondary as well as CAD primary prevention therapies.[71]

Anti-inflammatory Agents

Inflammation after ACS significantly contributes to recurrent ischemic events.[36] Lipid lowering with rosuvastatin was effective in primary prevention with raised high-sensitivity C-reactive protein (hsCRP) levels (indicative of underlying inflammation).[72] Secondary prevention trials with a novel monoclonal antibody targeting interleukin-1b (canakinumab) reported significant benefit in secondary prevention,[73] while therapy with low-dose methotrexate as an anti-inflammatory agent did not report significant benefit.[74] Anti-inflammatory treatment with colchicine after ACS has recently shown some promise.[75] In the COLCOT (Colchicine Cardiovascular Outcomes) trial, colchicine showed 23% reduction of MACE compared to placebo at 30 days in MI patients.[76] Similar findings were observed among patients with CCS in the LoDoCo2 trial.[77] On the other hand, in the COPS (Colchicine in Patients with Acute Coronary Syndromes) trial,[78] in ACS patients results showed significantly increased risk of death with colchicine. At present, there is no recommendation for colchicine in CAD secondary prevention.

ADHERENCE TO SECONDARY PREVENTION

One of the most important aspects of secondary prevention is adherence to therapies. Adherence is defined as remaining attached to the medication regimen and adequate adherence is use of therapies >80% of times.[79] Studies have reported that in chronic diseases, only 50% patients are adherent to therapies at 12 months and just 20% take medications in appropriate dose. Observational studies from all over the world, especially developing countries, have shown that most patients were not prescribed either the full spectrum of lifestyle-related interventions or pharmacological therapies. Studies in US and North America have reported that <50% patients adhere to appropriate therapies at 5-years post-ACS while the rates are much lower (<10%) in developing and underdeveloped countries of Asia, Africa, and Latin America.[80] There are numerous barriers to adherence and secondary prevention **(Table 5)**. Although universally important, these factors are more relevant in middle- and low-income countries such as India.[6]

Interventions to Promote Adherence

Outcomes of interventions to promote adherence are limited. A number of interventions directed at healthcare system, healthcare professionals, and patients have been suggested **(Table 6)**. There is some evidence that technology-based interventions, pharmacists' level interventions, and health-worker based interventions are useful in promoting adherence and influencing intermediate outcomes.[81]

An important factor that promotes adherence in CHD primary and secondary prevention is self-management of risk factors.[26] Adherence to healthy lifestyles and pharmacological therapy in asymptomatic high-risk individuals is a herculean task, and patient empowerment and personalized medicine to support lifelong adherence to lifestyle changes and drug therapies can be useful. Technology-based strategies to promote adherence to healthy lifestyles and drug therapy are available, and given the universality of smartphone devices the potential for this personalized approach is enormous.[82,83]

CONCLUSION

Secondary prevention in CHD is crucial to reduce mortality and morbidity from this condition. A high level of adherence to secondary prevention interventions including aggressive lifestyle changes and appropriate pharmacotherapy can lead to a significant decline in recurrent coronary events. Suggested interventions include regular physical activity, intake of healthy diet, smoking and tobacco use cessation, weight management, and alcohol moderation. Pharmacotherapy interventions found useful are antiplatelet therapy (short-term dual and long-term single), target-oriented lipid-lowering therapy with statins (ezetimibe, bempedoic acid, or PCSK9 inhibitors in statin nonresponsive or intolerant),

TABLE 5: Barriers to adherence and secondary prevention.

Community level barriers	Health system barriers	Provider barriers	Patient-related factors
• Low perceived needs • Lack of heart-friendly infrastructure • Government policies for food, tobacco • Media apathy	• Resource constraints • Poor access and availability • Lack of advocacy	• Lack of understanding of patient needs • Prescribing complex regimens • Failure to explain benefits and side effects • Lack of focus on lifestyle changes • Lack of continuity of care • Low clinical referrals • Clinician perceptions • Overtreatment	• Older age • Female gender • Low socioeconomic status • Social isolation • Comorbidities • Multiple stakeholders • Disparate messages • Finance and insurance • Geographic factors

TABLE 6: Interventions to promote adherence.

System level	Provider level	Individual level
• Prioritization of secondary prevention • Education of providers and patients • Simplify referral and enrollment processes • Increase resources for secondary prevention services • Increase capacity and capabilities of health care providers • Increase capacity of programs	• Improve education • Teach adherence promotion techniques • Motivation • Cost awareness • Single pill combinations, polypills	• Discuss advantages/disadvantages of drugs • Motivational interviewing • Patient choice • Recommend intake in written format • Reminders using nurses, pharmacists, and family members • Discuss adherence at each visit • Continuous counseling strategies, telephone, etc. • Small number of single daily doses • Fixed combinations • Dose-dispensed medicines • Door-step level care (nonphysician health workers, community health workers, technology)

β-blockers (medium to long-term), and ACE inhibitors (ARBs in ACE inhibitor intolerant). Novel strategies include use of anticoagulant and anti-inflammatory drugs, and lowering triglycerides and Lp(a). Physician and patient level interventions are important to promote lifelong adherence to these strategies.

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CHAPTER 37

Genetic Risk Scores for Premature Coronary Artery Disease in India

Rajeev Gupta

ABSTRACT

Premature coronary artery disease (CAD) is endemic in India. Anecdotal evidence in the past suggested a significant prevalence of premature CAD among hospitalized CAD patients. Using a large database (*n* = 4,672), we reported that 30% of patients have premature CAD (age <55 years men, <60 years women). Prevalence of very premature CAD (<40 years men, <45 years women) is even lower (4–5%). The majority of these patients have standard risk factors [raised non-high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, smoking/tobacco], while almost half had no evidence of risk. Clinical risk stratification algorithms (e.g., Framingham risk score) and imaging-based risk stratification [carotid intima-media thickness (CIMT), coronary calcification score] do not provide prognostic information in the majority of patients with premature CAD. Genes that predispose to CAD have been reported for the last 20 years and include genes that influence lipid metabolism, blood pressure, vascular remodeling, mitosis, cell proliferation, neovascularization, transcription regulation, and others. Single-gene mutations that increase CAD risk are rare and include some lipid genes—*HMGCR, LDLR, APOB, PCSK9, NPC1L1*, etc. CAD is multifactorial and studies have now focused on the predictive capability of clusters of 10–500 single-nucleotide polymorphisms (SNPs) using a genetic risk score (GRS). After the advent of genome-wide association studies (GWAS), studies have identified millions of SNPs involved in atherothrombosis. Such genome-wide polygenic risk scores (GPS) are more useful than conventional methods of risk stratification. This is a better strategy for the identification of risk for premature CAD, as genes do not change with aging, and in the young, these scores can predict future CAD risk. Moreover, most of the risk attributable to high genetics-based risk scores can be mitigated by a lifelong adherence to a healthy lifestyle.

INTRODUCTION

Premature coronary artery disease (CAD), defined as the occurrence of the first clinical manifestation in men <55 years and women <60 years,[1] is highly prevalent in India and most low- and lower-middle-income countries.[2,3] The Global Burden of Diseases study has reported that among the young, ischemic heart disease (IHD) is one of the more important causes of morbidity and mortality, especially in lesser developed countries.[4] The study also reported that in the age group of 20–54 years, IHD led to more annual deaths in India compared to the USA, China, and countries in Europe and Central Asia.[5] **Figure 1** shows that in contrast to many large countries (China and USA) and European regions, premature IHD mortality is increasing in India. The annual mortality in the year 2000 was 191,053 (men 137,612; women 53,442) and has increased in 2019 to 286,055 (men 199,232; women 86,823) (absolute increase 49.7%, +2.5% per year).[5]

Studies from India have reported a significant proportion of patients with premature CAD among hospital admissions in both government and nongovernment hospitals.[6-17] The prevalence rates have not been properly documented in the absence of population data in most of the studies. Among 4,672 successive patients (men 3,736; women 936) who underwent coronary angioplasty at our hospital [part of the American College of Cardiology National Cardiovascular Data Registry (NCDR) Catheterization and Percutaneous Coronary Intervention (CathPCI) Registry], we observed premature CAD (men <55 years, women <60 years) in 1,399 patients (29.9%) and very premature CAD (men <40 years, women <45 years) in 212 patients (4.5%) **(Fig. 2)**.[17] The Atlas Writing Group of the European Society of Cardiology recently published data on premature CAD in Europe. It has been reported that there are large disparities between high- and middle-income countries of Europe in the proportion of premature deaths (<70 years)

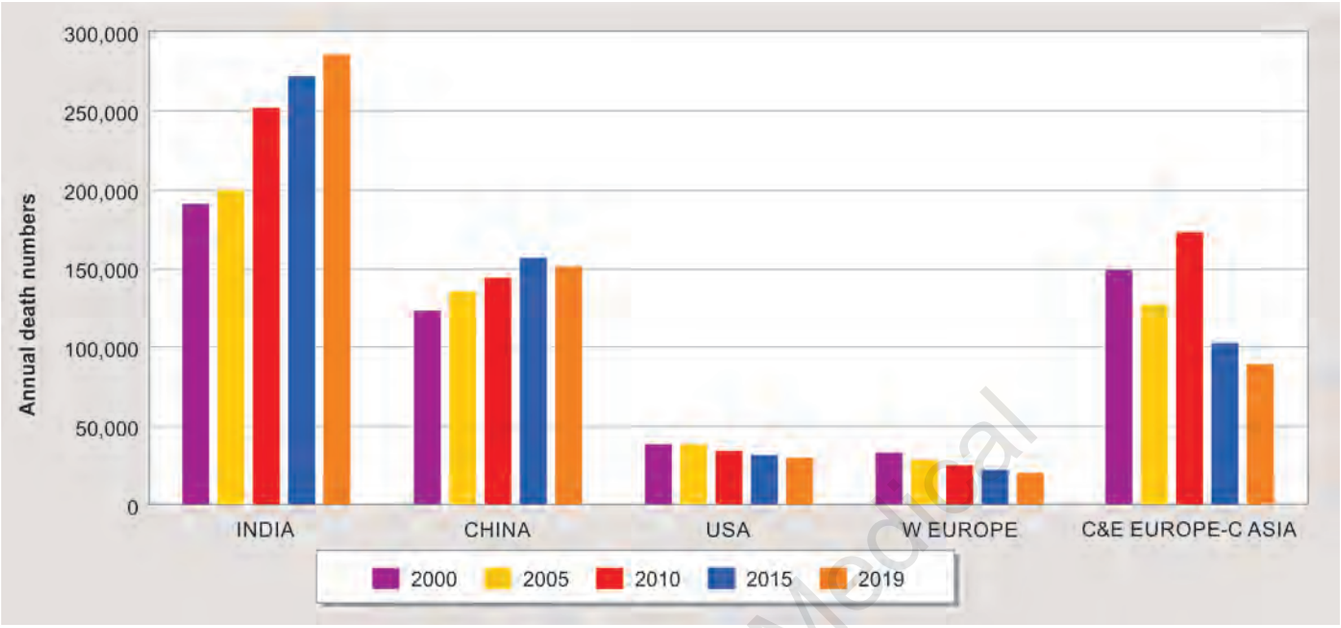

FIG. 1: Quinquennial trends (years 2000–2019) in ischemic heart disease (IHD) mortality among individuals aged 20–54 years in India compared to China, USA, Western European, and Central-Eastern European and Central Asian countries.
Source: Global Burden of Diseases Study.[5]

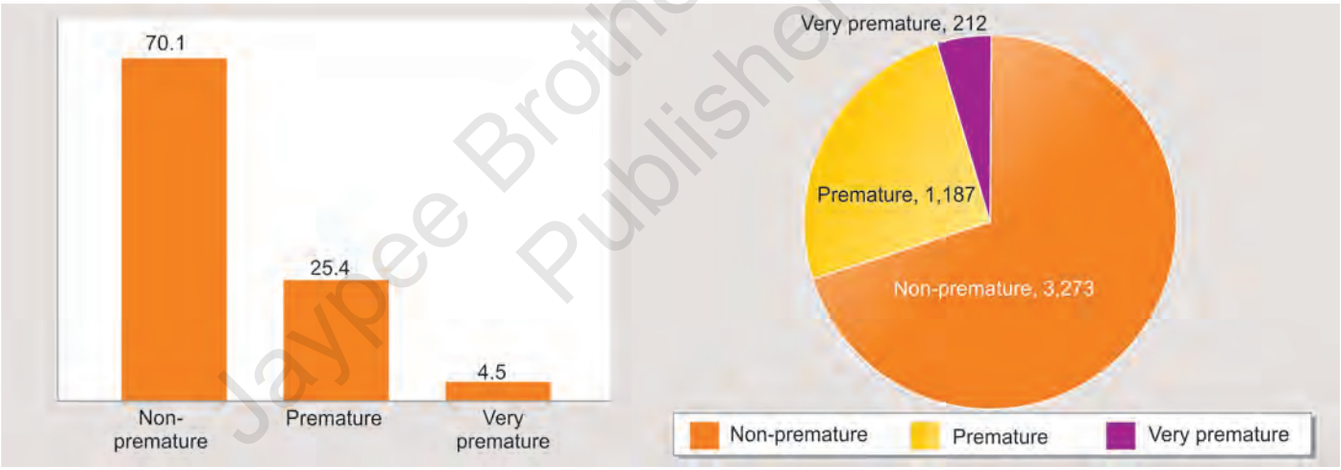

FIG. 2: Contemporary prevalence of premature coronary artery disease (CAD) among 4,672 patients at a single center in India.
Source: Gupta R, Sharma KK, Sharma SK, et al. Premature CAD, risk factors, clinical presentation, angiography and interventions: a hospital-based registry in India. 2022 [Submitted].

caused by cardiovascular disease (CVD). In men and women, respectively, 36% and 36% of deaths in middle-income countries and 24% and 16% of deaths in high-income countries of Europe were premature.[18]

Previous studies reported that the most important risk factor in premature CAD was smoking.[19,20] Case–control studies and registry-based studies have reported that both traditional coronary risk factors [smoking, hypercholesterolemia, low-density lipoprotein (LDL) cholesterol, hypertension, unhealthy lifestyles, etc.], as well as emerging risk factors [lipoprotein(a), triglycerides, metabolic syndrome, etc.], are important.[21-25] In our study, we found that raised total and non-high-density lipoprotein (HDL) cholesterol and smoking/tobacco use were important.[17] The important major risk factors and emerging risk factors are highlighted in **Table 1**.

Identification of risk in premature CAD is important. Early identification of risk can lead to the promotion of healthier lifestyles and other interventions that can mitigate or delay the onset of premature CAD.[24-26] In this narrative review, we shall focus on the limitations of traditional risk factors to identify premature CAD and focus on genetic risk stratification for earlier identification of coronary risk.

TABLE 1: Traditional and other risk factors identified in patients with premature coronary artery disease (CAD) in India.

	Traditional risk factors	Emerging risk factors
Lifestyle factors	• Smoking and tobacco • Sedentary lifestyle • Unhealthy diet	• Ambient/Household air pollution • Psychosocial stress
Biological factors	• Hypertension • Raised LDL cholesterol • Raised non-HDL cholesterol • Hypertriglyceridemia • Diabetes	• Abdominal obesity • Frailty • Lipoprotein(a) • Remnant lipoproteins • Impaired glucose tolerance • Homocysteine • Fibrinogen • Genetics and genomics

(HDL: high-density lipoprotein; LDL: low-density lipoprotein)

TABLE 2: Commonly used risk prediction tools.

Region/Country	Eponym
North America	• Framingham risk score, old, new • ACC/AHA pooled cohort equation
Europe	• SCORE • QRISK-1, QRISK-2, QRISK-3 • PROCAM
International	• World Health Organization • INTERHEART • GLOBORISK-2

(ACC: American College of Cardiology; AHA: American Heart Association)

CLINICAL RISK STRATIFICATION

The current literature is overwhelmed with models for predicting the risk of cardiovascular outcomes in the general population; however, most have not been externally validated or directly compared on their relative predictive performance, making them currently of unknown value for practitioners, policymakers, and guideline developers.[27-30] We suggest that instead of developing new CAD risk prediction models—in this era of large datasets, machine learning, and artificial intelligence—we should focus on externally validating and comparing head-to-head promising existing CAD models, tailoring these models to local settings, to investigate whether they may be extended with new predictors, and finally to quantify the clinical impact of the most promising models.[27]

The risk prediction tools in **Table 2** have been more validated than others and may be better for risk prediction in selected populations. On comparison of eight tools in a prospective study (two variants of Framingham risk score, ASSIGN, SCORE, PROCAM, QRISK-1, QRISK-2, and Reynold's risk score), it was concluded that only 10/56 (18%) comparisons exceeded 5% relative difference and most of the risk tools provide similar information.[29] The US Agency for Healthcare Quality and Research reviewed studies on cardiovascular risk prediction and concluded that there are risk prediction problems when these tools were applied to populations substantially different from the source cohorts.[30] Sometimes this was due to particularly low- or high-baseline risk in the destination cohort, and at other times to systematic differences in risk attributable to specific factors. For example, tools excluding patients with diabetes outperformed general risk prediction models that included these patients in their development when applied to nondiabetic cohorts. Diabetes is an important problem in India and therefore, the risk prediction models that do not include diabetes are likely to underestimate risks.[3] INTERHEART risk score (IHRS) has been developed using data from the case–control INTERHEART study.[31] The tool was aimed to derive and validate a new score for myocardial infarction (MI) risk using modifiable risk factors. This risk score has been applied to multicountry multiethnic Prospective Urban Rural Epidemiology (PURE) study.[32,33] The outcome data provided a good correlation with baseline risk. Laboratory and nonlaboratory-based risk scores have been developed by the World Health Organization (WHO) and Non-Communicable Disease Risk Factor Collaboration (NCDRiSC) groups (GLOBORISK-2).[27] However, none of these risk assessment tools has been evaluated in the Indian populations.

It has been observed that most of these tools are not applicable to Indians. Most investigators believe that Indians and South Asians are at twice the risk for CAD events as compared to Caucasians at the same level of risk, and it has been suggested that the risk factor may be multiplied by 1.8–2 times.[34] However, there are no prospective studies that have validated this assumption. Chow et al. evaluated the Framingham risk estimation tool using mortality data from Andhra Pradesh Rural Health Initiative and concluded that in India, equations recalibrated to summary national data are unlikely to be relevant to all regions of India and demonstrate the importance of local data collection to enable the development of relevant CAD risk tools.[35] Multiple risk factors have been included in various risk prediction scores. These include demographic and family history, lifestyle factors, clinical factors, comorbidities, biochemical factors, and others. Some are listed in **Table 1**. There are wide regional variations in cardiovascular risk factors (hypertension, hyperglycemia, and obesity) in India and it would be appropriate if a context-specific tool is developed for India.

Data are sparse regarding appropriate usage and the impact of using absolute cardiovascular risk scores in clinical practice in primary prevention settings. Systematic reviews, based on a few studies, support the conclusion that risk assessment combined with counseling is associated with small, favorable changes in provider prescribing behavior and risk factor control.[36] The American College of Cardiology/American Heart Association (ACC/AHA) performance measures for the primary prevention of CVD have specifically recommended the use of global risk estimation in clinical practice.[37] Likewise, recent American and European guidelines for primary prevention have recommended the use of absolute risk assessment for decision-making about the intensity of lifestyle and pharmacologic preventive interventions.[38,39]

IMAGING-BASED RISK STRATIFICATION

Multiple imaging modalities have been used for coronary risk prediction over the last few years and their role in risk stratification is being evaluated and applied in clinical practice.[40] Some of the commonly used technologies are listed in **Table 3**. Imaging modalities are potentially useful, especially in low- and intermediate-risk persons with no symptoms. Carotid intima-media thickness (CIMT) and other ultrasound-based techniques are low-cost tools and are potential game-changers in CAD risk prediction. However, prospective studies within India are needed to confirm their importance. Other technologies such as computed tomography (CT) scans, magnetic resonance imaging (MRI), and isotope-based technologies are useful but are expensive, especially in India. Three technologies are especially useful in risk prediction and risk stratification in premature CAD and could be important: (1) Ultrasonographic imaging of carotid and femoral arteries and aorta for estimation of plaque volume, (2) coronary artery calcium (CAC) scoring on CT scan [electron beam CT (EBCT) or multidetector CT (MDCT)], and (3) CT coronary angiography (CTCA). Limitations are discussed.

Many studies have shown an association between CIMT and future CAD events.[41-45] However, the major limitation of CIMT is that there is little or no additional prognostic value found by adding it to traditional risk scores.[27,40] This is due to discrepancies in its measurement and whether plaque volume estimation is to be included or excluded. Another limitation when using CIMT for risk prediction is the significant influence of age as it increases with aging. Some guidelines have recently excluded the use of CIMT for individual risk prediction in clinical practice.[39] Plaque volume measurements in carotid arteries, femoral arteries, and aorta are useful and provide important risk stratification information.[46] However, the use of CIMT or plaque volume in the prediction of premature CAD is imprecise.

Coronary artery calcium scoring adds value to other risk assessment methods and substantially increases the accuracy of risk stratification.[47] The incidence of cardiovascular events reported for patients classified as being at intermediate risk by the Framingham risk score and with an elevated CAC score is more than that reported for patients classified as being at high risk by the Framingham risk score and with a low CAC.[48] Use of CAC scoring is indicated in an intermediate-risk group and not in the high-risk group as aggressive preventive measures will already be indicated in high-risk asymptomatic patients.[45] Within the low-risk group, CAC estimation can identify a subgroup with significant long-term risk and for which preventive measures should be adopted. It has been identified as useful in risk prediction in premature CAD. Although the usefulness of CAC scoring in the prediction of CAD was not recommended by older American and European guidelines, evidence of its predictive utility and low cost has led to the revision of both European and American guidelines.[38,39] It is now recommended for the identification of subclinical CAD in the young and for risk prediction.

Multidetector computed tomography coronary angiography (MDCT-CA) or coronary computed tomography angiography (CCTA) is a useful first-line diagnostic test for appropriately selected patients with questionable symptoms of angina and low-to-moderate pretest probability of CAD.[49,50] However, its use for risk prediction in premature CAD could be important in India due to its high negative predictive value and easy availability, although the cost is a limiting factor. Improved spatial and temporal resolution and prospective gating with low radiation protocols help to exclude CAD when the clinical diagnosis is doubtful and is considered a gatekeeper to cardiac catheterization laboratory in the young.[40] Current guidelines do not support the use of CCTA over clinical risk with CAC scores in low-risk asymptomatic persons.[38,39] There is a significant additional diagnostic benefit when CCTA is added to standard care for patients with suspected angina as this may lead to changes in management that improve long-term survival.

All these techniques are not useful in very premature CAD where even the standard modifiable risk factors may be absent. Therefore, although useful in the identification of subclinical coronary disease in the young, they provide little prognostic information in these patients. More recent imaging technologies such as noninvasive CAD detection using thermography and very high-resolution ultrasonography may prove more useful.

TABLE 3: Imaging-based coronary risk prediction tools.

Imaging modality	Risk assessment technologies
Ultrasonographic imaging	• Common carotid intima-media thickness (CIMT) • Carotid plaques • Plaques in femoral arteries, aorta
Computed tomography (CT) scan	• Electron beam CT (EBCT) coronary calcium imaging • Coronary artery calcium scoring • CT coronary angiography (CTCA), multidetector CT (MDCT)
Magnetic resonance imaging (MRI)	• MRI-based coronary angiography • Cardiac MRI for myocardial disease
Plaque imaging	• CTCA • Cardiac MR imaging (CMRI) • Intravascular ultrasound (IVUS)
Novel techniques	• Optical coherent tomography (OCT) • Near-infrared spectroscopy (NIRS) • Thermography
Nuclear imaging	• Single-photon emission cardiac tomography (SPECT) • Positron emission tomography (PET)

GENETIC RISK FACTORS AND RISK STRATIFICATION

It has been known for decades, if not centuries, that CAD runs in families, and a positive family history of CAD, especially of premature CAD, has been considered important in some risk stratification tools.[51] Epidemiologists have reported, based on the presence of a history of premature familial CAD and studies on identical twins, that genetic risk factors account for 40–60%

of the predisposition for CAD.[52,53] Discovery and isolation of these genetic variants have been enabled by the development of new technologies in later years of the last century and in the present century. These researches have ranged from the identification of chromosomal locations responsible for CAD, detection of rare Single-nucleotide polymorphisms (SNPs) that greatly increase the risk of CAD to the more recent combination of multiple genes (initially 11–12 to more than a million) into polygenic risk scores (PGRSs) that increase the CAD risk.[51,54-56] The identification of genes and SNPs is especially important in the prediction of premature CAD in susceptible young adults and can be available any time after birth. Some of the common strategies for finding disease genes are given in **Table 4**.

MONOGENIC RISK FACTORS

In the initial years of gene-risk association studies, focus was on differences in SNPs among patients with CAD versus controls.[56] A number of genes were identified, but all these studies were underpowered to detect such associations.[57] Small case–control studies have also been performed in India and other countries in the South Asian region.[58] Most of these studies were futile as they failed to provide any new information.[59,60]

It was only after the development of large consortiums in North America, the UK, and Europe often involving hundreds of thousands of CAD cases and matched population-based controls that significant SNPs were identified.[61,62] Some of these are listed in **Table 5**. The functional significance of many of these genes is unknown. For example, the most important genetic association with CAD in Caucasians was found in chromosomal region 9p21. However, the functional significance of this chromosomal location and genes present adjacent to the chromosome still remains unknown.[51,56,63] Similarly, as shown in **Figure 3**, genes identified as important are involved in the causation of coronary arterial atherosclerosis or thrombosis via effects on mitosis proliferation, neovascularization and angiogenesis, nitric oxide signaling, vascular remodeling, blood pressure, lipid metabolism, inflammation, transcription gene regulation, etc.[51] However, of the 163 CAD risk loci highlighted in the figure, the functional significance of more than 60 genetic loci is unknown. Clearly, there is a need for many studies to identify the functional significance of these statistically significant SNPs, genes, and chromosomal locations.

TABLE 4: Common strategies for finding disease genes.

Study design	Participants	Strengths
Linkage studies	Relatives, large pedigrees, affected sib-pairs, discordant sib-pairs	• Can study multiple genetic markers simultaneously • Good for rare traits
Family based association studies	Parent–child trios, siblings	• Less prone to population stratification • Rich context for evaluation of gene and environmental influences
Candidate gene association studies	Unrelated individuals	Powerful study design for common traits
Genome-wide association studies	Unrelated individuals	Genotyping to simultaneously examine hundreds of thousands of genetic variants
Sequencing studies	Unrelated individuals	Good for rare variants

TABLE 5: Significant genetic loci and single-nucleotide polymorphisms (SNPs) identified in association studies.

Low-density lipoprotein cholesterol and lipoprotein(a)	Triglyceride risk lipoproteins	Inflammation	Cellular proliferation and vascular remodeling	Vascular toner and NO signaling	Uncertain pathways	
• SORT1 • *PCSK9* • *APOB* • ABCGS-ABCG8 • LPA • LIPA • *LDLR* • APOE	• LPL • TRIB1 • APO5-APO4-APOC4-APOA1 • ANGPTL4	• IL6R • CXCL12	• COL4A1-COL4A2 • MIA3 • REST-NOA1 • ZC3HC1 • 9p21 • PDGFD • SWAP70 • KSR2 • ADAMTS7 • BCAS3 • FLT1 • SMAD3	• GUCY1A3 • EDNRA • NOS3	• PPAP2B • WDR12 • VAMP5-VAMP8-GCXC • ZEB2 • AK097927 • MRAS • SLC22A4-SLC22A5 • ANKS1A • PHACTR1 • TCF21 • KCNK5 • PLG • HDAC9 • ABO • SVEP1 • SH2B3	• CYP17A1-CNNM2-NT5C2 • KIAA1462 • ATP2B1 • HHIPL1 • MFGE8-ABHD2-SMG6-SRR • RASD1-SMCR3-PEMT • UNE2Z-GIP-ATP5G1-SNF8 • PMAIP1-MC4R • ZNF507 • SLC5A3-MRPS6-KCNE2

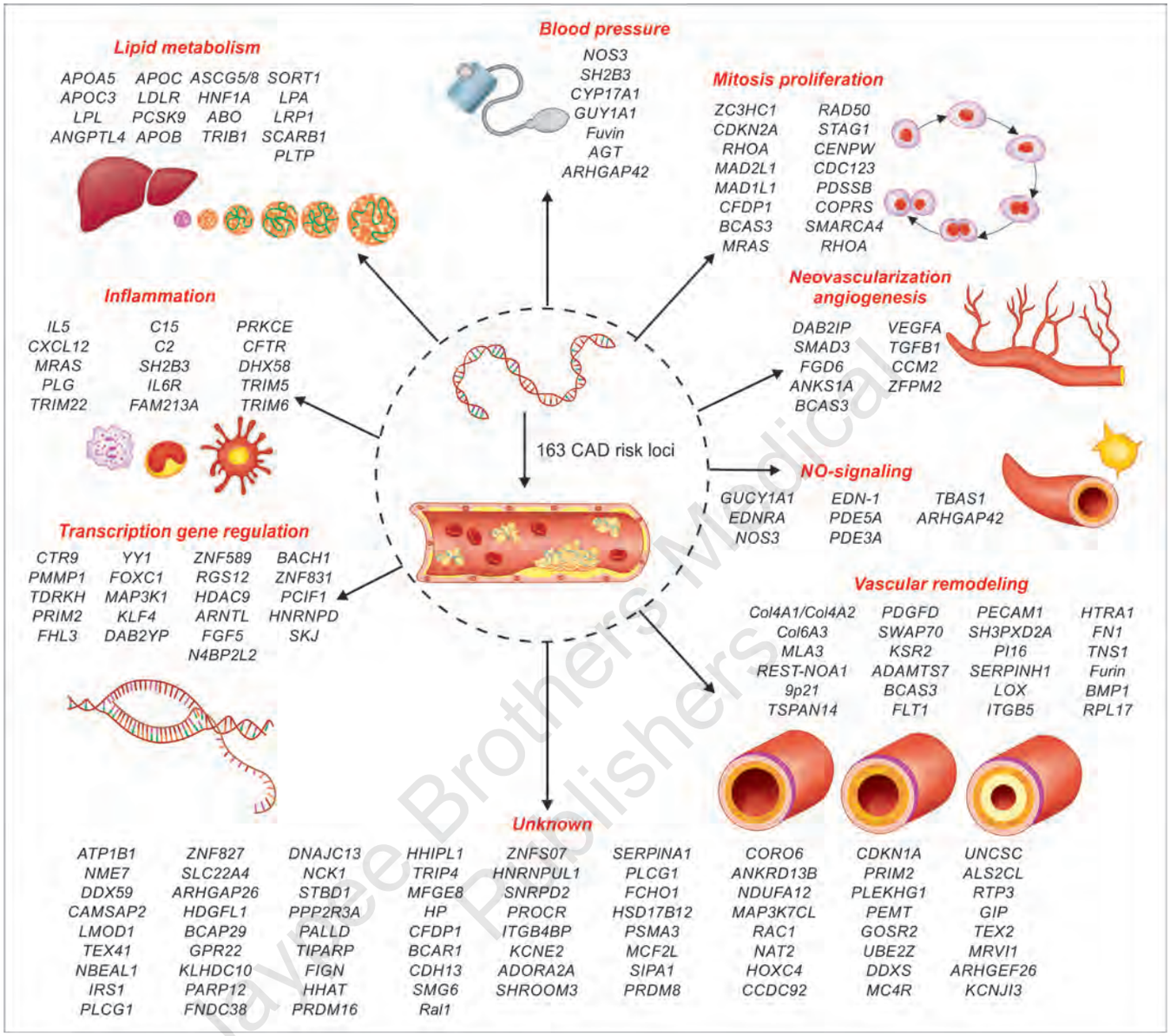

FIG. 3: Coronary artery disease (CAD) genetic risk variants and pathways of involvement.

Source: Adapted from Roberts R, Chang CC, Hadley T. Genetic risk stratification: a paradigm shift in prevention of coronary artery disease. JACC Basic Transl Sci. 2021;6:287-304.

LIPID GENES AND HYPERCHOLESTEROLEMIA

Single genes consistently failed to predict CAD unless it was a rare variant associated with major coronary risk factors. The most researched have been lipid-modifying genes and genetic loci that influence total and LDL cholesterol, triglycerides, HDL cholesterol, and lipoprotein(a).[64-70] There are well-identified genes that modify these lipid fractions:[64] LDL cholesterol by *HMGCR*, *PCSK9*, *APOB*, and *NPC1L1*;[65,66] HDL cholesterol by *CETP*;[67] triglycerides by *APOC3*, *ANGPTL3*, *ANGPTL4*, and *LPL*;[64,67-69] and lipoprotein(a) by *LPA*.[64,70-72] All these forms of lipid abnormalities are important in premature CAD. For example, an association of familial hypercholesterolemia mediated through LDL-receptors and *HMGCR* genes is well known. It is now very well known that the phenotype of familial homologous, as well as heterozygous hypercholesterolemia, can be mediated by >500 SNPs in the four genes mentioned above; other genes could also be involved, and therefore, it is important to have a polygene-based risk assessment.

An important contribution to patient care from the information of these genes is focused drug development. Richardson et al. conducted large-scale molecular profiling and genotyping to predict the effects of the therapeutic target on the human lipidome.[73] Eight drug targets were identified (*HMGCR*, *PCSK9*, *NPC1L1*, *CETP*, *APOC3*, *ANGPTL3*, *ANGPTL4*, and *LPL*). It was reported that genetically targeted Mendelian randomization influences metabolic traits as expected, e.g., the

correlation of LDL cholesterol-lowering targets—*HMGCR* and *PCSK9*—with a 249-trait metabolome (lipidome) was $r^2 = 0.91$.

Precise and individualized drug development following the identification of abnormal genes is a promise of genetic studies. As a prime example, statins for LDL cholesterol lowering were developed following LDL-receptor identification.[65,66] In recent years, identification of the *PCSK9* gene has influenced more efficient LDL cholesterol lowering with *PCSK9* monoclonal antibodies—evolocumab, alirocumab, and inclisiran—which are already in clinical practice.[74-79] Strategies to increase HDL cholesterol failed by using the CETP inhibitors, despite the identification of the *CETP* gene.[80] This has more to do with the absence of Mendelian randomization evidence of the role of HDL cholesterol in the process of atherosclerosis.[81] Similarly, although genetic targets for increased triglycerides have been identified some years ago,[82-85] there is still no gene-based drug development molecule in advanced clinical trials.[69] On the other hand, antisense molecules to reduce lipoprotein(a) are under clinical trials.[72,86,87]

Clearly, there is a need for more investment in the identification of lipid-modifying genes and to translate treatment from bench to bedside using modern technology.[51,55,57,88] Genetic studies focused on monogenic and high-rise high-penetrant variants would be of immense help for future drug development.

POLYGENIC RISK SCORES

It is well known that coronary atherosclerosis and acute coronary events are multifactorial.[89-91] The risk factors for CAD are well known **(Table 1)**, and some of the mechanistic genetic pathways and genes involved are shown in **Figure 3**. Failure to identify a single gene or a group of genes resulted in a rethink about the identification of a combination of genes for risk stratification in CAD.[50,54]

Some of the first studies were conducted in Europe and used genetic data from pre-existing prospective cohorts.[92,93] Ripatti et al.[92] used prospective data from population data from Sweden and Finland (FINRISK cohorts, Malmo Diet and Cancer cohort, and Malmo Preventive Project) and included 3,829 persons with prevalent CAD and 48,897 controls free of disease. In prospective cohort analyses, participants in the top quintile of 13 SNPs based on GRS has 1.66 times [95% confidence interval (CI), 1.35–2.04] increased risk in a model that adjusted for traditional risk factors **(Fig. 4)**. Paynter et al.[93] used data from the Women's Genome Health Study (USA) which evaluated genetic and clinical risk scores in 19,313 white women. Two types of GRS were computed, first with 101 SNPs and the second with 12 SNPs (after pruning). Evaluated alone, the GRS had a hazard ratio (HR) of 1.015 per risk allele ($p = 0.006$) with 3% greater risk in the lower tertile and 3.7% in the highest risk tertile. The significance disappeared after adjustment for risk factors and it was concluded that there was no significant association with the incidence of total CVD.

A combination of larger and gradually increasing numbers of SNPs was analyzed in subsequent prospective cohort studies. The SNPs were identified based on candidate gene association studies **(Table 5)** and were weighted according to the degree of risk found in these studies. SNPs with higher significance were given more weight and those with lower significance were given

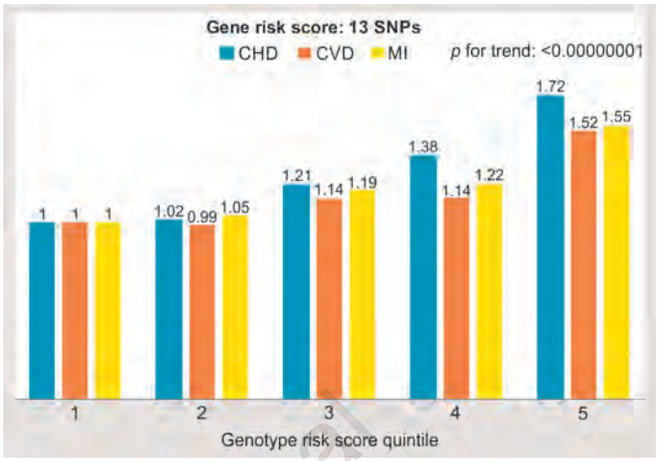

FIG. 4: Thirteen single-nucleotide polymorphism (SNP)-based genetic risk score and incident coronary heart disease (CHD), cardiovascular disease (CVD), and myocardial infarction (MI) in Swedish and Finnish cohorts.[92]

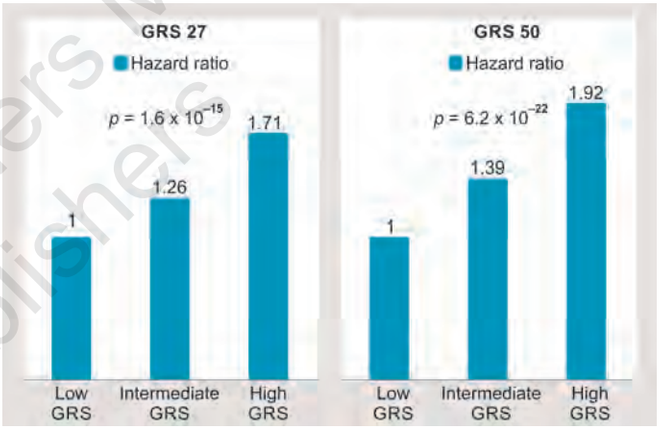

FIG. 5: Comparison of 27 versus 50 single-nucleotide polymorphism (SNP)-based genetic risk score (GRS) in the Malmo Diet and Cancer Study cohort.[94]

lesser weights. Tada et al. compared a 27 SNP-based score to a 50 SNP-based GRS using data from the Malmo Diet and Cancer study in 23,595 participants free of CAD at baseline.[94] During a median follow-up of 14.4 years, 2,213 participants experienced a first CAD event. After adjustment for traditional risk factors, both GRS27 and GRS50 were significantly associated with incident CAD; GRS27: HR 1.70, CI 1.48–1.98; GRS50: HR 1.92, CI 1.67–2.20 **(Fig. 5)**. An important finding of this study was that the younger participants in the study had a GRS50 HR of 2.40 (CI 1.85–3.12) demonstrating the ability to discriminate better in premature CAD.

More studies using a larger number of SNPs are now available as reviewed in various publications.[51,55,56] Khera et al.[95] used a 60 SNP-based GRS using data from the Atherosclerosis Risk in Communities (ARIC) and Women Genome Health (WGH) studies. The hazard ratio of the highest versus lowest quintile in ARIC was 1.75 (CI 1.46–2.10) and WGH was 1.94 (CI 1.58–2.39). Paquette et al.[96] used a 192

SNP-based GRS and reported that this risk score was better than the prediction of CAD in familial hypercholesterolemia. Predictive accuracy of the GRS was also reported by Mega et al.[97]

Genome-wide Polygenic Risk Scores

Subsequent to the development of very large analytical capabilities and identification of a larger number of SNPs involved in various processes of CAD **(Fig. 3)**, more and more SNPs have been incorporated into the GRS.[51] Genome-wide association studies (GWAS) based identification of variants of risk accelerated this development.

In one of the early studies using these capabilities, Abraham et al. developed a 49,000 SNP-based GRS that was evaluated using data from the FINRISK and Framingham Heart Study cohorts.[98] The 49,000 SNP-based GRS was also evaluated in other prospective studies (all Caucasians). Significant associations were found in all these studies. In the case–control design, the odds ratios of CAD varied from 1.28 (CI 1.17–1.41) in the Framingham Heart study to 1.74 (CI 1.63–1.86) in the Wellcome Trust Case–Control Consortium-CAD study **(Table 6)**. These studies heralded the era of big data using extreme computer capabilities for the calculation of GRS and to predict its usefulness in the prediction of CAD.

Subsequently, studies became bigger and better. From the initial strategy of inclusion of variants that achieved genome-wide statistical significance in prior GWAS with 50–200 SNPs, the strategies moved on to linkage-equilibrium-based thinning of variants from prior GWASs (40–50,000 SNPs), pruning based on statistical significance, and linkage disequilibrium of variants from prior GWAS (100–200,000 SNPs), to the currently available LDPred-based computational algorithm that assigns weights to all the available variants from prior GWASs via explicit modeling of linkage disequilibrium (millions of SNPs).[99]

In one of the earlier studies, Khera et al. proposed that it may be important to identify polygenic predictors of conditions that also have significant monogenic variants.[99] Five diseases were identified and evaluated: CAD, atrial fibrillation, type 2 diabetes mellitus, inflammatory bowel disease, and breast cancer—all these have monogenic variants that increase the risk as well as evidence of polygenic contributions. The GPS, which incorporated more than 6 million SNPs, identified an 8.0% population who had more than threefold greater risk of CAD. It was also observed that the GPS when compared with the presence of rare monogenic mutations (e.g., familial hypercholesterolemia genes) had a 20-fold greater risk. In another large study using a meta-analytic approach, Inouye et al. developed a meta-GRS consisting of 1.7 million SNPs and applied the data in the prospective UK Biobank cohort.[100] In this study of 22,242 CAD patients and 460,387 controls, the GRS had a hazard ratio of 1.71 (CI 1.68–1.73) per unit standard deviation (SD) increase in meta-GRS. Patients in the top 20% of meta-GRS had a hazard ratio of 4.17 (3.97–4.38). Both the studies recommended the inclusion of polygenic risk prediction in clinical care. Similar studies have been reported from other regions of the world.[101-104]

However, all these studies have focused on Caucasians, which is a major limitation regarding the external validity of PGRS. It may not be very useful in other populations such as South Asians, East Asians, other Asians, Africans, and native populations in the Americas and Europe.[51,55,58,105,106] Moreover, some studies have reported that additional discriminant value gained from the PGRS may not be superior to the information with the use of traditional risk scores such as Framingham and SCORE (Europe).[107] Mosley et al. evaluated two US-based prospective cohorts [ARIC and Multi-Ethnic Study of Atherosclerosis (MESA)] for the association of 6.6 million SNP-based GPSs with incident CAD. There was a significant association of 10-year incident CAD in both ARIC (1.24, CI 1.15–1.34) and in MESA (1.38, CI 1.21–1.58) per unit SD increase in GPS, but there was no improvement in net reclassification index.[108] The authors concluded that Polygenic Risk Score (PRS) did not significantly improve calibration in either cohort. Elliott et al. also reported a low predictive value of PRS as compared to clinical risk score in CAD.[101] Many editorials and some reviews have criticized the estimation of PRS as a more expensive method of estimating CAD risk.[109-111]

On the other hand, Wells et al. used data from Framingham Offspring and Coronary Artery Risk Development in Young Adults (CARDIA) studies and evaluated the usefulness of GPS in adults 18–35 years by comparing it with CAC (as a marker of atherosclerosis).[112] It was concluded that GPS improved model discrimination for coronary atherosclerosis although the improvements were smaller than those associated with modifiable risk factors. In another study to identify the importance of GPS in premature CAD, investigators used data from the UK Biobank.[113] GPS was calculated using 1.14 million SNPs. For incident MI, the case–control comparison revealed a HR per unit increase in SD of 1.52 (CI 1.50–1.54). The predictive value was the highest for men and women in the age group 40–41 years (men 2.00, CI 1.86–2.16; women 1.57, CI 1.37–1.79) **(Fig. 6)**. Both the studies thus showed the usefulness of PRS in premature CAD. Significant prognostic information following MI in the young (secondary prevention) has been reported.[114]

Studies among other ethnic groups are few and limited by small numbers. Case–control comparative studies in China and Japan reported the usefulness of GPS in CAD.[115-117] A large prospective study from China has recently reported a prospective evaluation of 540 SNP-based GRS.[118] In this study, Lu et al. developed a genome-wide association result with 540 SNPs in 2,800 patients and 2,055 control validation cohorts. This

TABLE 6: Forty-nine thousand single-nucleotide polymorphism (SNP)-based genetic risk scores and risk of incident coronary artery disease (CAD) in five prospective study cohorts.

Study acronym	CHD/non-CHD	Odds ratio (95% CI)
FINRISK study	757/11,919	1.74 (1.61–1.89)
Framingham Heart study	587/2,819	1.28 (1.17–1.41)
Wellcome Trust Case–control study-CAD	1,926/2,938	1.74 (1.63–1.86)
MIGen-Harps	488/531	1.57 (1.37–1.81)
ARGOS FH study	248/216	1.49 (1.21–1.81)

(CHD: coronary heart disease; CI: confidence interval)

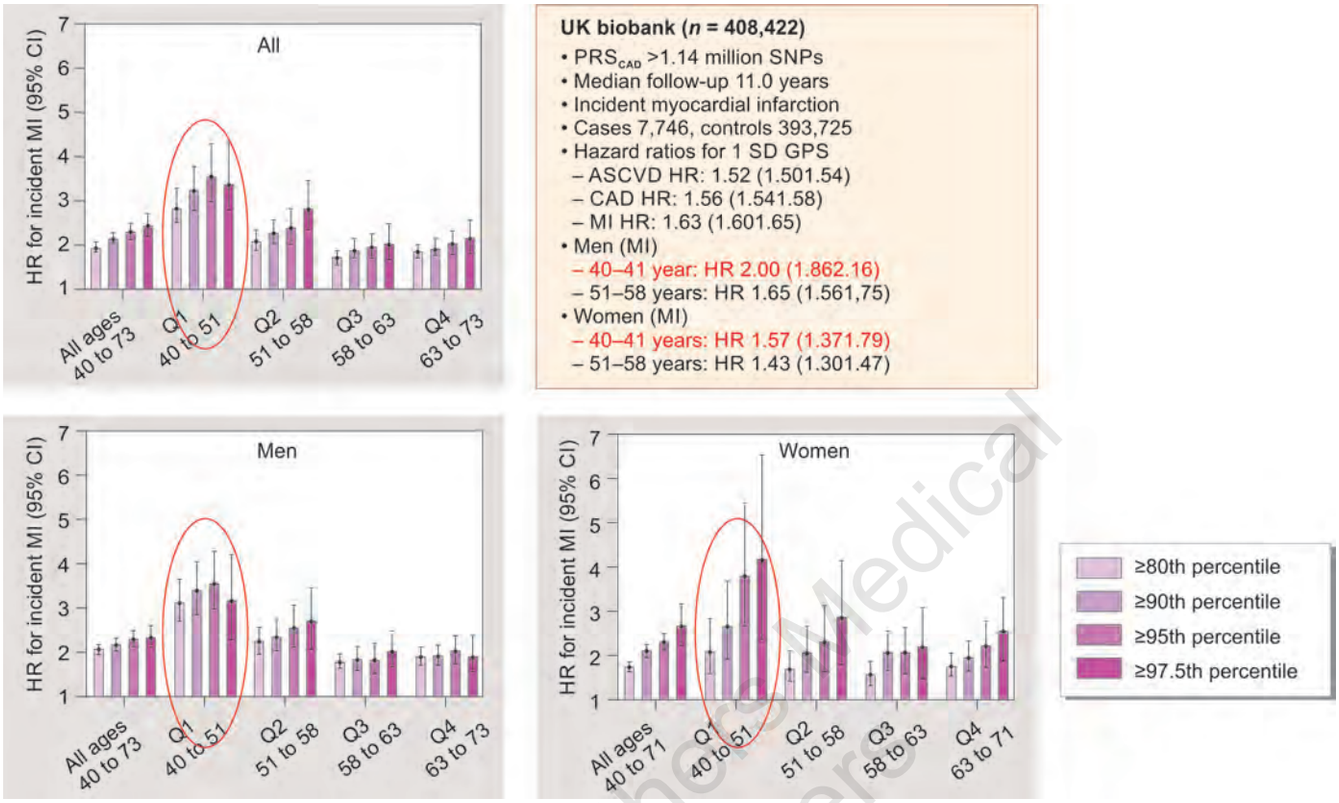

FIG. 6: Importance of polygenic risk scores (PGRS) in the young: UK Biobank.

(ASCVD: atherosclerotic cardiovascular disease; CAD: coronary artery disease; CI: confidence interval; GPS: genome-wide polygenic risk score; HR: hazard ratio; MI: myocardial infraction; SD: standard deviation; SNP: single-nucleotide polymorphism)

Source: Manikpurage HD, Eslami A, Perrot N, Li Z, Couture C, Mathieu P, et al. Polygenic risk score for coronary artery disease improves the prediction of early onset myocardial infarction and mortality in men. Circ Genom Precis Med. 2021;14:e003452.

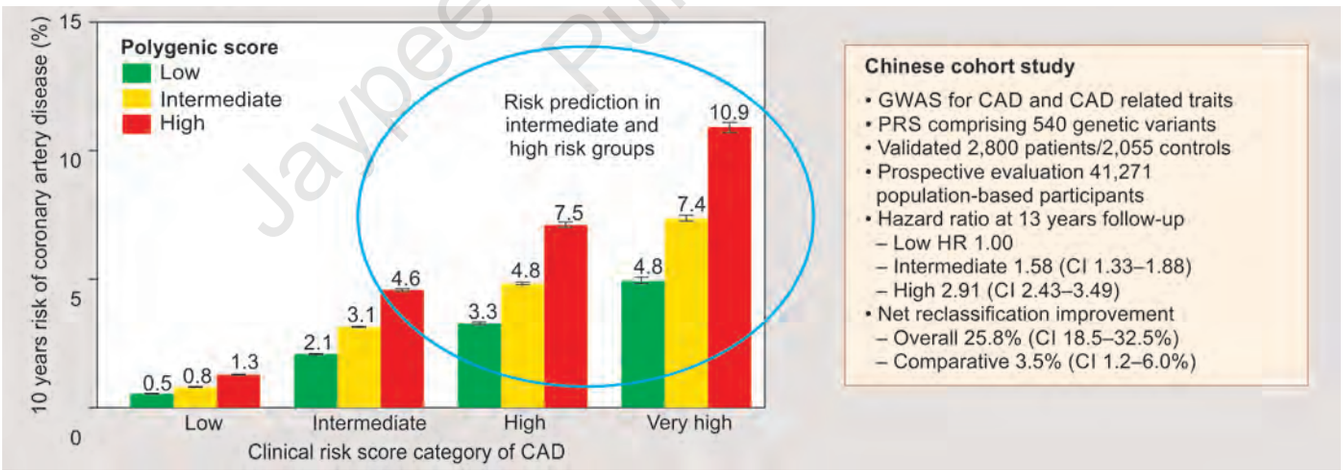

FIG. 7: Incremental value of low, intermediate, and high genetic risk scores (GRS) in 10-year risk prediction of coronary artery disease (CAD) in a Chinese cohort.

(CI: confidence interval; GWAS: genome-wide association studies; HR: hazard ratio)

Source: Lu X, Liu Z, Cui Q, Liu F, Li J, Niu X, et al. A polygenic risk score improves risk stratification of coronary artery disease: a large-scale prospective Chinese cohort study. Eur Heart J. 2022;43:1702-11.

was evaluated in 41,271 individuals prospectively followed for 13.0 years. It was calculated that individuals with the highest 20% of GRS had a threefold greater risk of CAD events (HR 2.91, CI 2.43–3.49). Moreover, the addition of GRS to the clinical score yielded a significant improvement in the net reclassification index. The GRS was most predictive of future cardiovascular events in the intermediate- and high-risk groups **(Fig. 7)**. It was concluded that the GRS could stratify individuals, especially

the young at high risk, and could be useful in the application of targeted intervention in these groups.

INDIAN DATA

We performed a study to develop and validate a 6.6 million SNP-based GPS for Indian and South Asian CAD patients using GWASs conducted in India, Bangladesh, and South Asian participants of UK Biobank.[119] The reference population consisted of 1,522 South Asians from the BRAVE consortium in Bangladesh and the UK Biobank South Asians. Using principal component analyses, the investigators calculated ancestry-adjusted GPS. In a case–control validation (comparison of top-percentile with middle quintile), it was determined that the GPS was predictive of risk in both the cohorts and the odds ratio in the top 2.5% was 5.56 (CI 3.40–8.98) in UK Biobank and 2.41 (CI 0.93–6.85) in BRAVE cohort. For the top 20% GRS, the odds ratio was 2.16 (CI 1.56–3.03) in UK Biobank and 1.87 (CI 1.09–3.22) in BRAVE cohorts.[119] When this GPS was evaluated in 1,800 CAD patients with premature CAD (age <55 years men/<60 years women) in Indian patients and 1,163 controls, the odds ratio of top 2.5% was 3.30 (CI 2.11–5.33) and the top 20% was 1.79 (CI 1.42–2.28). The study demonstrated that the new GRS which was tested across three population groups was useful in the prediction of CAD risk among South Asian populations **(Fig. 8)**.

There are only a few studies that evaluated the importance of GRS/GPS in other South Asian populations. In Pakistan, Shahid et al. performed a case–control study using a 21 SNP-based GRS among 405 cases and 220 controls.[120] The HR of GRS in the highest quintile was 2.96 (CI 1.5–3.6). It has also been suggested that the currently developed PGRSs by genetic risk analysis in Caucasians can be used for disease prediction in global populations.[121] All these studies show that GRS/GPS can be successfully used for risk prediction in South Asian and Indian populations similar to the Caucasian and Chinese populations. Additional research is required to improve the transferability of GPS across various racial and ethnic groups and facilitate their integration into clinical practice.[119] Larger prospective studies are required, especially to risk-stratify younger Indian patients. This is all the more important as premature CAD is an important problem in India.[2,3,122] and the standard risk factors may not be present in many of these patients.[24,123,124]

IMPLICATIONS

Genomic studies that have identified genetic risk factors and polygenes are important to guide risk stratification, especially to prevent premature CAD. In the Harvard-based Partners Young-MI Registry, >50% of patients with MI ≤50 years were not identified using standard risk stratification tools. In this cohort, >51% of patients were not eligible for statin treatment if ACC/AHA 2013 guidelines were used and 71% would not qualify for statins using the 2016 USPTF guidelines. Similar data have been reported in the NORIN-STEMI trial in Delhi.[16] Many of these patients would have been eligible if genetic risk stratification tools had been available. Early detection of genetic risk is not only important for risk stratification but as studies have shown that if these persons lead a healthy lifestyle, they can reduce the risk substantially as reported by Khera et al.[95] in the ARIC and WGH studies and Hasbani et al.,[125] who used data from the ARIC

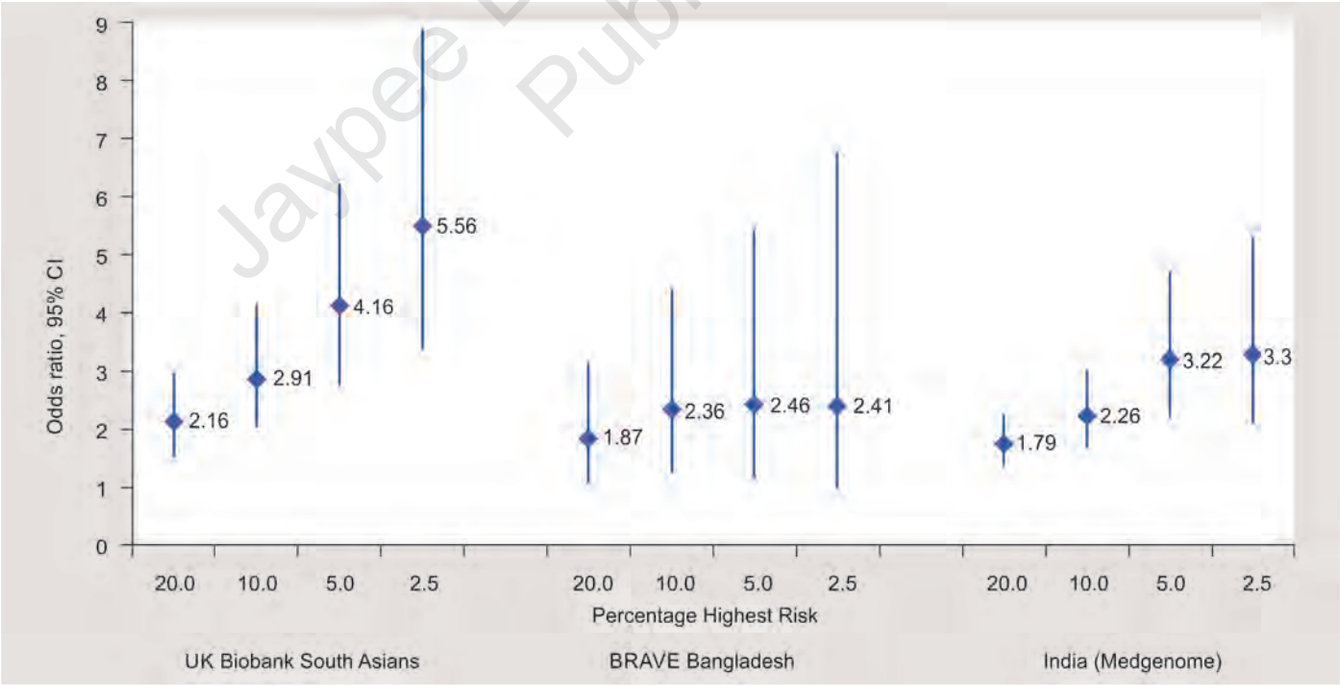

FIG. 8: Increasing hazard ratios for coronary artery disease (CAD) in UK Biobank South Asians (*n* = 7,244), Bangladesh BRAVE cohort (*n* = 491), and Indian Medgenome Study participants (*n* = 1,800 cases, 1,163 controls) with increasing genetic risk score (GRS)-based risk. The highest risk was observed in the top 2.5% of GRS in all the three cohorts.
(CI: confidence interval)

study. Statins have also been shown to be useful in reducing genetic cardiovascular risks in very high-risk individuals.[97]

CONCLUSION

In conclusion, premature CAD is endemic in India. Almost one-third of CAD patients presenting to the hospital cardiac catheterization lab have premature disease according to standard definition while about 5% have very premature (<40 years men, <45 years women) CAD. Standard risk factors identify <50% of patients with premature disease while imaging techniques miss even more of such patients. GRS do not change from birth and it has been shown that those with high genetic risk have a propensity for developing premature CAD. Promotion of aggressive lifestyle change in these individuals and prescription of statins in a selected few can significantly ameliorate cardiovascular risk. Individuals with a strong family history of CAD (premature cardiac deaths, acute coronary syndromes, etc.) should be assessed for genetic risk early in life. Whether early intervention is helpful in the prevention of CAD in high genetic risk individuals is a matter for future study. One such study is going on in Finland.[126] More studies are required in India to assess the prognostic utility of clinical versus GRS,[127] and to prospectively evaluate the influence of various lifestyle and pharmacological interventions in reducing genetic risk.

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CHAPTER 38

Exercise and Cardiovascular Health

Chetan P Shah, Charan Reddy KV

ABSTRACT

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. Among the many risk factors that predispose to CVD development and progression, a sedentary lifestyle, is now recognized as a leading contributor to poor cardiovascular health. Regular physical training, particularly aerobic exercises, is known to reduce blood pressure (BP), body weight, body fat, and waist circumference, along with increase in insulin sensitivity and high-density lipoprotein cholesterol (HDL-C) levels.[1] Regular aerobic training has been reported to be beneficial in both young and elderly people as it decreases aortic stiffness and enhances flow-mediated arterial dilation mediated by increased nitric oxide (NO) released from endothelial cells.[2] Consistent with this notion, death rates among men and women have been found to be inversely related to cardiorespiratory fitness levels, even in the presence of other predictors of cardiovascular mortality such as hypertension, smoking, and hyperlipidemia. Even low intensity exercise has a beneficial impact on the body when compared to a complete sedentary lifestyle. Indeed, for every metabolic equivalent (MET) of exercise achieved above 4 METS, there is a 12–20% reduction in cardiovascular mortality.[3] Despite the obvious benefits in reduction of cardiovascular mortality, there has been some controversy regarding the effects of occupational physical activity, mainly due to the risk of anaerobic component, which is largely dependent on the nature of the work performed and injuries. In this chapter, we discuss the pathophysiology and the beneficial effects of exercise on heart and other organs.

INTRODUCTION

Exercise has well-documented cardiovascular benefits. Regular physical activity and exercise are related to remarkable overall health advantages and significantly decreased cardiovascular disease (CVD) risk. Physically active people have lower blood pressure (BP), better insulin sensitivity, and better plasma lipoprotein profile. Several recent studies have shown that sustained physical activity is associated with decrease in markers of inflammation, improved metabolic health, decreased risk of heart failure, and improved overall survival.[4] Regular physical exercise decreases resting heart rate, BP and atherogenic markers, and increases physiological cardiac hypertrophy.[5]

The relationship between physical activity and BP has long been reported and strengthened by various studies. Regular physical activity of even lower intensity and duration, is associated with about 20% decrease in mortality in some cohort studies.[6] In normotensives, regular exercise reduces systolic blood pressure (SBP) by 3–5 mm Hg and diastolic blood pressure (DBP) by 2–3 mm Hg. In hypertensives, this effect is even more pronounced, with mean reduction of 7 mm Hg SBP, and 5 mm Hg DBP.[7] A reduction of 2 mm Hg in SBP and DBP lowers the risk of stroke by 14% and 17% respectively, and the risk of CAD by 9% and 6% respectively.[8] Hypertensives are hence encouraged to engage in aerobic exercise (AE) on a regular basis, such as walking, jogging or swimming for 30–45 minutes daily.

Given the increasing interest in exercise-based therapies, the beneficial effects of various exercises on different organs have been described in **Figure 1.**

EFFECT OF VARIOUS TYPES OF EXERCISE ON CARDIOVASCULAR SYSTEM

- *Aerobic exercise*: Regular AE has been shown to reduce resting BP and BP reactivity to various stressors and is

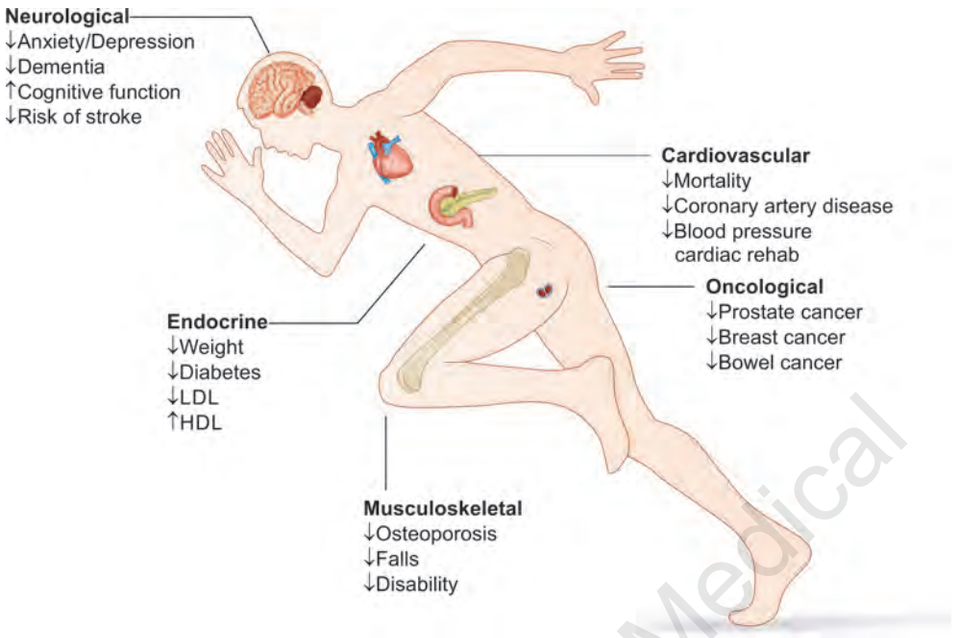

FIG. 1: Benefits of regular exercise on various organs.

most beneficial to the heart. This type of exercise consists of regular, purposeful movement of joints and large muscle groups. Examples of AE include fast walking, jogging, running, cycling, and swimming.

- *Dynamic resistance exercise*: Dynamic resistance exercises (DRE) can lower BP, but only modestly. Keeping the aim of progressive increase in muscle strength, DRE is done against an opposing force with purposeful movement of joints and large muscle groups. Muscles contraction occurs concentrically or eccentrically. Weight lifting and circuit training with equipment (like resistance-training machines) are two examples of DRE.
- *Isometric resistance exercise*: Isometric resistance exercise (IRE) involves sustained static contraction of muscles without any change in the length of the involved muscle groups or joint movement. Examples of IRE are high and low plank, squats and pressing against the wall.

Choosing an appropriate exercise regimen is often challenging, as it is individualized. As a part of the initial treatment in the past, it was recommended that individuals with stage 1 hypertension without coronary risk factors and without evidence of CVD, and those having other risk factors, but not diabetes should perform AE. Prior to initiating an exercise program, drug therapy may be started among those with diabetes, stage 2 or 3 hypertension (HTN) or CVD.[9]

However with newer findings, suggesting that DRE and IRE can measure up to AE as antihypertensive lifestyle therapy, has given rise to the concept of combined or "concurrent training (CT)".[7] CT can be defined as the combined practice of aerobic and strength exercise in the same training session is presented as an effective antihypertensive treatment **(Fig. 2)**.[10]

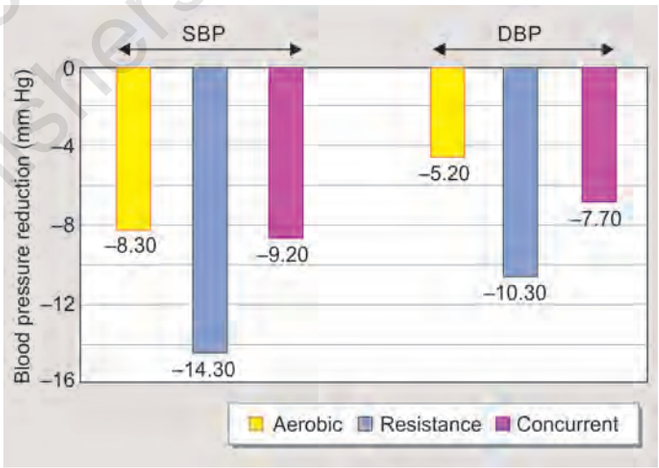

FIG. 2: Blood pressure reduction following aerobic, resistance and concurrent training (CT) in hypertension (HTN) patients.

PHYSIOLOGICAL EFFECTS OF EXERCISE ON BLOOD PRESSURE

Regular physical activity can lead to various endocrine, immune and vascular changes. The mechanisms leading to reduction in BP by physical activity are usually related to cardiac remodeling, endothelial function regulation and decreased oxidative stress.[10,11] For maintaining perfusion of active muscles, cardiac output is increased and redistributed by AE. Neurohormonal as well as hydrostatic mechanisms triggers this response, which increase systolic volume first and subsequently enhancing the heart rate. Increased cardiac output results in increased SBP,

whereas reduction in DBP occurs due to reduced peripheral vascular resistance (PVR), which facilitates perfusion of large muscle groups.

Prominent vasodilator substances released after exercise are nitric oxide (NO), prostaglandins (PG), adenosine, and adenosine triphosphate (ATP). All of these substances lead to arteriolar vasodilation and reduction in PVR. Chronic or long-term response to exercise is a positive effect on BP due to changes in sympathetic nervous system activity, modulation of renin-angiotensin-aldosterone system (RAAS), improved insulin sensitivity, increased levels of NO, PG and improvement in lipoprotein-lipid profile. Chronic exercise can also lead to vascular changes, which include increased vascular length, lumen diameter, number of precapillary sphincters, and neoangiogenesis.

PHYSIOLOGICAL EFFECTS OF EXERCISE ON LIPIDS AND ATHEROGENESIS

Plasma lipids are the important predictors of CVD risk. Numerous studies demonstrated that regular physical activity can reduce CVD risk by influencing circulating lipoprotein levels. It was found in these studies that endurance training is linked to higher levels of circulating high density lipoprotein (HDL) and, to a lower extent, lower triglyceride levels, which is known to reduce the risk of coronary heart disease.[12]

Along with the changes in plasma lipids, exercise has a direct effect on the homeostasis of the arterial wall, which helps to slow the progress of atherosclerotic disease and contributes to the well-known decline in coronary artery disease. Increased regular physical activity (~2,200 kcal/week) can improve VO_2max and promote regression of atherosclerotic lesions among individuals having symptomatic coronary artery disease.[13] Exercise results in increased vasodilatory responses to acetylcholine that was related to enhanced total endothelial nitric oxide synthase (eNOS) expression and phosphorylation of protein kinase B (Akt). This elevated eNOS expression can suppress vascular lipid peroxidation and superoxide levels, thereby retarding the neointimal atherogenesis and subsequent vessel injury.[14]

PHYSIOLOGICAL EFFECTS OF EXERCISE ON INSULIN SIGNALING

Systemic insulin sensitivity has a significant impact on cardiovascular health, because resistance to insulin signaling is identified for promoting the heart disease development by changing the blood lipid profile. Exercise can result in improvement in insulin resistance and prevention of the formation of advanced glycation end products (AGEs). AGEs are essentially proteins and lipids, which underwent non-enzymatic glycation and oxidation and frequently cross-link with collagen and elastin fibers, resulting in vascular compliance loss (means arterial stiffening).

Exercise leads to improved insulin sensitivity in endothelium, skeletal muscle, and adipose tissue; these acts as main contributors to systemic insulin resistance among type 2 diabetic patients.[15] Exercise conditioning is related to adaptive remodeling in the expression and upregulation of one or more parts of the insulin receptor/insulin receptor substrate (IRS)/PI3K/Akt signaling cascade, resulting in increased glucose uptake through increased insulin-independent sarcolemmal translocation of GLUT4 glucose transporters.

VARIOUS CARDIOVASCULAR AND PERIPHERAL ADAPTATION TO PHYSICAL EXERCISE

Regular physical activity confers many health benefits including improved life-expectancy and promote various beneficial effects on the body. To improve an individual's health, current European and American guidelines recommend at least 150 minutes of moderate-intensity exercise per week for adults.[16,17] However, intense levels (15 MET every week) of exercise results in sustained five- to six-fold increased cardiac output for long term, which is fulfilled by wide range of unique structural, electrical, and functional cardiac adaptations known collectively as the "athletes heart", which are generally reversible **(Fig. 3)**.

SUDDEN CARDIAC DEATH IN SPORT

Sudden death of an athlete during or immediately following competition may happen on rare occasions. These tragic events are uncommon, and affects young athletes (with CAD, cardiomyopathies, accessory pathways or ionchannel disorders) as well as middle-aged athletes having advanced coronary atherosclerosis.[18] There is variation in prevalence of sudden cardiac death (SCD) as per the techniques of collection of data. However, as per the most accurate data, the young competitive athletes[19] as well as middle-aged marathoners had prevalence rate of 1 in 50,000.[20] Males constitute majority of the victims (90%). Deaths in competitive athletes receive a lot of media attention; however, recreational athletes account for >90% of all exercise-related SCDs.[21,22] Due to low event rates, there is controversy related to cardiovascular screening for identifying athletes who are predisposed to SCD related to exercise. However, as per data of large prospective study conducted in Italy, assessment of young athletes with the 12-lead ECG was found to be effective in decreasing the SCD risk.[23] The program was successful because of the ECG role for detection of ion-channel disease and accessory pathways; a large number of patients having primary cardiomyopathy had an abnormal ECG. On the contrary, death of majority of the middle-aged athletes is due to CAD that reveals itself on the surface ECG on rare occasions. As per the current recommendations for recognition of middle-age athletes who have greatest risk of SCD, an exercise stress test should be followed.[24] But, majority of the abnormal exercise tests are found to provide false-positive result[25] and low-predictive accuracy[26] among asymptomatic middle-age athletes. According to current data, the technique found to be most effective for prevention of SCD in this population are by-stander cardiopulmonary resuscitation as well as early use of an automated external defibrillator.[27] The reputation of exercise is unaffected in majority of cases of SCD in sport, as

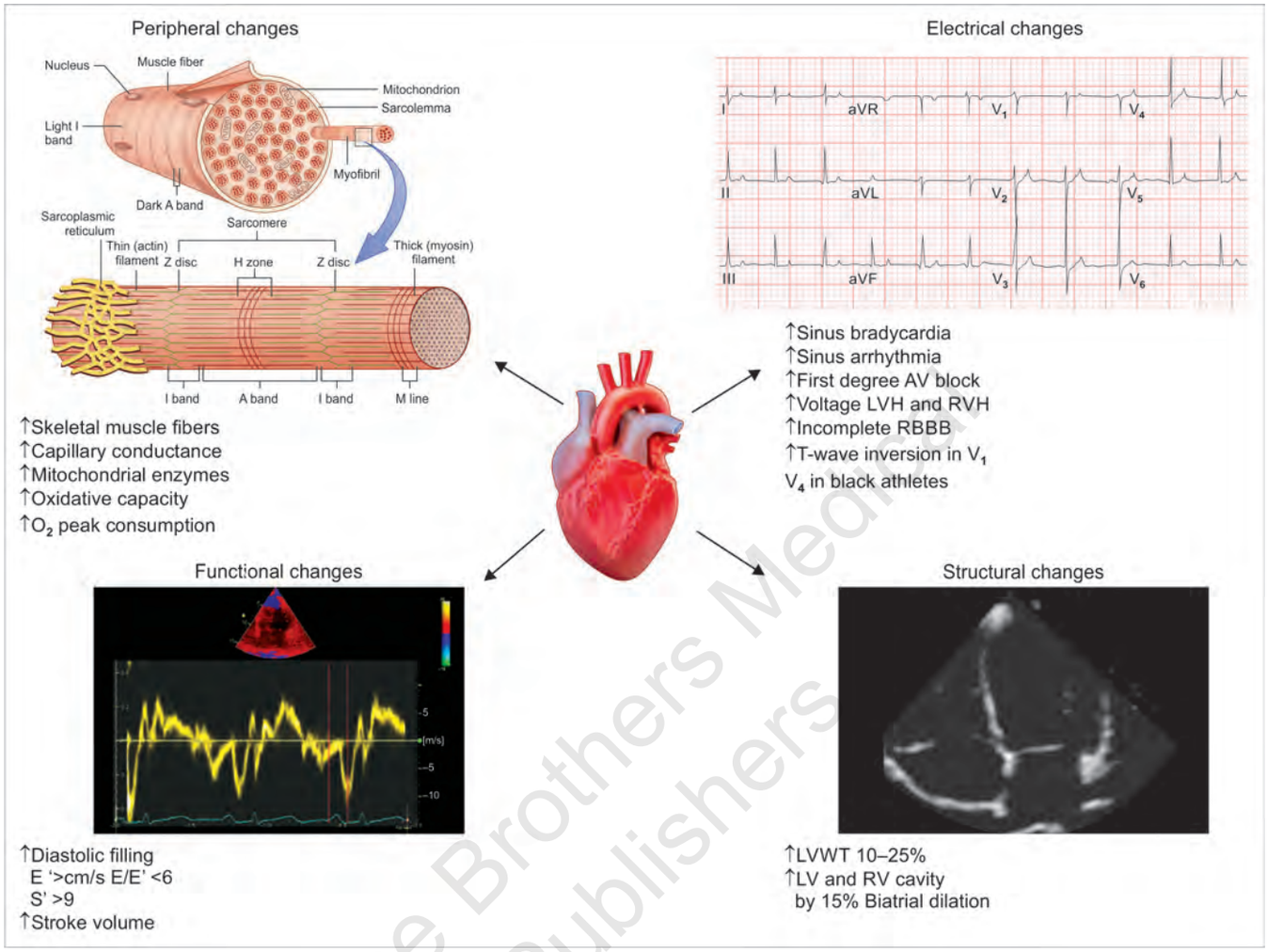

FIG. 3: Various adaptations in heart to strenuous exercise.

exercise is acts merely as trigger for arrhythmogenesis among those individuals who are predisposed instead of directly involved in the pathological substrate development.

CAN EXERCISE DAMAGE A PREVIOUSLY NORMAL HEART?

Over the last two decades, there has been an increase in the number of people participating in grueling endurance events such as cycling sportives, marathons, triathlons, and iron man races. Several studies have found elevated blood levels of biomarkers of cardiac damage among most of the athletes.[28] There is a debate on the mechanism as well as effects of elevated biomarkers of cardiac damage after exercise. But, question raises whether among some of the people having previously normal heart, an association was found between repeated bouts of life long-endurance exercise and adequate myocyte necrosis for creating an arrhythmogenic substrate via myocardial fibrosis as well as adverse myocardial remodeling **(Fig. 4)**.

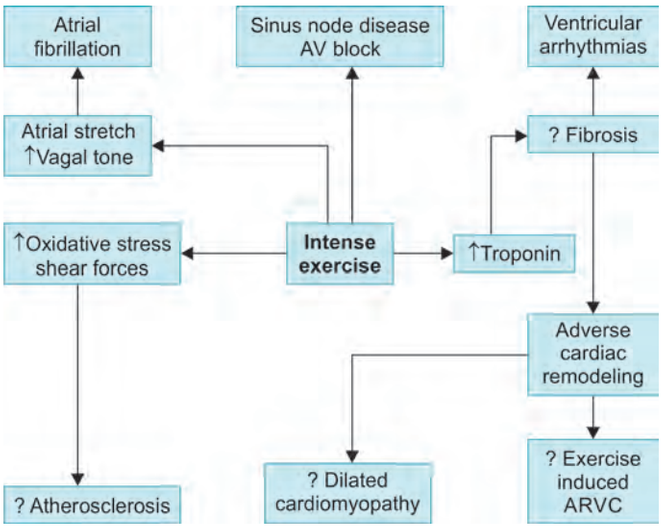

FIG. 4: Speculated mechanisms for the detrimental effects of exercise.
(ARVC: arrhythmogenic right ventricular cardiomyopathy; AV: atrioventricular; DCM: dilated cardiomyopathy)

Some of this theory is supported by evidence from animal models. In the study by Benito et al. rats were exercised on a treadmill for duration of 16 weeks that is equal to 10 years in human terms.[29] There was development of eccentric LV hypertrophy, diastolic dysfunction, and diffuse fibrosis in the atria as well as right ventricle among exercising rats at 16 weeks. It was important to note that during electrophysiological studies, ventricular tachycardia was inducible in 42% of the exercising rats in comparison to 6% in sedentary rats. The role of chronic endurance exercise in myocardial fibrosis has been explored in cross-sectional studies in humans. Breuckmann et al. undertook CMRI in 102 men aged ≥50 years old who had completed at least five marathons during the past 3 years and had no history of heart disease or diabetes.[30] Veteran marathon runners exhibited a three-fold greater prevalence of LGE, an indicator of myocardial fibrosis, compared with sedentary controls (12% vs. 4%). Möhlenkamp et al. assessed coronary artery calcium scores in the same cohort and found that a larger proportion of marathon runners had coronary artery calcium scores. 100 Agatston Units compared with controls matched for age and Framingham risk factors (36% vs. 21%).[31] Shearing forces within coronary arteries during high heart rates, circulating interleukins due to inflammation and the production of free radicals were implicated as possible factors.

CONCLUSION

Regular physical activity provides numerous health benefits such as increased life expectancy. Exercise causes a series of electrical, structural, and functional changes in the heart that enhance overall health. Despite a wide range of benefits, the adherence to exercise has always been a problem. This may be due to substantial shortcomings in knowledge about the benefits of exercise and the fact that the various exercise interventions are dependent upon specific patient clinical characteristics such as sex, race/ethnicity, medication use, adiposity, and cardiometabolic profile. Unstructured and unmonitored high-intensity exercise regimens have been documented to have serious cardiac complications, which are to be avoided. As per the current understanding, an undue emphasis should not be placed on AE alone. Aerobic *or* resistance exercise alone or aerobic and resistance exercise (DRE) or IRE in combinations (i.e., concurrent exercise) have proven to be more robust in achieving patient adherence.

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CHAPTER 39

Lipid Profile: Clinical Interpretation and Management Strategies

SS Iyengar, Saikat Kanjilal

ABSTRACT

Primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) mandates measurement of serum lipids. Low-density lipoprotein cholesterol (LDL-C) is universally accepted as a cause of ASCVD and thresholds and targets have been identified. Non-high-density lipoprotein cholesterol (HDL-C) and apolipoprotein B (ApoB) need to be assessed in some cases. Serum triglyceride (TG), which are a marker of TG-rich lipoproteins and remnants, has gained the attention of lipidologists recently. Lipoprotein(a) [Lp(a)] is a new frontier.

Management strategies for dyslipidemia commence with a discussion with the individual, ASCVD risk assessment, and therapeutic lifestyle interventions before embarking on drug therapy and/or lipoprotein apheresis. Therapeutics should follow a shared decision.

"The aim of interpretation is not agreement but understanding"

—Donald Davidson

INTRODUCTION

To face the daunting challenge of increasing burden of atherosclerotic cardiovascular disease (ASCVD) in our country, it is necessary to have a coordinated and concerted response in primary and secondary preventive measures. Dyslipidemia is one of the major modifiable risk factors: It is an easily detectable, largely treatable, and effectively controllable condition.

The INTERHEART study has highlighted the significant association of raised serum apolipoprotein B (ApoB), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and non-high-density lipoprotein cholesterol (HDL-C) with myocardial infarction.[1]

Interpretation of these lipid metrics and meaningful management measures, along with detection and control of other ASCVD risk factors, holds the key to ASCVD prevention.

ATHEROSCLEROTIC PROCESS

Trapping of ApoB particles within the arterial wall is the fundamental step in the pathophysiology of atherosclerosis. Under most circumstances, 90% of circulating ApoB particles are low-density lipoprotein (LDL) particles. Any ApoB-containing lipoproteins < 70 nm in diameter {LDL, intermediate-density lipoprotein (IDL), very-low-density lipoprotein (VLDL), chylomicron remnants, and lipoprotein(a) [Lp(a)]} can cross the endothelial barrier and initiate the atherosclerotic process.

LIPID PROFILE

A standard lipid profile consists of measurement of TC, triglycerides (TG), HDL-C, and LDL-C **(Fig. 1)**. Non-HDL-C is calculated as TC minus HDL-C and it reflects a comprehensive measure of all cholesterol found in atherogenic lipoproteins. Because each particle contains one molecule of ApoB, ApoB equals the number of atherogenic particles in plasma that can enter the arterial wall.

Lipid Profile and Clinical Interpretation

Why should it be done?

The goal of lipid-lowering therapy is to reduce the number of circulating ApoB lipoproteins that get trapped in the arterial wall.

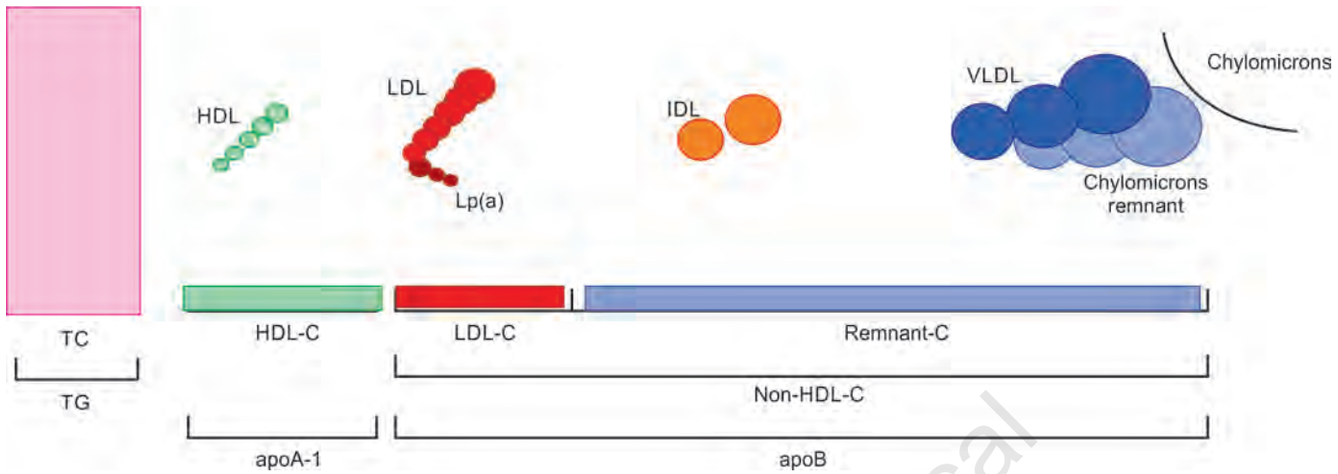

FIG. 1: Lipoproteins according to density and size.
[HDL: high-density lipoprotein; IDL: intermediate–density lipoprotein; LDL: low-density lipoprotein; LDL-C: low-density lipoprotein cholesterol; Lp(a): lipoprotein(a); TG: triglycerides; VLDL: very-low-density lipoprotein]

In our country, ASCVD arrives earlier, manifests in a more severe form, and has a higher mortality.[2-4]

Considering this and the well-accepted dictum about lowering atherogenic lipids that "Lower is better, earlier is better and longer is better," appropriate aggression is necessary in managing dyslipidemia in our country.

Low-density Lipoprotein Cholesterol Causes Atherosclerosis

Cholesterol is an essential molecule and has important cellular functions. Cholesterol can be synthesized by cells themselves or acquired from circulating LDL. This explains that very low levels of LDL are not associated with any safety issues.[5] Low LDL-C levels, i.e., below 40 mg/dL, are present in the newborn babies, where cholesterol requirements are very high.[6]

A large number of meta-analyses of prospective cohort studies, Mendelian randomization reports, epidemiological data and randomized clinical trials, and trials that cover more than 2 million participants have shown a robust and remarkably consistent relationship between the magnitude and the duration of exposure of LDL-C and the attendant risk of ASCVD.[7]

Statins reduce LDL-C and the risk of atherosclerotic events and mortality.

The meta-analysis by Cholesterol Treatment Trialists' (CTT) collaboration (five trials of more vs. less intensive statin therapy of 39,612 individuals with a follow-up of 5.1 years, and 21 trials of statin vs. control involving 129,526 individuals and a median follow-up of 4.8 years) demonstrated that further lowering of LDL-C resulted in reducing the risk of heart attack, revascularization, and ischemic stroke, each 38.6 mg/dL reduction leading to 20% decrease in the annual rate of major vascular events. There were no safety issues. It also suggested that reduction of LDL-C by 77.2–115 mg/dL would decrease the risk by about 40–50%.[8]

All-cause mortality was reduced by 10% per 38.6 mg/dL LDL reduction ($p < 0.0001$). It was mainly due to reduction in cardiac mortality.

In another meta-analysis, there were 46,675 (27%) women out of 174,149 participants. Statin therapy showed similar effectiveness for the prevention of major vascular events in men and women.[9]

INDIAN DATA

In a report using a fasting sample of 67,000 participants, it was found that the most prevalent dyslipidemia in this group was borderline, and high LDL-C (>100 mg/dL) and low HDL-C (men 54.9%, women 64.4%) were also highly prevalent. Severe hypercholesterolemia, i.e., LDL-C 220 mg/dL or more, was present in 1:357 (men 1:326, women 1:402) in a population-based study and it was 1:209 (men 1:271, women 1:126) in hospitalized patients.[10]

Another large study (FitHeart) covering more than 20 states used fasting blood samples and uniform laboratory method in urban Indian subset. A total of 46,919 subjects aged 18–96 years participated. The mean [1 standard deviation (SD)] age was 49.6 ± 13.2 years. The pan-India averages were: TC 176.7 ± 42.1 mg/dL, LDL-C 110.5 ± 34.0 mg/dL, HDL-C 43.2 ± 11.7 mg/dL, non-HDL-C 133.5 ± 41.3 mg/dL, and TG 162.3 ± 106.7 mg/dL.[11]

Recent multicentric studies have reported that hypercholesterolemia, defined as TC 200 mg/dL or more, is present in 25–30% of urban and 15–20% rural subjects.[12]

Awareness of hypercholesterolemia was seen in 17.5% men and 13.2% women with high cholesterol, treatment with statins was seen in 7.5% men and 6.7% women, while control to targets of TC was seen in 4.5% men and 3.7% women. The authors concluded that: "Focus on dyslipidemia management is urgently required in India to halt the rising tide of coronary heart disease."[13]

What are the lipid parameters to be estimated?

The lipid panel usually consists of measurement of TC, TG, HDL-C, and LDL-C. There is no additional test required for non-HDL-C, which is derived by subtracting HDL-C from TC. In special situations, ApoB should be estimated.

In general, LDL-C, non-HDL-C, and ApoB concentrations are very highly correlated. As a result, under most circumstances, they provide very similar information about ASCVD risk. However, under certain circumstances, including among people with elevated TG levels, diabetes mellitus (DM), obesity, or very low achieved LDL-C levels, the calculated or directly measured LDL-C level may underestimate both the total concentration of cholesterol carried by LDL and, more importantly, the total concentration of ApoB-containing lipoproteins, thus underestimating the risk of ASCVD. In around 20% of patients, there may be discordance between measured LDL-C and ApoB levels. Statin therapy reduces the LDL-C more than ApoB. The decrease in LDL-C is greater than the ApoB lowering by 15%. Hence, on-treatment ApoB is a more reliable index of the residual risk.

Low-density lipoprotein cholesterol measures the cholesterol content of LDL and Lp(a).

Non-HDL-C measures the cholesterol content of all atherogenic lipoprotein particles.

Apolipoprotein B provides an accurate estimate of the total concentration of atherogenic particles under all circumstances; it is the preferred measurement to further refine the estimate of ASCVD risk.

The Swedish AMORIS (Apolipoprotein-related MOrtality RISk) study measured ApoA-1 and ApoB in more than 175,000 individuals followed prospectively for up to 25 years. Myocardial infarction was best predicted by ApoB levels followed by non-HDL-C and then LDL-C.[14]

A meta-analysis of 12 epidemiological studies including 233,455 individuals concluded that ApoB, with an RR of 1.43 per 1 SD increment, was superior to non-HDL-C (1.34) and LDL-C (1.25) in the association with future fatal or nonfatal cardiovascular disease (CVD) events ($p = 0.001$).[15]

Fasting versus nonfasting?

The lipid profile (or its components) does not require fasting in most cases. TC and HDL-C are minimally affected by fasting. If the nonfasting plasma TG component of the lipid profile returns at >4.516 mmol/L (400 mg/dL), a fasting lipid profile should be done. This practice would be convenient for patients, clinicians, and laboratories alike.[16]

Changes in nonfasting versus fasting levels are +26 mg/dL for TG, –8 mg/dL for TC, –8 mg/dL for LDL-C, +8 mg/dL for remnant cholesterol, and –8 mg/dL for non-HDL-C. Lp(a), ApoB, and HDL-C show no difference.[17]

Lipoprotein(a)

Lipoprotein(a) may have relevance in causing premature ASCVD in Indians. The coronary artery disease in Asian Indians (CADI) study showed that levels of Lp(a) are significantly elevated among Indians. Approximately 25% of Indians and other South Asians have elevated Lp(a) levels (≥50 mg/dL). As per the Lipid Association of India (LAI), a level of 20–49 mg/dL is a moderate-risk factor, whereas Lp(a) ≥ 50 mg/dL is a high-risk feature. The American College of Cardiology/American Heart Association (ACC/AHA) 2018 guidelines consider an elevation of Lp(a) as a risk-enhancing factor when Lp(a) is >50 mg/dL. The recommendations for measuring Lp(a) are:

- Family history of premature ASCVD or
- Personal history of ASCVD not explained by major risk factors.

Since the serum Lp(a) levels are reported to remain same throughout life without intervention, it is recommended that levels should be checked at least once in a lifetime.[16]

When to measure lipids?

It is recommended that a lipid profile should be obtained at the age of 18 years along with records of body mass index (BMI), blood pressure, and blood sugar values as a part of universal screening. It may be done earlier if there is a family history of premature coronary artery disease or of familial hypercholesterolemia.[18]

If not done earlier, it should be done at the earliest opportunity. In patients presenting with an acute atherothrombotic event, blood should be collected at the time of presentation to the emergency department for lipid profile including Lp(a), not worrying about fasting or nonfasting state.[19]

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK ASSESSMENT

The process of risk assessment is the beginning of the journey in the management. It gives an opportunity to discuss, share the decision, and institute preventive measures. The assessed risk decides the intensity of intervention and therapeutic goals, including lipid targets. It should be a global risk assessment, and not merely lipid numbers.

There are guidelines galore and a number of score cards for risk assessment. There are two which are suitable for the Indian population—one from LAI expert consensus statement[16] and the other Q-Risk score from the British Heart Society.[20] LAI recommendations are easy to use and no calculations are required and QRISK3 has considered Indian ethnicity in its preparation.

LIPID TARGETS

Lipid Association of India has identified the following risk categories—low, moderate, high, and very risk. Since all ASCVD cases cannot be lumped into one risk category, LAI proposed extreme risk categories—A and B, depending on the comorbidities, number of vascular territories involved, and the presence of familial hypercholesterolemia.[19]

All lipidologists and clinicians accept that low LDL-C is safe and "lower is better." It is also amply proven that there is no lower threshold for LDL-C, below which it does not confer benefit or does harm. CTT collaboration studies,[8,9] IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial),[21] FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial,[22] and ODYSSEY OUTCOME (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab)[23] data clearly

demonstrated the safety and efficacy of extremely low levels of LDL-C. India participated in FOURIER and ODYSSEY OUTCOME trials.

The targets for LDL-C, non-HDL-C, and ApoB are given in **Table 1** (LAI recommendations)[16] and **Table 2** [European Atherosclerosis Society (EAS) recommendations].[24]

How to achieve the lipid goals?

Therapeutic lifestyle intervention is an essential and integral part of this exercise. A fair trial of this measure should be given to those in low-risk group before considering drug therapy.

There are a number of drugs available in the armamentarium to reduce atherogenic lipids. Statin is the first line, followed by ezetimibe, bempedoic acid, PCSK9 inhibitors (monoclonal antibodies—evolocumab and alirocumab), small interfering ribonucleic acid (siRNA) molecules (inclisiran), and ANGPTL3 monoclonal antibodies (evinacumab).

Statins

Statins have been extensively studied and there is substantial evidence that they are effective and safe in reducing cardiovascular events and mortality.[25]

High-intensity statins are needed mostly in high-risk group. However, the dose has to be chosen to achieve the LDL-C targets **(Table 3)**.

Statins are extremely well tolerated. However, statin intolerance is seen in clinical practice and may lead to its discontinuation. About 20% of patients exhibit statin intolerance mainly because of muscle symptoms.[26] It is possible to continue statins in some of these patients by changing the preparation, dosage, and frequency.

Ezetimibe

Ezetimibe reduces absorption of cholesterol from small intestine, resulting in LDL-C reduction of 15–25%. In IMPROVE-IT study, ezetimibe when added to statin therapy leads to incremental lowering of LDL-C levels. The median LDL-C level achieved was 53.7 mg/dL. It reduced a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke by absolute 2% points. It also demonstrated that lowering LDL-C to low levels is beneficial.[21]

Bempedoic Acid

Bempedoic acid works by inhibiting adenosine triphosphate citrate lyase (ACL), an enzyme critical to the hepatic synthesis of cholesterol. In a trial of patients who had statin intolerance, bempedoic acid together with ezetimibe reduced LDL-C by 28.5% more than ezetimibe alone.[27]

A cardiovascular outcome trial—CLEAR Outcomes—is ongoing involving 14,000 patients with statin intolerance and high-risk ASCVD with bempedoic acid versus placebo.[28]

PCSK9 Inhibitors

PCSK9 monoclonal antibodies, evolocumab[22] and alirocumab,[23] reduce LDL-C concentrations by up to 60% and reduce the risk of cardiovascular events. They prevent downregulation and destruction of cell membrane LDL receptors, in turn leading to lower circulating LDL particle concentrations. They have also been studied in patients with statin-associated muscle symptoms.[29]

TABLE 1: Treatment goals of low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (HDL-C), and apolipoprotein B (ApoB) [Lipid Association of India (LAI) recommendations].[16]

Risk category	LDL-C goal (mg/dL)	Non-HDL-C goal (mg/dL)	ApoB goal (mg/dL)
Low risk	<100	<130	Not applicable*
Moderate risk	<100	<130	Not applicable*
High risk	<70	<100	<80
Very high risk	<50	<80	<65
Extreme risk category A	<50 (<30 optional)	<80 (<60 optional)	<65
Extreme risk category B	<30	<60	<50

*Apolipoprotein B is estimated only in selected situations.

TABLE 2: European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines.[24]

Low risk	• SCORE < 1% • LDL-C < 116 mg/dL
Moderate risk	• SCORE ≥ 1% and <5% • Young patients (<35 years for type 1 and <50 years for type 2) with diabetes duration <10 years, without other risk factors • LDL-C < **100 mg/dL**
High risk	• Markedly elevated single risk factors (LDL-C >190 mg/dL, BP >180/110 mm Hg) • FH without other major risk factors • Patients with diabetes without target organ damage, with diabetes duration ≥10 years or another additional risk factor • Moderate CKD (eGFR 30–59 mL/min/1.73 m^2) • SCORE ≥5% and <10% • LDL-C <**70 mg/dL** and a ≥50% reduction
Very high risk	• Clinical or imaging ASCVD • Diabetes with target organ damage, one or at least three major risk factors, or early onset of type 1 diabetes with a duration >20 years • Severe CKD (eGFR <30 mL/min/1.73 m^2) • SCORE ≥10% • FH with ASCVD or with another major risk factor (LDL-C <**55 mg/dL**) and a ≥50% reduction • Recent MI within 2 years (LDL-C <40 mg/dL)

(ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; FH: familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction)

TABLE 3: Statin dosing and intensity.

Drug	Low-intensity dose (LDL-C reduction <30%)	Moderate-intensity dose (LDL-C reduction 30% to <50%)	High-intensity dose (LDL-C reduction >50%)
Atorvastatin	NA	10–20 mg	40–80 mg
Fluvastatin	20–40 mg	80 mg	NA
Lovastatin	20 mg	40 mg	NA
Pitavastatin	1 mg	2–4 mg	NA
Pravastatin	10–20 mg	40–80 mg	NA
Rosuvastatin	NA	5–10 mg	20–40 mg
Simvastatin	10 mg	20–40 mg	NA

Note: Dosages are daily doses.

(LDL-C: low-density lipoprotein cholesterol; NA: not applicable)

Inclisiran

Inclisiran is an siRNA agent that inhibits translation of the PCSK9 protein and thus its formation. Adding inclisiran to statin reduced LDL-C levels by about 50%. Infrequent administration is its advantage as it is given subcutaneously, followed by a second dose after 90 days, and then every 6 months thereafter.[30,31]

Evinacumab

Evinacumab is a monoclonal antibody that blocks ANGPTL3. (ANGPTL3 inhibits lipoprotein lipase leading to increased plasma LDL-C levels.) A phase 3 study of 65 patients with homozygous familial hypercholesterolemia on maximally tolerated lipid-lowering therapy showed that evinacumab infusion every 4 weeks reduced LDL-C by 49% at 24 weeks, and it was effective even in patients with no functional LDL receptors.[32]

Lipoprotein apheresis may have to be instituted in some patients with familial hypercholesterolemia.[33]

TREATMENT OF HYPERTRIGLYCERIDEMIA

Plasma TG are elevated when there is overproduction and impaired clearance of TG-rich lipoproteins—VLDL and chylomicrons. This leads to increased remnant lipoproteins and small, dense LDL. The elevated risk of ASCVD in hypertriglyceridemia is believed to result from the exposure of the artery wall to these lipoproteins.

In high-risk individuals, if LDL-C target is achieved, but serum TG level is >150 mg/dL (fasting) or >175 mg/dL (nonfasting), one should exclude secondary causes, be more aggressive with lifestyle intervention, and consider adding eicosapentaenoic acid.[34]

Elevated Lipoprotein(a)

At present, there are no guideline-recommended drugs for Lp(a). PCSK9 inhibitors (evolocumab and alirocumab) do reduce Lp(a) by about 20% as seen in FOURIER[22] and ODYSSEY OUTCOME[23] studies. At best, it is an off-label indication in patients with ASCVD and markedly elevated Lp(a).

CONCLUSION

- *Screen for lipids*: Universal screening at age 18 years (or earlier if there is a family history of premature ASCVD or familial hypercholesterolemia) along with BMI, blood sugar, and blood pressure
- Nonfasting lipid profile will do. Do fasting lipids if TG > 400 mg/dL or during follow-up.
- Lipid profile reporting should include TC, TG, HDL-C, LDL-C, and non-HDL-C. Direct LDL-C estimation is preferable.
- In individuals with obesity, diabetes, metabolic syndrome, high TG, low LDL-C, and high risk, ApoB should be estimated. On treatment, ApoB is a more reliable indicator of residual risk.
- Assess ASCVD risk. This gives an opportunity to discuss with the individual and make a shared decision in instituting therapeutics and identifying lipid targets.
- Low-density lipoprotein cholesterol is the primary target, and non-HDL-C is the co-primary target.
- Apolipoprotein B has to be estimated in certain situations.
- Therapeutic lifestyle intervention is the first and an integral component of the management of dyslipidemia.
- Statins form the first line of drug therapy.
- If not at goal, add ezetimibe, bempedoic acid, and PCSK9 inhibitors sequentially.
- Consider eicosapentaenoic acid in high-risk individuals, if the LDL-C goal is reached but the TG > 150 mg/dL (fasting) or >175 mg/dL (nonfasting) after excluding secondary causes and ensuring strict lifestyle measures.
- Ensure adherence.

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CHAPTER 40

Lipoprotein(a): Atherogenic Risk and Management Challenges

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ABSTRACT

Lipid management in atherosclerotic cardiovascular disease (ASCVD) is mainly low-density lipoprotein (LDL) centric. Lipoprotein(a) [Lp(a)] is a biomarker, which can help us to refine the current strategies of ASCVD risk assessment and management. It is estimated that approximately 20% of the world's population has elevated Lp(a).

It has a role in both primary and secondary prevention, also for incident calcific aortic stenosis. The increase in the risk associated with Lp(a) is attributed to procoagulant effects of apolipoprotein(a) [Apo(a)], with atherogenic and proinflammatory effects attributed to its oxidized apolipoprotein B (ApoB)-related phospholipids.

Although Lp(a) is an independent risk factor for ASCVD, the latest international clinical guidelines do not recommend direct reduction of plasma Lp(a) concentrations. Recent clinical trials have shown that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and newer generation antisense ribonucleic acid (RNA) molecules can effectively reduce plasma Lp(a) levels.

This chapter focuses on the structure, prognostic evidences, its pathogenicity, and also new therapeutic drugs for Lp(a) lowering. It is time for cardiologists to consider using it routinely in their practice.

INTRODUCTION

Lipid management in atherosclerotic cardiovascular disease (ASCVD) is mainly low-density lipoprotein (LDL) centric. Lipoprotein(a) [Lp(a)] is a biomarker, which can help us to refine the current strategies of ASCVD risk assessment and management. It is estimated that approximately 20% of the world's population has elevated Lp(a).[1] *Lp(a)* gene is an underappreciated causal factor(s) for premature coronary artery disease (CAD).[2,3]

Lipoprotein(a) is an LDL-like lipoprotein with apolipoprotein(a) [Apo(a)] which is linked to apolipoprotein B (ApoB) through one disulfide bond. Lp(a) is a risk factor for ASCVD such as myocardial infarction (MI) and ischemic stroke. Lp(a) is known for its pathological roles in thrombosis and atherosclerosis. It has a role in both primary and secondary prevention, and also used for incident calcific aortic stenosis. The increase in the risk associated with Lp(a) is attributed to procoagulant effects of Apo(a), with atherogenic and proinflammatory effects attributed to its oxidized Apo B-related phospholipids.

In recent years, epidemiological studies, genome-wide association studies, and Mendelian randomization studies have shown a strong association between increased levels of lipoproteins and increased risks of coronary heart disease (CHD) and cardiovascular disease (CVD).[4-8]

Although Lp(a) is an independent risk factor for ASCVD, but the latest international clinical guidelines do not recommend direct reduction of plasma Lp(a) concentrations. The main reason was that there is no effective clinical medicine, which has been proven to provide benefit with lowering of plasma Lp(a) concentrations. Recent clinical trials have shown that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and newer generation antisense ribonucleic acid (RNA) molecules can effectively reduce plasma Lp(a) levels. The results of pelacarsen-based HORIZON trial are also eagerly awaited which will test the hypothesis that reducing LP(a) in patients with elevated Lp(a) ≥ 70 mg/dL and established CVD will reduce the risk of an expanded major adverse cardiac event [MACE; cardiovascular (CV) death, nonfatal MI, nonfatal stroke, and urgent coronary revascularization requiring hospitalization].

WHAT IS LIPOPROTEIN(a)?

Lipoprotein(a) was first discovered by Kare Berg about 60 years ago.[9] It is a form of LDL and is an independent risk factor for ASCVD, valvular aortic stenosis, and peripheral vascular disease.

Lipoprotein(a) has two components: (1) LDL with apolipoprotein B100 (Apo-B100) and (2) Apo(a) which is attached to ApoB via a disulfide bridge. There are many different Apo(a) isoforms which determine the function of Lp(a).

An individual's Lp(a) level is 80–90% genetically determined with full expression by 1–2 years of age and adult-like levels are achieved by 5 years of age approximately. The plasma concentration of Lp(a) is hardly affected by lifestyle, environmental, and dietary factors.[1]

PATHOGENICITY OF LIPOPROTEIN(a)

Lipoprotein(a) is proatherosclerotic, prothrombotic, and proinflammatory.

Atherosclerosis

Lipoprotein(a) is more atherogenic than LDL cholesterol (LDL-C) because it contains proatherogenic properties not only of LDL-C but also of Apo(a). Apo(a) potentiates atherothrombosis through its content of oxidized phospholipids and the presence of lysine-binding sites. Lysine-binding sites in Apo(a) promote Lp(a) accumulation in vascular tissues and induce endothelial dysfunction.

Elevated Lp(a) is strongly associated with the development of high-risk vulnerable plaques with complex morphology [thin-cap fibroatheroma heavily infiltrated by macrophages and rare smooth muscle cells (SMCs) overlying a large necrotic core] that are prone to rupture.[10,11] Large amounts of Lp(a) are concentrated in the culprit lesions in patients with acute coronary syndrome (ACS) than in patients with stable angina.[12]

Thrombosis

Lipoprotein(a) inhibits and interferes with fibrinolysis, thus promoting thrombosis. Apo(a) has a very similar structure to plasminogen and has been shown in vitro to inhibit fibrinolysis. Therefore, it could promote thrombosis at vulnerable arterial plaques leading to obstruction.

Inflammation

Lipoprotein(a) can promote inflammation by inducing the inflammatory cytokines. Apo(a) can induce macrophages to release interleukin-8, tumor necrosis factor, and monocyte chemotactic protein.[13] Lp(a) can directly induce monocyte chemotaxis and attract monocytes by direct and indirect mechanism by vascular endothelial cells.[14]

ETHNIC GENDER AND AGE CONSIDERATIONS OF LIPOPROTEIN(a)

Age

Lifelong elevated levels of plasma Lp(a) are associated with ASCVD, including stroke. Considering the fact that individuals with extremely elevated Lp(a) >180 mg/dL demonstrate an ASCVD risk similar to those who have heterozygous hypercholesterolemia,[15] universal Lp(a) screening of all children is suggested. Though there is no consensus for universal screening, there is some agreement regarding cascade screening of Lp(a) in children when a parent has been identified with elevated Lp(a) particularly if there is a family history of premature ASCVD.[1]

Gender

There are notable sex differences in plasma Lp(a) concentrations. Lp(a) levels remain relatively stable throughout life in men and tend to increase in females with age after menopause.[16] There is evidence to demonstrate that elevated Lp(a) levels were associated with an increased risk for CHD in postmenopausal females.[17]

Ethnicity

Ethnicity has a significant effect on Lp(a) levels. The genetic factor is a major reason of diversity in Lp(a) levels, whereas age and gender do not affect these.[18] Lp(a) levels, Apo(a) isoform size distribution, and *LPA* single nucleotide polymorphisms can vary across different races. Black ancestry is associated with the highest Lp(a) levels followed by South Asians. It is evident that elevated Lp(a) is independently associated with ASCVD irrespective of racial and ethnic groups.

One analysis from the Atherosclerosis Risk in Communities (ARIC) study showed that Lp(a) concentration was similarly associated with ASCVD risk in both blacks and whites.[19]

However, the fundamental pathophysiology of Lp(a) is likely to be similar in various ethnic groups. Therefore, a universal Lp(a) threshold for increased risk has been suggested.[1]

ISSUES IN THE MEASUREMENT OF LIPOPROTEIN(a)

There is uncertainty for clinicians regarding the clinical use of Lp(a) because the methodology for measuring Lp(a) is not reliable. Moreover, its target levels and measurement are not standardized. Lp(a) is expressed as mass (mg/dL); however, reporting Lp(a) concentration unit (nmol/L) is preferred. Moreover, converting between these two units, using a single conversion factor of 2.5 is not possible because of the variable number of repeated units in different Apo(a) isoforms, which leads to the overestimation of larger isoforms and underestimation of smaller isoforms. To overcome this challenge, it is recommended to report Lp(a) levels as concentration (nmol/L) using an assay standardized against the WHO/International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference material.

LIPOPROTEIN(a) AND PRIMARY PREVENTION

Most of the available studies have established the role of elevated Lp(a) levels for primary prevention of patients, but it is not included in established risk algorithms [American College of Cardiology (ACC)/American Heart Association (AHA) pooled

Cohort Equations and the Systematic Coronary Risk Evaluation (SCORE)]. Lp(a) improves CVD prediction when added to the Framingham and Reynolds Risk Score.[20] If the plasma Lp(a) levels are elevated, it is clinically relevant to perform a thorough risk assessment. If the calculated 10-year ASCVD risk is borderline (5.0–7.4%), intermediate (7.5–19.9%), or if there is family history of early ASCVD or familial hypercholesterolemia, such population might be screened for Lp(a) levels and if elevated it favors more aggressive LDL-C lowering therapy.[1,21,22]

LIPOPROTEIN(a) AND SECONDARY PREVENTION

In spite of antiplatelet therapy and statins, there is a residual risk of ASCVD in patients with elevated plasma Lp(a). In a multicentric study of 7,562 patients with CAD, who had experienced a CV event (CVE), the potential impact of Lp(a) was studied as a predictor for recurrent CVEs. The results showed that the events group had significantly higher Lp(a) levels than nonevents group (20.6 vs. 15 mg/dL, $p < 0.001$). Cox regression analysis showed that Lp(a) was independently associated with the risk of recurrent CVEs with no significant differences in the use of other drugs between groups.[23]

In a substudy of Berlin C&S (Cream & Sugar) study, 250 patients with acute ischemic stroke with elevated Lp(a) (>30 mg/dL) were included, and it was demonstrated that the risk for a recurrent event was significantly higher in patients with acute, first-ever ischemic stroke with elevated Lp(a) levels [hazard ratio 2.6; 95% confidence interval (CI) 1.19–5.67].[24]

Whether Lp(a) lowering brings benefit in terms of ASCVD risk reduction is unclear. In a Mendelian randomization analysis, it is suggested that an absolute reduction in Lp(a) by approximately 100 mg/dL is required to reduce CHD risk similar to reduction of LDL-C by 38.67 mg/dL.[15] However, another similar study estimated that to reach the same effect as 38.67 mg/dL reduction of LDL-C, Lp(a) should be reduced by 65.7 mg/dL.[25]

In a prospective cohort study of 2,527 individuals from the Copenhagen General Population Study with CVD at baseline, Lp(a) lowering by 50 mg/dL for 5 years may be needed to reduce 20% MACE risk reduction in the secondary prevention setting.[26]

LIPOPROTEIN(a) AND RISK STRATIFICATION

It is known that LDL-C is linked to an increased risk of CVD; studies have shown that even in patients who attain LDL-C goals, Lp(a) carries an additional risk of CVEs.[27]

In a substudy of JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) trial, Lp(a) concentrations were assessed in 9,612 multiethnic participants treated with potent statin therapy, and it was shown that Lp(a) was a significant determinant of residual risk for CVEs.[28]

A recent analysis of prospective studies of 126,936 individuals from the Danish population (Copenhagen City Heart Study and Copenhagen General Population Study) showed that Lp(a) was strongly associated with CV and all-cause mortality regardless of LDL concentration.[29]

Hyperlipoproteinemia(a) has an independent prognostic value but what is the effect of Lp(a) reduction on CV outcomes is not established. To answer this question, a recent population-based study demonstrated that Lp(a) lowering by 50 mg/dL (105 nmol/L) may reduce the CVD risk by 20% in a secondary presentation setting.[26]

Lipoprotein(a) is not incorporated in established ASCVD risk calculators. In the Bruneck study of 826 participants followed for 15 years for CVEs, when Lp(a) was included in Framingham Risk Score and Reynolds Risk Score, it improved the CVD prediction in those originally classified as being at intermediate ASCVD risk.[20]

Another analysis conducted in 16,777 European Prospective Investigation of Cancer (EPIC)—Norfolk study participants demonstrated that CVD risk prediction using either the ACC/AHA or the SCORE algorithm can be improved by adding Lp(a) levels, but only in participants initially categorized as intermediate risk.[22]

For the SCORE algorithm, the improvement was more pronounced when using the Lp(a) threshold for 30 mg/dL rather than the European Atherosclerosis Society (EAS) recommended threshold of 50 mg/dL.[30]

LIPOPROTEIN(a) MEDIATES CALCIFIC AORTIC VALVULAR STENOSIS

It has been suspected that Lp(a) is a risk factor for calcific aortic valvular stenosis (CAVS). Recent data from the ASTRONOMER trial (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin)[31] showed that patients with preexisting mild-to-moderate aortic stenosis and elevated levels of Lp(a) and OxPL-ApoB had a faster progression rate, with annual changes in peak aortic jet velocities, and a need for aortic valve replacement.[32] The enzyme autotaxin has been identified as an important contributor molecule in CAVS.[33] In a case–control study in 150 patients with CAVS plus CAD and 150 matched patients with CAD without CAVS, patients with CAVS had elevated autotaxin mass and activity, Lp(a) (>50 mg/dL), and OxPL-ApoB (>2.02 nM).[34] Therefore, for the development and progression of CAVS, Lp(a) carries both autotaxin and OxPL into aortic valve leaflets and initiates inflammation and calcification.

LIPOPROTEIN(a) AND GUIDELINE RECOMMENDATION

Numerous epidemiological, genome-wide association, and Mendelian randomization studies and meta-analysis have established that there is association between plasma Lp(a) and CVD risk. But none of the clinical guidelines recommend either any therapy for direct reduction of plasma Lp(a) concentration or guidance on when Lp(a) should be measured.

The AHA/ACC 2018 guidelines on the management of blood cholesterol have suggested Lp(a) as a risk-enhancing factor, especially at higher levels of Lp(a) (≥50 mg/dL or ≥125 nmol/L)

for adults aged 40–75 years. Though there is limited guidance about when Lp(a) should be measured, AHA/ACC 2018 guidelines mention its measurement as a relative indication if there is a family history of premature ASCVD.[35]

According to the 2019 European Society of Cardiology (ESC)/EAS guidelines for the management of dyslipidemia, it is recommended that an adult should have at least one Lp(a) measurement during his lifetime in order to recognize those who have inherited exceptionally higher levels of plasma Lp(a) (>180 mg/dL or >430 nmol/L). This is because such populations may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolemia.[36]

ELEVATED LIPOPROTEIN(A) IN INDIANS

The three main features of malignant CAD found among Indians, that is, premature onset, severity, and high mortality at young age, are also present in CAD patients with markedly elevated Lp(a) levels. Young Indians exhibit a strong association of elevated Lp(a) with CAD.[37]

Enas et al.[38,39] were the first to report high Lp(a) levels among Indians residing in the United States. Lp(a) levels ≥ 30 mg/dL were found in 25% and >20 mg/dL in 44% of Indians.

Elevated plasma Lp(a) genetically predisposes Indians to CAD and acute myocardial infarction (AMI). Many case–control studies have shown an association of elevated Lp(a) levels with CAD, AMI, and stroke, especially in young Indians,[40-45] and nutritional and environmental factors further increase the risk.[43,46]

In a study of 70 ACS patients (aged < 55 years) with no established risk factors, Mukherjee et al.[47] found high Lp(a) in 41%. Similarly, Bansal et al.[48] in a case–control study of 30 Indians aged <30 years documented premature CAD and 30 age- and gender-matched healthy individuals found that Lp(a), ApoA1, and ApoB were better discriminators of premature CAD as compared to conventional lipid parameters.

A study of young Indians (<45 years) with AMI found Lp(a) ≥ 20 mg/dL in 70% of Indians with CAD but only 10% had Lp(a) > 30 mg/dL.[42] In the INTERHEART Lp(a) study, odds ratio (OR) for AMI from Lp(a) > 50 mg/dL was significantly higher in South Asians (OR 2.14) than in whites (OR 1.36).

In a recent Indian study of 160 CAD patients, Sawhney et al. demonstrated that patients with elevated Lp(a) (>50 mg/dL) exhibited severe disease angiographically. Lp(a) was higher in young CAD patients as compared to elderly patients.[49]

The National Heart, Lung, and Blood Institute (NHLBI) working group has estimated that 1.43 billion of the world population have Lp(a) ≥5 0 mg/dL, of whom 469 million are South Asians.[50] The prevalence of diabetes is 8.5% and that of prediabetes is 5%, compared with 25% for elevated Lp(a).[50] The prevalence of elevated Lp(a) among Indians in the United States was 25% using a threshold of ≥30 mg/dL.

TREATMENT IN ELEVATED LIPOPROTEIN(A)

Due to the lack of specific targets in Lp(a) metabolism, there is an unmet need for specific Lp(a)-lowering treatment options. The following section describes the impact of the currently available therapies on plasma Lp(a) concentrations **(Table 1)**.

Statins

Effects of statins on the metabolism of Lp(a) are not completely known, and there are conflicting studies with some studies suggesting an increase in Lp(a) levels following statin therapies. A recent meta-analysis of six randomized clinical trials found increases in Lp(a) levels (8.5–19.6%) following statins compared to the placebo group (0.4–2.3%).[51]

However, in another meta-analysis of 29,069 patients from randomized controlled statin trials—AFCAPS,[52] CARDS,[53] 4D,[54] JUPITER,[28] LIPID,[55] MIRACL,[56] and 4S[57] trials, there was a pooled 0.4% (95% CI −7 to 7) change in Lp(a).[58] Still, there was heterogeneity among these trials with three showing a mean increase (between 2 and 15%) and four showing a mean decrease (between −1 and −13%) in Lp(a) levels.

However, more contemporary studies show that statin therapy in itself does affect Lp(a) levels, though importantly, those who continue to have high Lp(a) levels on a statin are at increased ASCVD risk even if LDL-C is improved.

Based on the available data, the authors recommend initiating a moderate-to-high-intensity statin therapy in adults aged 40–75 years with a 10-year ASCVD risk of 7.5 to ≤20% with Lp(a) ≥ 100 nmol/L.

Low-density lipoprotein present in Lp(a) is not reduced by statins; hence, a patient with inadequate response to statins can be associated with high Lp(a).

TABLE 1: Effect of lipid lowering therapy on Lp(a) levels.

Treatment	Change in plasma Lp(a) level	Outcome
Statins	Neutral or slight increase +0–20%	• Lp(a) is an independent predictor of CV events • Robust due to LDL-C reduction
PCSK9 inhibitors	20–25% reduction	• Relative risk reduction of 0.6% per 1 mg/dL reduction • Meaningful reduction only for patients with higher baseline Lp(a) (>21.2 mg/dL)
Niacin	−31%	No impact on CV events
Ezetimibe	Neutral (−7%)	Modest Lp(a) reduction
Mipomersen	26% reduction	
Pelacarsen	Up to 80% reduction	Currently unknown

[CV: cardiovascular; LDL-C: low-density lipoprotein cholesterol; Lp(a): lipoprotein(a); PCSK9: proprotein convertase subtilisin/kexin type 9]

Ezetimibe

The use of statin treatment alone is not able to decrease the risk associated with elevated plasma Lp(a). High-risk patients with LDL-C ≥ 70 mg/dL [non-high-density lipoprotein cholesterol (non-HDL-C) ≥100 mg/dL] and a Lp(a) ≥ 100 nmol/L, on maximum tolerated dose of statins, should be given other lipid-lowering therapies such as ezetimibe on top of statins. Ezetimibe has been shown to significantly reduce the Lp(a) levels though subtle.[59] In a systemic review and meta-analysis of seven randomized controlled trials (RCTs) with 2,337 patients, ezetimibe monotherapy (10 mg/day) showed a small but statistically significant reduction (7%) in Lp(a) levels in patients with primary hypercholesterolemia.[59]

Nicotinic Acid

High-dose niacin (2–4 g/day) can reduce Lp(a) by 25–40%.[60] However, niacin did not show any ability to reduce the concentration of Lp(a) at low doses. However, due to the potential adverse reactions, such as migraines, tachycardia, and liver toxicity, the recent European guidelines do not recommend the use of niacin as a way to reduce Lp(a).[36]

Hormone Replacement Therapy

Sex hormones are known to influence the Lp(a) metabolism. The use of desogestrel-containing oral contraceptives has a significant reducing effect on Lp(a) levels, especially in nonsmoking women.[61]

The favorable effects of hormone replacement therapy on Lp(a) are also evident in women without established CV disease with a possible impact on CV mortality over the years.[62] However, robust evidence to reduce hard clinical endpoints by lowering Lp(a) is still missing.

PCSK9 Inhibitors

PCSK9 monoclonal antibody treatment can effectively reduce Lp(a) levels for up to 32% in subjects with hypercholesterolemia and on statins.[63] The Lp(a)-lowering effect was confirmed in a pooled analysis of data from four phase II trials of evolocumab. Inhibition of PCSK9 with evolocumab treatment for 12 weeks resulted in significant dose-related reduction in Lp(a).[64] Evidence from FOURIER[65] and ODYSSEY OUTCOME[66] trials has shown that if we reduce elevated Lp(a) in ASCVD patients with LDL-C goal, there is a further reduction in CVE. A secondary analysis of the ODYSSEY OUTCOME trial showed that changes in Lp(a) levels after alirocumab therapy reduced the risk of major adverse CVEs by 0.6% for each 1 mg/dL reduction in Lp(a) levels, again independent of LDL-C reduction.[67]

Currently, PCSK9 inhibitors are not indicated to lower Lp(a) and should not be used for this specific purpose.

RNA Therapeutic Drugs

- *Nucleic acid–based therapies*: These rely on small interfering RNAs (SiRNAs). Inclisiran is a long-acting SiRNA, which reduces the hepatic production of PCSK9 and causes marked reduction in LDL-C levels. In the phase 2 (ORION-1) trial, inclisiran reduced Lp(a) by 25.6%, in addition to a 52.5% reduction in LDL.[68]
- *Antisense oligonucleotide therapy*: It is a gene-based therapy designed to selectively interface with a specific region of a gene, thus enabling the transcription and translation process of, for instance, Apo(a) messenger RNA (mRNA) to reduce the synthesis of Apo(a) in the liver.

  In a randomized placebo-controlled phase I study, ISIS-Apo(a)Rx showed dose-dependent reduction in Lp(a) levels by up to 78% (at the highest dose of 300 mg) in healthy volunteers with Lp(a) levels > 100 mg/dL.[69] In a phase 2 trial, the efficacy of IONIS-Apo(a)Rx was also confirmed in patients with higher Lp(a) levels.[70]

  A phase 2 trial for AKCEA-Apo(a)-L_{Rx} (pelacarsen) showed it to be a safe and feasible drug for patients with established CVD and elevated plasma Lp(a) levels at screening. The reduction in Lp(a) levels was dose dependent, as 35% for the lowest dose tested (20 mg, every month) and 80% at the highest dose (20 mg, every week). Importantly, no serious adverse events have been reported for these Apo(a) antisense therapies.[71]
- *Pelacarsen*: The Lp(a) HORIZON trial is an ongoing phase 3 multicenter trial to assess the impact of reducing Lp(a) with pelacarsen on CVEs in CVD patients and it is shown that pelacarsen 80 mg significantly lowers direct Lp(a)-C.[71]
- *Mipomersen*: This binds to the homologous ApoB mRNA.[72-74] Due to the inhibition of the synthesis of ApoB-100, the plasma concentration of LDL, ApoB, and Lp(a) can be significantly reduced. In the existing phase III randomized trial, in patients with hypercholesterolemia of different causes, mipomersen continuously reduced the median plasma Lp(a) level by 26.4%.[72] Mipomersen is approved by the Food and Drug Administration (FDA) for lowering LDL-C, ApoB and other lipoproteins in homozygous familial hypercholesterolemia.

  Both niacin and mipomersen may reduce Lp(a) by a mean of 20–38 and 26%, respectively.[72,75] However, there is no evidence that this reduction in Lp(a) leads to a reduced risk of ASCVD events. Therefore, these drugs are not recommended for patients with elevated Lp(a).

CONCLUSION

Though Lp(a) was discovered 60 years ago, our knowledge of Lp(a) continues to evolve. It is a biomarker associated causally with ASCVD. However, due to certain important questions being unanswered, international clinical guidelines do not recommend direct reduction of plasma Lp(a) concentrations. In general, the higher the Lp(a) level, the greater the average risk for CVD but optimal cutoffs remain elusive. Lp(a) levels < 30 mg/dL are considered optimal, with negligible Lp(a)-mediated risk. Lp(a) levels < 50 mg/dL are recommended as optimal by EAS. Lp(a) needs consideration to be incorporated in future CVD algorithms. Specific therapies are being developed to prove that reducing the genetically elevated Lp(a) levels may reduce the risk of CVD and CAVS.

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CHAPTER 41

Prevention of Atherosclerosis in Childhood and Adolescents

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ABSTRACT

Exposure to cardiovascular (CV) risk factors (obesity, dyslipidemia, arterial hypertension, diabetes, smoking, and unhealthy lifestyle) in children and adolescents leads to the development of early preclinical atherosclerosis and subsequent premature CV events in adulthood. Nonpharmacological interventions of lifestyle counseling in childhood and adolescence have shown modest benefits of CV risk markers and on CV health. The development of atherosclerosis may be prevented by optimization of apolipoprotein B-containing lipoproteins (low-density lipoprotein-cholesterol) in plasma and keeping them in physiological range from an early age. Dyslipidemia should be investigated in individuals of pediatric age group who have a positive family history of premature cardiovascular disease, familial dyslipidemia, or fall in clinical situations of secondary dyslipidemia. Statins have been successfully used to treat children with familial hypercholesterolemia (FH), and emerging data indicates the prevention of atherosclerosis in this high-risk group using such strategies.

INTRODUCTION

Atherosclerotic cardiovascular (CV) disease remains the leading cause of both death and disability all over the world. Although CV events caused by atherosclerosis typically manifest at or after middle age, the disease process begins in early life. Cohort studies beginning in early childhood have shown that children exposed to CV risk factors (e.g., dyslipidemia, hypertension, obesity, and smoking) are more prone to developing preclinical atherosclerosis and CV events in adulthood. Although modern CV science has discovered causal risk factors of atherosclerosis, deciphered its natural course, and developed effective means to intervene subsequent events, we are still facing the ongoing global pandemic of atherosclerotic diseases. Atherosclerosis mostly goes undetected for too long and if at all preventive measures are initiated, they either come too late or are inadequate. Unfortunately, the knowledge of the epidemiological and clinical importance of atherosclerosis and its implication is still low, especially when dealing with pediatric patients.[1] Guidelines for primary prevention of CV disease do not address such prevention in childhood or adolescents, a group for which primary prevention should logically hold the most promise.

Identification, prevention, and control of the following risk factors, as early as possible in the life, are expected to reduce the risk of CV disease later in life:

- High blood pressure
- Smoking
- Obesity
- Physical inactivity
- Hypercholesterolemia

HIGH BLOOD PRESSURE

High blood pressure or hypertension is a serious condition in childhood and often goes undetected because it causes no symptoms. Hypertension in children is not a congenital heart disease. It can be primary or secondary. Primary hypertension is mostly due to heredity and therefore, children born into families with a history of high blood pressure need to get regular blood pressure checkups. Secondary hypertension is more common in children, which is a result of other diseases involving the heart, kidney, renal arteries, or endocrine in nature.

Hypertension is diagnosed with blood pressure readings correlated with the child's age, sex, and height.

Treatment of hypertension in childhood involves the following measures:

- Maintaining a healthy body weight. Children who are overweight usually have higher blood pressure than those who are not.
- Increasing their physical activity
- Limiting salt intake
- Ceasing cigarette smoking

Pharmacological intervention is only taken once these steps do not reduce the blood pressure. The investigation and treatment of secondary causes of hypertension are also necessary in children and adolescents.

SMOKING

According to the worldwide data, nearly 25% of high school students use some kind of tobacco product, and nearly 4,000 kids under the age of 18 years try their first cigarette every day. About 9 out of 10 smokers start smoking before they finish their graduation. As per literature, children who stay smoke-free in school may never smoke. Among young people who otherwise have a very low risk of heart disease, cigarette smoking can cause as many as 75% of the cases of heart disease.

Smoking is the single most preventable cause of heart diseases in children and adolescents.

It causes atherosclerosis, tachycardia, and tachyarrhythmias. The chemicals in cigarette and tobacco smoke lead to atherosclerosis and later plaque rupture, causing acute coronary syndrome at a young age.

Nicotine can also lead to raised fibrinogen levels, which can result in hypercoagulability and thrombus formation, leading to acute myocardial infarction and thromboembolic phenomena. Cholesterol levels are raised secondary to tobacco and smoking. This rise in hypercholesterolemia can lead to acute coronary syndrome.

Management of Cessation of Smoking

- Children and adolescents should be explained and counseled regarding the adverse effects of smoking (cardiac abnormalities).
- Explain to them how smoking can damage the lungs and reduce the supply of oxygen, thus leading to their inability to play sports.
- Dangers and consequences of smoking should be an open discussion between parents and children.
- Compliment teens who do not smoke.
- Being a role model for your child helps. If any parent smokes, then he/she should quit. Also, do not allow others to smoke in your home.
- Explain and advise them on how to quit; be helpful, motivating, and supportive.
- Help them figure out the reasons why they should quit, such as lowering their chances of heart attack, stroke, or cancer, and improvement of quality of life.

OBESITY

Obesity is one of the major risk factors of heart disease. Obesity in children is rampant and has become a major problem in recent times. There has been a sharp rise in obesity-related problems such as type 2 diabetes mellitus, which can be attributed to the present sedentary lifestyle and food habits. Obese children are more likely to grow to be obese adults; thus, preventing or treating obesity in childhood may reduce the risk of adult obesity. In turn, this helps reduce the risk of heart disease, diabetes, and other obesity-related diseases.

When determining body fat in children and teens, body mass index (BMI) provides a guideline based on weight and height to determine underweight and overweight. Assessing BMI depends on the child's age because as children grow, the amount of body fat they have changes. Also, girls and boys will have different amounts of body fat as they grow, so age-specific and sex-specific charts are used to plot children's BMI.

Obesity in young children may be primary or secondary. Primary causes may be due to sedentary lifestyle and dietary habits. Secondary causes of obesity are secondary to an underlying medical condition or endocrine disorder. Lifestyle modifications are essential for the management of obesity. The following may be helpful:

- Control portions of food and have them eat fewer calories.
- Limit junk food and be aware of the snack foods being consumed.
- Keep tabs on the school food and midday meal for obese children.
- Monitor the quantity of meal of the child.
- Increase their physical activity.
- Limit the amount of sedentary time for the child—watching TV and playing on the computer.

Childhood obesity is usually hard to manage because often, even after a healthy body weight is achieved, the child may go back to their old habits and become obese again. The child needs to review a constant diet and exercise plan, which maintains and reiterates reasonable weight loss goals and lifestyle changes.

PHYSICAL INACTIVITY

Active children usually grow up to be active adults. Physical activity not only prevents heart disease but also leads to the prevention of risk factors that are responsible for coronary heart disease (CHD).

- Physical activity helps control weight.
- Regular exercise leads to better and stronger bone development.
- Exercise improves the child's physical and mental health.
- Exercise lowers blood pressure, increases high-density lipoprotein (HDL), reduces stress levels, and improves CV health.

The American Heart Association advises that all children 5 years and older should get at least 60 minutes of exercise every day. This should include a mix of moderate- and high-intensity activities. It can be achieved by:

- Reducing sedentary activities
- Increasing outdoor and aerobic activities such as playing sports
- Enrolling the child into sport activities which suit his/her interests
- Creating family outings that involve some type of physical activity

DYSLIPIDEMIA IN CHILDHOOD AND ADOLESCENCE

Dyslipidemia is one of the major underdiagnosed and untreated risk factors of heart disease in children. Numerous studies worldwide[2,3] have established that the atherosclerotic process begins at the fetal age. Long-standing exposure of vascular bed to raised low-density lipoprotein cholesterol (LDL-C) levels accelerates the deposition of cholesterol in the vessels, leading to vascular inflammation, atherosclerosis, and finally premature CHD.[4] This has been demonstrated in the Bogalusa heart study[5] and the pathobiological determinants of atherosclerosis in youth (PDAY) study.[6] As both the levels of LDL-C and the duration of exposure to LDL-C are determinants of the risk, the concept of LDL burden has been developed (g/dL × number of years). Once the LDL burden limit has been reached, the probability of atherosclerotic heart disease is high[7] **(Fig. 1)**.

Hence, early detection and treatment of hypercholesterolemia in children and adolescents in terms of lifestyle modifications, healthy eating habits, and pharmacological intervention[7,8] can lead to reduced LDL burden and prevent premature atherosclerosis.

Dyslipidemia in childhood can be primary or secondary. Primary form of dyslipidemia, or familial hypercholesterolemia (FH), is usually an autosomal dominant disorder[7] and is caused by different gene mutations. These mutations cause either absent or nonfunctional LDL receptors (LDL-R) on the hepatocyte surface, leading to an ineffective LDL clearance, increase of LDL-C in the blood, and its accumulation in the vascular wall.[7,9] Various mutations in the apolipoprotein B encoding gene (*APOB* gene) and in proprotein convertase subtilisin/kexin type 9 (*PCSK9* gene) can lead to FH. A rare recessive form of FH can be due to the mutations of the *LDL-R adaptor protein 1* gene.[9]

Homozygous FH (HoFH) is a rare disease, whereas heterozygous FH (HeFH) is a common disorder (1 in 200–250 of the general population).[7]

Secondary forms of dyslipidemia can be caused by exogenous or endogenous factors.[10] Exogenous causes include drug therapies (corticosteroids, isotretinoin, beta-blockers, some oral contraceptives, and some chemotherapeutic and antiretroviral agents), alcohol abuse, and excessive intake of saturated fatty acids.[10] Endogenous causes are due to endocrine, renal, infectious, inflammatory, and cardiac diseases.

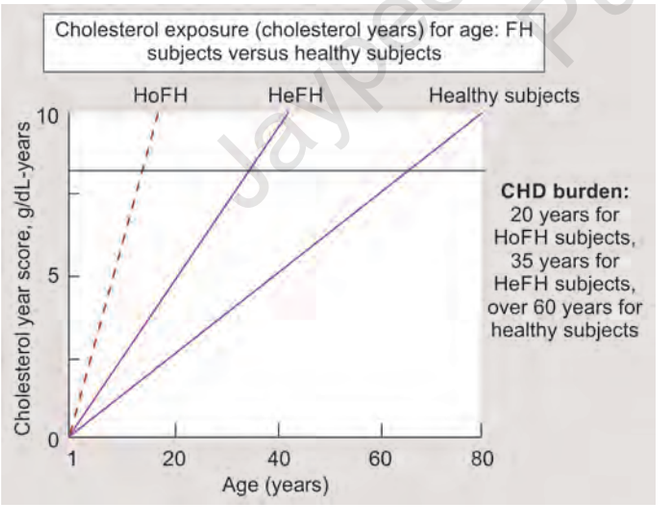

FIG. 1: Cholesterol exposure per year and correlation with age onset of CHD.

(CHD: coronary heart disease; FH: familial hypercholesterolemia; HeFH: heterozygous familial hypercholesterolemia; HoFH: homozygous familial hypercholesterolemia)

Source: Modified from Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, et al. Familial hypercholesterolemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Hear J. 2015;36:2425-37.

Detection of Hypercholesterolemia in Childhood and Adolescence

Early detection of hypercholesterolemia in children is very important in order to identify subjects at high CV risk.[11-13] Public awareness regarding this needs to be addressed. Screening should be initiated in the offspring of parents with a history of coronary artery disease (CAD) at a younger age and this should be started as early as 10 years of age.[12]

Following are the different strategies recommended from time to time for screening of FH in children and adolescents:

- *Universal screening*: Population screening for a specific age group
- *Selective screening*: Screening for a specific (high-risk) population
- *Cascade screening*: From an index case (parent) to family members (including children)
- *Reverse screening*: From an index case (child/adolescent) to other family members
- *Child–parent screening*: From children screened at a specific age to parents

Diagnosis of Hypercholesterolemia in Childhood and Adolescence

Familial hypercholesterolemia may be suspected in children in three situations:

1. A child from a family where HeFH has been identified or suspected (clinical/genetic criteria)
2. A child from a family with a history of premature (before age 55 years in men and 60 years in women) CHD
3. A child from one or both parents displaying primary hypercholesterolemia

According to the Dutch lipid clinic criteria and the Simon Broome criteria for diagnosing FH:[13]

- Any child with LDL-C >190 mg/dL on two consecutive occasions has a high probability of FH.[7]
- An LDL-C >160 mg/dL in a child with a family history of premature CHD in a close relative and/or baseline high cholesterol in one parent indicates a high probability of FH.
- If the parent has a genetic diagnosis of FH, an LDL-C >130 mg/dL in the child suggests FH.[7]

Deoxyribonucleic acid (DNA) testing is the gold standard of the diagnosis. When a pathogenic *LDL-R* mutation is found in a first-degree relative, children and/or adolescents should also be genetically tested.

In case of a parent's death for CHD, a child with hypercholesterolemia (even if mild) should be tested genetically for FH and lipoprotein(a) [Lp(a)] levels should be assayed.

All children above the age of 5 years should be offered testing if a parent is identified with FH.[7] LDL-C levels should be measured at least twice over 3 months in a fasting state to ascertain the diagnosis.[14]

The optimal window for screening is between 2 and 10 years of age. A dietetic treatment is not advisable before 2 years of age, as lipid restriction may lead to brain and development delays.[15,16]

Risk Stratification

In cases with FH, life-long elevation of LDL-C imposes a significantly higher risk of premature CHD (20-fold) as compared to acquired hyperlipidemia in midlife. Other predictor variables to increase the risk may be genetic risk scores, clinical/biochemical and inflammatory markers,[17] and imaging parameters [intima-media thickness (IMT), coronary artery calcium score].[18,19] However, traditional CV risk factors and history of premature CHD continue to be most practical predictors of CHD risk.[7,15]

Risk assessment also consists of cholesterol and triglyceride levels and can be divided into acceptable, borderline, and high **(Table 1)**.[10]

Management of Hypercholesterolemia in Childhood and Adolescence

At least 6 months of dietary and lifestyle treatment are needed before starting any possible pharmacological treatment.

Any dietary intervention should be tailored around the child's nutritional needs.

Children must receive enough macronutrients and micronutrients to maintain physical and neurological development and should not follow the same diet as their parents. Thus, nutritional advice for children with hypercholesterolemia must be planned by an expert pediatric lipidologist and nutritionist.

Nutritional Habits

The child and his or her family must understand the best nutritional habits, keeping in mind to maintain healthy growth as well. A low-lipid diet is recommended with daily cholesterol intake of lower than 200 mg and limitation of saturated fatty acids, which should account for energy intake lower than 10% of total daily calories.[7]

Mediterranean diet is an ideal model in children, a weekly intake of fish, legumes, fruits, and vegetables; low intake of salt; use of low-fat oil; and putting a strong limitation to fried foods. The ideal diet should have the following characteristics:[20] 12–14% of total daily calories from proteins, with an animal/vegetable protein ratio of 1:1; 55–60% of total energy intake from carbohydrates; and 25–30% of total daily calories from lipids. Food intake should be ideally divided into five meals: breakfast, lunch, dinner, morning break, and afternoon break with calories intake as follows: 20% from breakfast and morning break, 40% from lunch, 10% from afternoon break, and 30% from dinner.

No lipid restriction is recommended for children below 2 years of age.

TABLE 1: Cholesterol and triglyceride levels considered as acceptable, borderline, or high in childhood.

	Acceptable	Borderline	High
Total cholesterol (mg/dL)	<170	170–199	≥200
LDL-cholesterol (mg/dL)	<110	110–129	≥130
Triglycerides (mg/dL)			
0–9 years	<75	75–99	≥100
10–19 years	<90	90–129	≥130
Non-HDL cholesterol	<120	120–144	≥145
HDL-cholesterol	≥45	40–44	<40

(HDL: high-density lipoprotein; LDL: low-density lipoprotein)

Nutraceuticals

Nutraceuticals may be considered for a short period, together with nutritional treatment. Few studies suggest that alimentary fibers, such as psyllium, glucomannan, guar gum, and oats, can lower total cholesterol and LDL-C levels.[21,22] The use of phytosterol (1–2 g/day) can reduce the total cholesterol levels in children with mild hypercholesterolemia and in children with FH, but long-term safety has been questioned. Other nutraceuticals that have been tested in children include red yeast rice,[23,24] omega-3 and omega-6 long-chain polyunsaturated fatty acids,[25] soy proteins,[26,27] and probiotics.[28] Red yeast rice can lower LDL-C levels, inhibiting hepatic cholesterol metabolism.[23,24] Omega-3 long-chain polyunsaturated fatty acids, in particular docosahexaenoic acid, act in improving the quantitative level of HDL-C and reducing triglyceride levels.[25] Soy protein has a lipid-lowering effect by blockage of bile acid and/or cholesterol absorption, as well as the stimulation of LDL-R.[26,27] Probiotics can reduce blood cholesterol levels by production of short-chain fatty acids that can interfere with cholesterol biosynthesis and increase in bile acid excretion.[28]

Lifestyle Modifications

An adequate amount of physical activity and sport is essential for the treatment of patients with hypercholesterolemia. Secondary causes of CHD risk, such as cigarette smoking, obesity, diabetes, and hypertension, should be eliminated.

Initiation of these adequate lifestyle approaches early in childhood can lead to the possibility of continuation in adult life.

Pharmacological Intervention

In the present era, statin therapy is the main pharmacological treatment for hypercholesterolemia. It has been proven to be safe and effective. Simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, and rosuvastatin are approved in children in Europe and the United States. In the United States, pravastatin can be used from 8 years of age, whereas all other mentioned statins can be used from 10 years of age. In Europe, the use of rosuvastatin has been approved in children from 6 years of age.[29,30] The targets during statin treatment can be

either maintaining LDL-C levels <130 mg/dL from 10 years of age or reducing 50% of pretreatment cholesterol levels in children aged between 8 and 10 years.[7] Reaching these targets may require ezetimibe or bile acid sequestrants to be added to the statin therapy.[11,31]

Ezetimibe acts with a selective inhibition of intestinal cholesterol absorption and is approved in children starting from 10 years of age; it is usually well-tolerated and has a few side effects.

Bile acid sequestrants have been the only possible pharmacological treatment for hypercholesterolemia in childhood for many years. However, they have significant gastrointestinal (GI) adverse effects such as diarrhea, abdominal pain, and nonpalatability and hence, compliance is very low.

In severe cases, especially in HoFH, LDL-apheresis is an option and can be started from 2 years of age.

Lomitapide and mipomersen are two new recently approved drugs for HoFH therapy.

Lomitapide is an oral drug that inhibits microsomal triglyceride transfer protein.

Mipomersen is a subcutaneous drug that binds to the messenger ribonucleic acid (RNA) encoding for APOB-100, preventing its translation.[7]

Human monoclonal antibodies PCSK9 inhibitors (alirocumab, evolocumab, and bococizumab) represent a novel group of anticholesterol drugs,[7] which lower both LDL and Lp(a) levels.[7]

In clinical practice, pharmacological therapy for hypercholesterolemia in pediatric patients must be discussed with the patient and parents in great detail as parents often find it difficult to accept it, especially for young children.

Follow-up of Treatment of Pediatric Dyslipidemia

Clinical evaluation should be done every 6 or 12 months, to monitor adherence and tolerance to nutritional, lifestyle, and pharmacological therapies and more importantly to monitor growth of the child. Though statin adverse effects are rare in pediatric age, myopathies and hepatotoxicity have been reported. Thus, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine phosphokinase (CPK) should be checked before starting treatment and then periodically at every visit.[32]

As in adults, the highest reduction in LDL occurs at the lowest dose of statins,[33] the use of high dose of statins in children may be avoided and should only be initiated if essential in very high-risk situations such as HoFH.

Pediatric patients with very high LDL or with adverse effects of drugs, multiple CHD risk factors, and/or HoFH should be followed up in a specialized lipid center.

Summary: Recommendations for Management of Children and Adolescents with HeFH

- HeFH must be diagnosed as early as possible so as to "gain decades of life."
- A late diagnosis of FH leads to a considerable reduction in the duration and quality of life.
- Genetic diagnosis of FH is important for awareness of the early start of the atherosclerotic process in order to obtain a greater adherence to the therapy and as an important knowledge for future offsprings.
- Positive family history for premature CHD is a very important risk factor, but it fades out if a prompt and adequate treatment is started. Analyzing family history for CHD including second-degree relatives may be a good suggestion.
- Clinical signs and symptoms of HeFH are not common in pediatric ages, except for Achilles tendon pain.
- Nutritional and lifestyle treatment must be started in the earliest stages of life and must be well established before puberty.
- Smoking habit must be strictly discouraged.
- In case of HeFH, statin therapy is available from 8 years of age. For patients with HoFH, statin therapy must be started as early as possible.
- Statin therapy lasts lifelong; therefore, it is important to stress its safety, both for clinical health and for therapy adherence.
- Therapy should be started as early in girls as in boys, considering that statin therapy must be discontinued in case of pregnancy and/or lactation.
- If therapeutic target is not reached, adding a second pharmacological treatment might be necessary.

Long-term Care for Pediatric Population with Dyslipidemia

Optimal long-term care of children and adolescents with dyslipidemia requires a multidisciplinary approach consisting of a dietician, lipidologist, pediatrician, gynecologist, and cardiologist.[11,12] Education starting from the early stages of childhood emphasizing on regular nutritional and lifestyle changes will go a long way to obtain and maintain a long-lasting compliance,[32] along with a reduction of other risk factors of CHD. Female adolescent patients must be informed that oral contraceptives can cause an increase in LDL-C and triglyceride levels, leading to a prothrombotic action. Statins can be teratogenic. Therefore, when planning a pregnancy, statin therapy should be ideally stopped 3 months before conception and during pregnancy and lactation.[33,34] Thus, a planned network approach connecting all professionals involved in the management and treatment of children with dyslipidemia is essential.

CONCLUSION

- Cohort studies beginning in childhood have revealed that exposure to CV risk factors (obesity, dyslipidemia, arterial hypertension, diabetes, and unhealthy lifestyle) in children and adolescents leads to development of preclinical atherosclerosis and subsequent CV events in adulthood.
- Nonpharmacological interventions of lifestyle counseling in children have shown modest benefits of CV risk markers and on CV health in children and adolescents.
- The development of atherosclerosis may be prevented by optimizing APOB-containing lipoproteins in plasma

and keeping them in a physiological range from an early age. Dyslipidemia in particular should be investigated in the pediatric age group that has positive family history of premature CVD, familial dyslipidemia, or fall in clinical situations of secondary dyslipidemia.

- Statins have been successfully used to treat children with FH, and emerging data indicates prevention of atherosclerosis in this high-risk group using such strategies.
- In high-risk pediatric group other than FH, consensus on effective pharmacological strategies is yet to be established.

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CHAPTER 42

Management of Dyslipidemia in Statin Intolerance

Manu Gupta, Rajeev Gupta, Nitesh Arora, Anuj Gupta

ABSTRACT

Lipid-lowering therapy is important for secondary prevention of cardiovascular disease (CVD) as well as for primary prevention for those at increased risk. Dyslipidemia, especially increased low-density lipoprotein cholesterol (LDL-C), is a strong atherosclerotic (CVD) (ASCVD) risk factor. Lowering LDL-C has remarkable cardiovascular benefits. 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase inhibitors (statins) have been the main LDL-C lowering drug. Statins became the implacable first-line treatment against atherogenic dyslipidemia. Adverse effects of statins may limit their use in certain patients. Patients with familial hypercholesterolemia, which results in an extremely high level of LDL-C, and patients who are intolerant or unresponsive to statins are other hurdles of statin treatment. Various new classes of drugs that target different steps of lipid production have been developed to treat hyperlipidemia. The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor increases the expression of low-density lipoprotein (LDL) receptor in hepatocytes by enhancing LDL receptor recycling. The microsomal triglyceride transport protein (MTP) inhibitor and antisense oligonucleotide (ASO) against apolipoprotein B (APOB) reduce the APOB-containing lipoprotein by blocking the hepatic LDL synthesis pathway. The apolipoprotein A1 (APOA1) mimetic peptides pursue the beneficial effect of high-density lipoprotein cholesterol and can reverse the course of atherosclerosis.

INTRODUCTION

Dyslipidemia leading to atherosclerotic cardiovascular disease (ASCVD) is a major risk factor. Statins are the benchmark drugs of modern medicine, which have proven to decrease cardiovascular (CV) morbidity and mortality when used for primary and secondary prevention. These drugs act by inhibiting the 3-hydroxy-3-methylglutarylcoenzyme (HMG-CoA) reductase enzyme and decreasing cholesterol synthesis, and are metabolized via hepatocytes through cytochrome P450 isoenzymes (except for rosuvastatin and pitavastatin, which are minimally metabolized by cytochrome P450). Statin-related adverse events are thought to arise because of multiple genetic predispositions, including P450 isomerism, drug–drug interactions, vitamin D levels, and immune effects, leading to increased inhibition of HMG-CoA reductase and its cellular and subcellular effects. This chapter aims to focus on the management of dyslipidemias in the subjects of statin intolerance. There are two main approaches that are currently available:

1. Elevation of high-density lipoprotein cholesterol (HDL-C) directly with cholesterol ester transfer protein (CETP) inhibitors
2. Promotion of the reserve cholesterol transport pathway, e.g., infusion of apolipoprotein A1 (APOA1) containing recombinant high-density lipoprotein (HDL) particles or lipid-poor HDL particles[1]

DEFINITIONS AND DIAGNOSTIC CRITERIA FOR INTOLERANCE TO STATIN THERAPY

Various definitions define statin intolerance **(Box 1)**.

PREVALENCE OF THE PROBLEM

Identifying patients who are truly statin intolerant is important to reduce unnecessary discontinuation of therapy in patients who can benefit from avoiding the subsequent increase in CV risk. While the benefits and safety profile of statin therapy

BOX 1 Definitions of statin intolerance.

- Statin intolerance can be defined as any adverse event (AE) considered unacceptable by the patient, and/or some laboratory abnormalities, both attributed to statin treatment and leading to its discontinuation[2]
- Inability to tolerate at least two statins, one at the lowest starting daily dose and another at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal laboratory analysis, temporally related to statin treatment, reversible upon statin discontinuation, reproducible by rechallenge (restarting medication), and excluding other known factors[3]
- Inability to tolerate at least two statins at any dose or increasing doses, and symptoms are not attributable to drug–drug interactions or conditions known to increase statin intolerance. Symptomatic criteria are intolerable muscle symptoms (pain, weakness, or cramps with or without creatine kinase changes) or severe myopathy, and they must appear in the first 12 weeks after initiating treatment or dose increase. Symptoms must improve or disappear within 4 weeks of statin discontinuation[4]

are clear, adverse effects such as statin-related myopathy remain elusive, posing diagnostic and therapeutic challenges. Statin intolerance is widely reported in clinical practice, often leading to its discontinuation. The major symptoms associated with statin intolerance include muscle symptoms including myalgia, myopathy, myositis, and myonecrosis, (collectively known as statin-associated muscle symptoms).[5] Other statin-related symptoms that affect the quality-of-life of a patient include headache, dyspepsia, nausea, alopecia, and erectile dysfunction.[6] The prevalence of statin intolerance was found to be 9.1%. Age, female gender, diabetes mellitus, obesity, hypothyroidism, chronic liver disease, and renal failure were significantly associated with statin intolerance.[7] In a retrospective study, it was noted that among patients with myocardial infarction (MI) who were put on statin therapy, around 1.65% were found to be statin intolerant, with a higher rate of recurrent MI (hazard ratio 1.5) compared to statin adherent beneficiaries.[8] Muscular symptoms were reported by 10.5%, in the PRIMO statin study with a median time of onset of 1 month following initiation of statin therapy. Muscular pain prevented even moderate exertion during everyday activities in 38% patients, while 4% were confined to bed or unable to work.[9]

MANAGEMENT OF DYSLIPIDEMIAS IN STATIN INTOLERANCE

The management of dyslipidemias in statin-intolerant patients required a step-care approach. The approaches are elevation of HDL-C directly or promotion of the reserve cholesterol transport pathway.[1] Before trying the above approach, switching with other statin or alternative daily dose has also proven beneficial.

Switching the Therapy

Switching to a different statin, which is metabolized using a different enzyme pathway, can be tried. However, there are no set guidelines regarding switching to other statins. Evidence of switching to a non-cytochrome P450 statin comes from a pilot study[10] in which rosuvastatin was used in patients unable to tolerate other statins in the dose of 5 mg and 10 mg with a median 44-week follow-up. The follow-up showed a modest decrease in low-density lipoprotein cholesterol (LDL-C) levels, without an increase in liver enzymes and discontinuation of the drug only in 1 out of 61 patients due to severe muscle symptoms.

Alternate-day Dosing

Statins with a longer half-life allow an alternate-day dosing schedule, which has shown a considerable decrease in symptoms as well as significant lipid-lowering. Atorvastatin breaks down into two active metabolites with a half-life ranging from 20 to 30 hours, making it suitable for alternate-day dosing. An Indian study[11] compared daily dosing to alternate-day dosing of atorvastatin 20 mg for 12 weeks and concluded that there was no significant difference between the reductions in LDL-C levels amongst the two groups. However, symptoms related to intolerance were not evaluated in this study. Similarly, rosuvastatin has a half-life of 19 hours, which can be used for alternate-day dosing. When tested in patients intolerant to other statins, 72.5% of them tolerated the alternate-day regimen (mean dose 5.6 mg) for 4 ± 2.9 [mean ± standard deviation (SD)] months, with a mean reduction in LDL-C of 34.5% ($p < 0.001$) in the patients who tolerated the regimen, enabling approximately 50% to achieve LDL-C goal. However, 27.5% patients re-experienced the symptoms of intolerance during alternate-day regimen.[12]

Ezetimibe

Ezetimibe acts by inhibiting Niemann–Pick C1-Like 1 (NPC1L1) receptor and prevents the absorption of cholesterol from the small intestine, reducing the LDL-C levels from 15 to 22% as monotherapy or in combination with statins. Ezetimibe can be tried along with lower doses of statin, which can reduce the intolerance while providing extra advantage, or as a monotherapy. Evidence for use in statin intolerance comes from the GAUSS-3 trial[13] and ODYSSEY ALTERNATIVE trial[14] where ezetimibe was used in patients with statin intolerance and reduced the LDL-C to 16.3 and 14.6%, respectively. However, muscle-related symptoms were noted in 41.1 and 28.3% patients in respective trials and 20.2 and 6.8% patients had to stop treatment due to these symptoms.

Proprotein Convertase Subtilisin Kexin Type 9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an important regulator of LDL-C through its role in the regulation of expression of LDL receptors (LDLRs) on the surface of the hepatocytes. PCSK9 binds to the LDLR, leading to its internalization and degradation of the LDLR. Thus, by inhibiting PCSK9, there is an increase in LDLR on hepatocytes with a consequent decrease in circulating LDL molecules. There are two Food and Drug Administration (FDA)-approved PCSK9 inhibitors, alirocumab and evolocumab, available in a prefilled syringe/delivery system. The dose of alirocumab is 75 mg subcutaneously (SC) every 2 weeks or 300 mg SC every 4 weeks, whereas evolocumab can be administered in 140 mg SC every 2 weeks or 420 mg SC once monthly. When compared

with ezetimibe 10 mg daily dosing in patients with confirmed statin intolerance, in GAUSS 3 trial,[13] evolocumab reduced the LDL-C levels to 52.8% (vs. 16.7%) from baseline, had lower muscle-related adverse effects (20.7%), and discontinuation was noted in 0.7% of patients. In the ODYSSEY ALTERNATIVE trial,[14] alirocumab was compared with ezetimibe and decreased the LDL-C levels to 45% from baseline (vs. 14.6% for ezetimibe) whereas muscle-related adverse events were 32.5% (vs. 41.1%) and discontinuation rate was 15.9% (vs. 20.9%).

Microsomal Triglyceride Transfer Protein Inhibitor Lomitapide

Microsomal triglyceride transfer protein (MTP) is predominantly expressed in hepatocytes and enterocytes, whose action is required in the synthesis of apolipoprotein B (APOB)-containing lipoproteins. MTP has a critical role in the synthesis of very-low-density lipoprotein (VLDL) and chylomicrons in the liver and intestine.[15,16] Inhibition of MTP results in the decreased synthesis and secretion of VLDL in the liver by inhibiting the lipidation of APOB.[17] MTP inhibition can reverse the increased hepatic production and secretion of VLDLs caused by insulin resistance. An orally active small molecule inhibitor of MTP, lomitapide has been approved for the treatment of homozygous familial hypercholesterolemia.[17]

Antisense Oligonucleotide against Apolipoprotein B (Mipomersen and Volanesorsen)

Apolipoprotein B is the major structural protein of atherogenic lipoproteins (APOB-containing lipoproteins). It has a key role in the assembly and secretion of VLDL from the liver.[18] Plasma APOB concentration is a reliable index of the total number of atherogenic lipoproteins such as small dense LDL-C.[18] A single-stranded antisense oligonucleotide (ASO) may be used to target the desired messenger ribonucleic acid (mRNA) of interest. This antisense strand is complimentary to mRNA and so it binds with it and prevents the translation of mRNA. Currently, ASO studied in clinical trials includes mipomersen, which inhibits APOB mRNA, and volanesorsen, which inhibits APOC-III.

Mipomersen is a polynucleotide of 20 bases, which binds to a segment of human APOB-100 mRNA as it is complimentary to mRNA, thus blocking the translation of the gene product. Reducing the synthesis of APOB-100 consequently decreases the production of VLDL particles. After VLDL particles' secretion into the circulation, lipoprotein lipase (LPL) and hepatic lipase progressively hydrolyze triglycerides (TGs) within the VLDL particle core, forming intermediate-density lipoprotein particle core and progressively smaller species of lysosomal acid lipase (LAL). Thus, a spectrum of atherogenic APOB-containing lipoproteins is decreased once mipomersen reduces APOB-100 biosynthesis. There is no interaction with statins, ezetimibe, or other lipid-lowering medications with which mipomersen might be used in combination, as it does not depend on cytochrome p450 for metabolism.[19] Mipomersen 200 mg SC once a week was assessed in different patient populations, which showed reduction in all APOB-containing lipoproteins. A meta-analysis of eight randomized controlled trials (RCTs) has shown that with mipomersen, mean LDL-C was reduced by about 32%. In the same meta-analysis, it was seen that mipomersen increased the risk of injection site reaction and flu-like symptoms. However, the most important adverse effects are transaminitis and hepatic steatosis. Mipomersen is known to cause accumulation of fat in the liver by its unique mechanism of action; because it is inhibiting APOB, TG-rich fats are accumulated in the liver. Because of the increased risk of hepatic enzymes and hepatic steatosis, mipomersen is approved only for homozygous familial hypercholesterolemia (HoFH). All these trails were small studies with short duration of follow-up. Long-term studies to assess the safety and efficacy of mipomersen are lacking.[20]

Volanesorsen is an ASO-targeting APOC-III mRNA that is critical in the regulation of TG-rich lipoproteins' clearance. Volanesorsen reduced plasma TGs by 70% and APOC-III by 80–90%.[21,22]

Apolipoprotein A1 Mimetic Peptides

High-density lipoprotein cholesterol is a protective factor of ASCVD.[23] APOA1 is designed to mimic the effect of APOA1 and HDL-C to reverse the progression of atherosclerosis.[24] APOA1 is a component of mature HDL that takes cholesterol from macrophages in atherosclerotic lesions via ATP-binding cassette A1 (ABCA1), triggering reverse cholesterol transport. For modifying ASCVD risk, APOA1 in comprising HDL-C makes it as an attractive target.

Small Interfering RNA that Inhibits Translation of the Protein PCSK9 Inclisiran

Inclisiran acquired FDA approval in December 2021 as an add-on drug in cholesterol-lowering therapy.

Dose: 284 mg on day 1, day 90, and every 6 months thereafter as a subcutaneous injection.

Currently, only injection site-related adverse events have been reported; the current Phase III trials ORION 10[14] and ORION 11[25] have noted a 52.3% and 49.9% reduction in LDL-C from baseline. This is a promising molecule with 3-monthly and 6-monthly dosing. However, safety aspects and effects on CV morbidity and mortality are yet to be determined. Inclisiran is a double-stranded RNA complex, which has both sense and antisense strands. Once it is delivered into the hepatocytes, the antisense strands bind with RNA-induced silencing complex. This complex then binds with PCSK9 mRNA, leading to its degradation. As a result, less PCSK9 protein is formed. Due to less PCSK9, more LDLRs can be recycled to the hepatic membrane for LDL-C uptake.[26]

The ORION Phase III studies have evaluated the safety as well as efficacy in heterozygous familial hypercholesterolemia (HeFH); ORION-10 and -11 are in ASCVD or ASCVD risk-equivalent patients. In all these trials, patients were already on maximally tolerated statins with or without ezetimibe. The regimen that they used in these trials was 300 mg of inclisiran given SC at day 1, after 3 months, and every 6 months thereafter. In all these trials, inclisiran reduced LDL-C significantly and this reduction was sustained for a prolonged period. LDL-C was reduced by about 40% in ORION-9, 52% in ORION-10, and 50%

in ORION-11. Injection site reactions were more in inclisiran arm in all the trials; other adverse effects were similar compared to the placebo.[25]

Ongoing ORION-5 trial is assessing the efficacy of inclisiran in HoFH, while ORION-4 trial is assessing the CV outcomes with inclisiran.

ATP Citrate Lyase Inhibitor Bempedoic Acid

This novel nonstatin drug inhibits cholesterol biosynthesis in the same pathway as statins, just two steps upstream. Bempedoic acid acts by inhibiting ATP citrate lyase—the enzyme involved in cholesterol biosynthesis. It is an oral pro-drug converted to active metabolite bempedoic acid coenzyme A (CoA) only in the liver but not in muscles. Because the active metabolite is generated by the activity of acyl-CoA synthetase-1 and this enzyme is present only in the liver, theoretically this drug is free from muscle-related side effects because of its unique site of action.

With a daily dose of 180 mg at 12 weeks in the Phase III trial, bempedoic acid reduced LDL-C by 16% from baseline, and adverse events including hyperuricemia (2.1% vs. 0.5%), gout (1.4% vs. 0.4%), decreased glomerular filtration rate (GFR) (0.7% vs. <0.1%), and increased levels of hepatic enzymes (2.8% vs. 1.3%) were noted as compared to the placebo.[27]

Four Phase III trials—CLEAR tranquility, CLEAR serenity, CLEAR wisdom, and CLEAR harmony—assessed different patient populations. In all these trails, bempedoic acid was used at a dose of 180 mg once-a-day tablet. Bempedoic acid reduced LDL-C in all these trials either as monotherapy or in various combinations with statins and ezetimibe, but more reduction in LDL-C was seen patients who were not on statin or on only low-intensity statin therapy. Bempedoic acid also reduced total cholesterol, non-HDL-C, APOB, and high-sensitivity C-reactive protein (hsCRP).[27]

Importantly, the occurrence of muscle-related symptoms was similar compared to the placebo group in all the trials. In the CLEAR Harmony trial, new-onset diabetes or worsening hyperuricemia was less in bempedoic acid arm, whereas gout and hyperuricemia were more in bempedoic arm. There was a slightly increased risk of tendon disorders in patients with chronic kidney disease, those taking corticosteroids or fluoroquinolone drugs, and patients aged >60 years. After the initiation, bempedoic acid transiently reduced GFR; thereafter, it improved gradually.[27]

Though bempedoic acid showed efficacy in reducing LDL-C, the effect of this drug on CV morbidity and mortality is yet to be determined. CLEAR-outcomes trial is an ongoing Phase III trial that is seeking to bridge this knowledge gap by assessing the effect of the acid on major CV events.

Nutraceutical Agents

Red Yeast Rice

Red yeast rice is formed by fermenting yeast (*Monascus purpureus*, *Monascus pilosus*, *Monascus floridanus*, *Monascus ruber*, and *Pleurotus ostreatus*) in rice. The red color is due to secondary fermentation and production of red pigments. Fermentation leads to the production of lipid-lowering agents known as monacolins, which amount to 1.9% in red yeast rice. A subtype—monacolin K, which was first isolated by professor Akira Endo and found structurally like lovastatin—acts by inhibiting HMG-CoA reductase. However, the bioavailability of this naturally occurring statin is different, ranging from 5 to 100%. Consumption of red yeast rice in doses of 1,200–4,800 mg (containing 1.2–4.8 mg monacolin K) has proven to reduce LDL-C by 39.4 mg/dL in 2–24 months as compared to placebo, with a small increase in HDL-C and reduction TGs.[28] It can produce similar muscle-related symptoms;[29] however, it is found to be tolerable even in statin-intolerant patients, possibly by differences in bioavailability of the monacolins. Another concern is the presence of citrinin, a mycotoxin metabolite derived from *Monascus* fermentation, which can produce hyperplasia of the renal tubular epithelium, renal adenomas, and sometimes renal tumors if its dose exceeds 50 µg/day. It can also cause reproductive toxicity and certain embryo toxicities. The European Food Safety Agency has set a maximum limit for citrinin to a dose of 20 µg/day.[29] Thus, red rice yeast being beneficial during statin intolerance, its potentially hazardous effects need to be kept in mind during patient selection.

Phytosterols

Phytosterols are cholesterol-like compounds found in foods of plant origin and include plant sterols and plant stanols. It is noted that intake of phytosterols (2 g/day) is associated with a significant reduction (8–10%) in LDL-C. Thus, several guidelines recommend an intake of 2 g/day to reduce the LDL-C levels. Although phytosterols decrease LDL-C levels, their effect on reducing CV diseases remains uncertain.[30]

Recent publications have alerted to another potential deleterious effect of the intake of oxidized phytosterols. Plant sterols (but not stanols, because they are saturated) may oxidate, forming oxidized phytosterols and, similarly to what is observed with cholesterol oxidation, these substances are believed to be atherogenic.[31]

Exercise

Aerobic exercise has been shown to improve the prognosis of cardiovascular disease (CVD). It is defined as any form of physical activity that produces an increased heart rate and respiratory volume to meet the oxygen requirements of the activated muscle. Compared to medications, aerobic exercise is easier to carry out and has fewer side effects. Exercise can have a positive impact on symptoms and physical health.[32] In a prospective cohort study of exercise and lipid metabolism, individuals were grouped by evaluating the peak metabolic equivalents (METs) achieved during the exercise endurance test, adaptation conditions, and different statin treatments. After 10 years, for individuals who took statins, the mortality risk decreased while their fitness increased; the hazard ratio in patients who were highly fit (>9 MET) was 0.3 when compared with those who were least fit (<5 MET). Therefore, the authors concluded that the risk of mortality is significantly reduced when combined with statin therapy and aerobic exercise compared to either method alone, and that aerobic exercise is required for individuals with dyslipidemia.[33]

- *Aerobic exercise and HDL-C*: HDL-C levels are more sensitive to aerobic exercise than both LDL-C and TG.[34]
- *Aerobic exercise and LDL-C*: Unlike HDL-C, the effect of exercise on LDL-C is inconsistent in humans and there are even completely contrary results.[35] LDL-C is classified according to its size and density. Although the current results on the LDL-C response to the aerobic exercise are discordant, studies have still indicated the potential occurrence of important CV-protective improvements in LDL-C subfractions. LDL-C subfractions that directly relate to CV events are smaller, denser LDL particles.[36]
- *Aerobic exercise and TG*: Exercise can induce lower plasma TG concentrations. However, many studies have shown that sedentary individuals have no change in TG levels after a single exercise session.[37]
- *Aerobic exercise and postprandial lipemia*: The finding is that postprandial triacylglycerolemia predicts CV events better than fasting triacylglycerol (TAG) concentrations[38] (Mestek et al.).[39] The postprandial lipid was of more sense in lipid metabolism than fasting state, and it may have a greater role than fasting blood lipids in the prediction of CV risk factors.
- *Aerobic exercise and non-HDL-C*: The mechanism of exercise-induced lipid changes is unclear; exercise itself may increase blood lipid consumption, hence decreasing lipid levels.[40] It is suggested that non-HDL-C was a better indicator of CVD risk than traditional lipids such as HDL-C, LDL-C, and TG. As a predictor of future CV risk, non-HDL-C was more persuasive than LDL-C to some extent. Mechanisms may involve the increased activity of LPL. LPL is responsible for chylomicrons and VLDL–TAG hydrolysis in granules.[41] Most of the catalytically active LPL is located in the vessel wall and then isolated from the endothelium surface and released in the blood after an intravenous injection of heparin.[42] Therefore, the detected LPL is often the postheparin LPL.

CONCLUSION

A significant amount of residual ASCVD risk is remaining even under optimal statin treatment and a significant portion of patients is intolerant or unresponsive to statin therapy. The PCSK9 inhibitor facilitates the uptake of LDL-C by enhancing LDLR recycling. It showed favorable effects for additional lowering of LDL-C when added to statin. The MTP inhibitor and ASO against APOB are reducing APOB-containing lipoprotein. The APOA1 mimetic has been shown to alter or reverse the natural course of atherosclerosis despite the range of LDL-C level in preclinical studies, but the efficacy in clinical studies is modest. For the improvement of anti-atherosclerosis therapy, a new class of drugs shall be beneficial in statin-intolerant patients.

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CHAPTER 43

Coronary Artery Calcification in Risk Stratification of Coronary Artery Disease

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ABSTRACT

Atherosclerosis is the leading cause of coronary artery disease, which is the major killer of modern times. Calcification of the atherosclerotic plaque is a chronic pathological manifestation with varied importance from risk stratification to complexity during an intervention. Coronary artery calcification can be readily evaluated and qualified using computed tomography (CT) scan whereas modern intracoronary imaging modalities, e.g., intravascular ultrasound (IVUS) and optical coherence tomography (OCT), provide vivid imaging and understanding of the distribution of the calcification, which helps in the proper selection of the debulking devices during complex coronary intervention. No specific medical therapy is yet convincingly proved to be significantly beneficial to reduce coronary artery calcification, although statins can reduce the atherosclerotic cardiovascular disease (ASCVD) risk but not the calcium score. Guidelines now recommend the quantification of coronary artery calcium score as an additional risk marker to direct proper risk-reducing medical therapy for better long-term outcomes.

INTRODUCTION

The accumulation of calcium salts in body tissues is known as calcification, which usually occurs in bone formation but the deposition of calcium in soft tissues leads to their hardening and is considered abnormal. Coronary artery calcification (CAC) is the deposition of calcium in the coronary artery. CAC is a risk factor for adverse outcomes in the general population and in patients with coronary artery disease (CAD). CAC occurs when calcium builds up in the plaque found in the walls of the coronary arteries, which supply blood to the heart muscle. CAC is prevalent in patients with coronary heart disease (CHD); it is linked with major adverse cardiovascular events. It symbolizes arteriosclerosis where the arteries that carry oxygen and nutrients from the heart to the rest of the body become thick and stiff, restricting the blood flow to organs and tissues unlike healthy arteries that are flexible and elastic. The calcified arteries are thus thick and stiff.[1]

PATHOPHYSIOLOGY OF CORONARY CALCIFICATION

Coronary artery calcification was formerly understood to be an organized, regulated, benign process similar to bone formation that occurs only when other aspects of atherosclerosis are also present. There are two types of calcifications: (1) metastatic calcification, which occurs in normal tissues in which patients are generally hypercalcemic, and (2) dystrophic calcification, which occurs secondary to injury or necrosis while the patients are usually normocalcemic. The pathological deposition of calcium in vascular structures/arteries is mainly due to inflammation, vascular injury, and repair; this makes it a very important area of study. CAC commences as micro-calcifications and grows into larger calcium fragments, which ultimately result in sheet-like deposits. The spotty calcification is generally linked with unstable plaques and extensive calcification is noted as stable plaque. CAC is associated with the progression of advanced atherosclerosis, which is observed to occur synchronously with the development of plaque.

- *Nonhepatic gamma-carboxyglutamic acid (Gla)-containing proteins (e.g., osteocalcin)*: These are actively involved in the transport of calcium out of vessel walls and are suspected to have key roles in coronary calcification.[2,3]
- *Osteopontin and its messenger ribonucleic acid (mRNA)*: These are involved in bone mineralization and calcified atherosclerotic lesions.
- *mRNA for bone morphogenetic protein 2A*: This is a potent factor for osteoblastic differentiation, and the cells that are capable of osteoblastic differentiation are found in atherosclerotic plaque.

- *Elevated calcium or phosphorus*: Such environmental factors promote apatite nucleation and crystal growth.
- Loss of inhibitors of mineralization mainly promotes medial calcification in animal models, whereas osteogenic mechanisms involving bone-forming proteins, such as osteopontin, collagen type I, osteoprotegerin, and so on, also have been proposed to play a role in calcification.
- Alkaline phosphatase is central to early calcium deposition and has been proposed as a molecular marker of vascular calcification (VC).
- Vascular smooth muscle cells (VSMCs) produce matrix vesicles, which regulate mineralization in the vascular intima and media.
- Other cell types (e.g., microvascular pericytes and adventitial myofibroblasts) have the potential to generate mineralized matrix and undergo osteoblastic differentiation, resulting in calcified deposits.[4]
- *Renin–angiotensin–aldosterone system*: It plays a role in medial artery calcification because angiotensin II type-1 receptor blockers abolished CAC development in a pre-clinical model.
- In diabetic individuals, advanced glycation end products might promote mineralization of microvascular pericytes, and tight glycemic control might slow down CAC in type 1 (but not type 2) diabetes.
- The transcription factor proliferator-activated receptor-gamma might deter calcification by inhibiting Wnt5a-dependent signaling in VSMCs.
- *Osteoprotegerin*: This is the receptor activator of the nuclear factor-kappa B ligand. Its pathway has emerged as a potential link between osteoporosis and CAC. Osteoprotegerin acts as a decoy receptor, which counteracts the pro-osteoclastic and bone-resorptive effects of the receptor activator of the nuclear factor-kappa pathway. Mice deficient in osteoprotegerin experience increased calcification and plaque progression. However, human epidemiologic data suggest that higher osteoprotegerin levels are associated with CAC and cardiovascular events. Further study is required to elucidate the role of this pathway in CAC pathogenesis.

Successively, studies determined that calcification is associated with arterial stiffness, which increases the risk of adverse cardiovascular events.[4] Although other theories of the mechanisms underlying VC have been proposed, some are more clearly relevant to the process of medial rather than intimal calcification. However, actual bone formation inside the vessel wall is rarely observed in human coronary arteries. Although the way in which calcium fragments or sheets are formed is poorly understood, it is believed that the development of calcium sheets stabilizes plaques. The VSMCs can undergo osteogenic transformation into osteoblast-like cells; such changes have rarely been observed in human atherosclerosis.[2,3,5,6] Factors including intraplaque hemorrhage are associated with calcification and may worsen its advancement; further work is needed to understand its mechanism. Overall, calcification patterns vary widely, depending on the location. The peripheral arteries tend to have greater collagen deposition and calcification and show medial calcification in addition to intimal sclerosis. On the other hand, some arterial beds, such as the internal thoracic artery, are reported to be resistant to atherosclerosis and also to calcification.

There are various stimuli in the initiation and progression of calcification, which may differ depending upon the stage of plaque as well as the surrounding milieu. The death of smooth muscle cells (SMCs) is also considered the driving force for early microcalcification. This is followed by the infiltration of macrophages into the lipid pool, which also undergoes cell death and calcification. Cell death provides phospholipid-rich debris that serves to nucleate apatite—a process that starts within lipid pools and progresses with inflammation and further cell death, leading to the development of a necrotic core.

EPIDEMIOLOGY OF CORONARY ARTERY CALCIFICATION

Coronary artery calcification is both age- and gender-dependent; CAC increases with aging, it occurs in over 90% of men and 67% of women older than 70 years.[7] There is a strong racial variation in the degree of CAC, which might underlie important differences in clinical outcomes. The multi-ethnic study of atherosclerosis (MESA) has reported a total of 6,814 whites, African Americans, Hispanics, and Chinese people aged 45–84 years with no history of clinical cardiovascular disease for coronary calcification. The prevalence of coronary calcification (Agatston score > 0) in these four ethnic groups in males was 70.4, 52.1, 56.5, and 59.2% ($p < 0.001$), and in females was 44.6, 36.5, 34.9, and 41.9% ($p < 0.001$), respectively.[4] People with higher body mass index (BMI), higher blood pressure, abnormal lipids (higher low-density lipoproteins or triglycerides, lower high-density lipoproteins or those making use of lipid-lowering medication), glucose disorders (impaired fasting glucose, untreated or treated diabetes mellitus), a familial history of CAC or chronic kidney disease (CKD), or higher fibrinogen and C-reactive protein levels are more susceptible to CAC. However, calcium intake in dietary or supplementary form shows no significant adverse or beneficial effect on VC and cardiovascular endpoints. **Table 1** shows the risk factors for development of CAC.

TABLE 1: Risk factors for coronary calcification.

Risk factor	Intimal calcification	Medial calcification
Advanced age	Yes	Yes
Diabetes mellitus	Yes	Yes
Dyslipidemia	Yes	No
Hypertension	Yes	No
Male	Yes	No
Cigarette smoking	Yes	No
Renal etiology		
Dysfunction-reduced glomerular filtration rate (GFR)	No	Yes
Hypercalcemia	No	Yes
Hyperphosphatemia	Yes	No
Parathyroid hormone (PTH) abnormalities	No	No
Duration of dialysis	No	Yes

TYPES OF CORONARY ARTERY CALCIFICATION

There are two recognized types of CAC—intimal or superficial and medial artery calcification. Friedrich et al. have radiographically mentioned the types of calcification as absent, speckled, fragmented, or diffuse. Further, depending on the plaque morphology, the frequency and degree of calcification vary and thus on the histological basis, Burke et al. have classified calcification associated with atheroma as plaque ruptures, plaque erosion, thin-cap fibroatheroma, fibroatheroma, fibrous plaque, hemorrhage into plaque, and healed plaque rupture.[8,9] Apart from the above, CAC is classified as metastatic calcification that occurs in normal tissues in which patients are generally hypercalcemic and dystrophic calcification, which occurs secondary to injury or necrosis while the patients are usually normocalcemic.[1] Angiographic CAC is often classified into three groups: none/mild, moderate, and severe. Severe calcification is most commonly defined as radiopacities seen without cardiac motion before contrast injection, usually affecting both sides of the arterial lumen; and moderate calcification is defined as radiopacities noted only during the cardiac motion before contrast injection.[10] VC can be classified into two distinct forms, depending on its location within the intima (intimal calcification) or in the vascular medial layer. Medial calcification mostly affects the peripheral arteries of the lower extremities, resulting in the loss of elasticity, and is routinely observed in patients with peripheral vascular disease.[10]

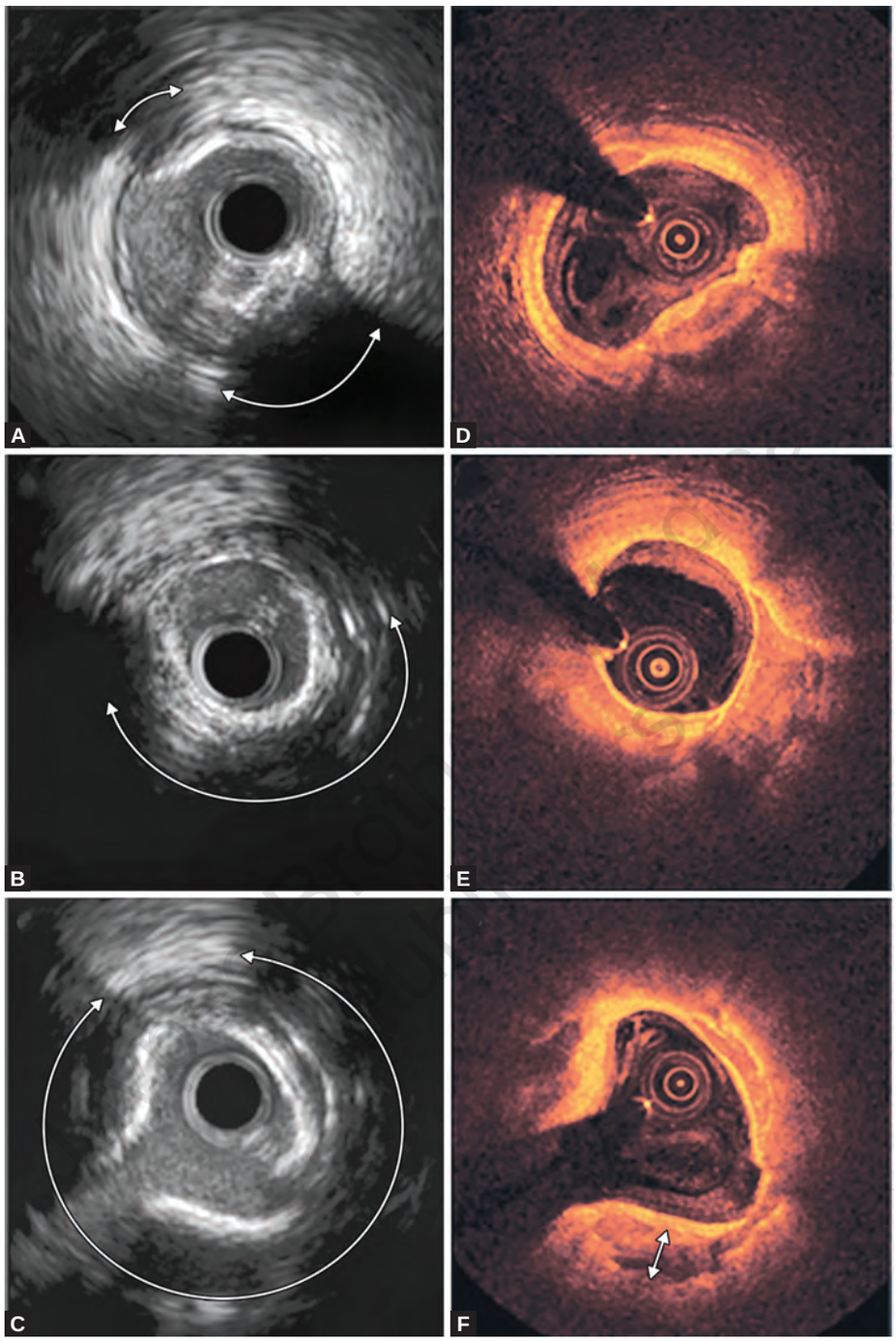
MODALITIES TO DETECT CORONARY ARTERY CALCIFICATION

The fragments and sheets of calcification can be easily identified by radiography as well as by computed tomography (CT) and intravascular imaging. The coronary computed tomography angiography (CCTA) technique is the greatest noninvasive imaging diagnostic utility with the most available correlation and prognostic outcomes' data.[4] Electron beam computed tomography (EBCT) detection of coronary calcification may be a better predictor of angiographic narrowing than thallium and electrocardiogram (ECG) stress testing.[10,11] CT scan-guided CAC estimation is extremely simple, does not require contrast, and lacks machine operator-based variation. Other techniques for determination of CAC include intravascular ultrasound (IVUS) and optical coherence tomography (OCT).[7] IVUS is substantially more accurate than cineangiography for CAC detection, with a sensitivity of 90–100% and specificity of 99–100%. Coronary angiography has low–moderate sensitivity compared with grayscale IVUS and CT for detection of CAC but is very specific (high positive predictive value). CAC CT is a noninvasive biomarker to determine the health of the heart. OCT provides higher resolution imaging (10–20 μm) than grayscale IVUS (150–200 μm). Because light (but not sound) can penetrate the calcified tissue, the thickness of calcification may be evaluated by OCT but not by IVUS. Radiofrequency analysis of the IVUS signal allows for in vivo characterization of coronary plaque components, including fibrotic plaque, fibrofatty plaque, necrotic core, and dense calcium. In the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study in which three-vessel coronary radiofrequency IVUS was performed, patients with the highest dense calcium volumes were more likely to have high-risk atherosclerotic features and had the highest 3-year rates of major adverse cardiovascular events (MACE), although not necessarily arising from the calcified plaque itself **(Figs. 1A to F)**.

The signature of calcified plaque on grayscale IVUS is a bright echo with acoustic shadowing, and the extent of calcification can be graded by several metrics. The arc of calcium is classified as none, one quadrant (0°–90°), two quadrants (91°–180°), three quadrants (181°–270°), or four quadrants (271°–360°). Calcium location is defined as superficial if present in the intimal–luminal interface, deep if present within the medial–adventitial border or closer to the adventitia than the lumen, or both superficial and deep. Deposits can be assessed relative to the thickest plaque accumulation as concordant (center of calcium arc ≤ 45° of thickest plaque accumulation), perpendicular (center of calcium arc 45°–135° from thickest plaque accumulation), or opposite (center of arc of calcium ≥ 135° from thickest plaque accumulation). Further, IVUS can measure the calcium length. Virtual histology in IVUS is an interesting research modality that can characterize the atheroma components, namely lipid, fibrous, necrosis, hemorrhage, and calcification **(Figs. 2A and B)**. However, because ultrasound does not penetrate calcium, calcium thickness cannot be determined and volume cannot be calculated. The limitation of IVUS for the detection of changes in calcium makes it less than ideal as a tool to monitor calcium progression or regression. OCT, on the other hand, has the ability to image beyond calcium. CAC cannot be detected well and quantified in cardiac magnetic resonance imaging (CMRI) due to the motion although CMRI can detect myocardial calcification or calcification of valves. Further, many imaging modalities have proposed spotty calcification to be a predictor of unstable plaque and have suggested more extensive calcification to be associated with stable plaques.

CLINICAL SIGNIFICANCE OF CORONARY CALCIFICATION

The extent of CAC strongly correlated with the degree of atherosclerosis and the rate of future cardiac events.[12,13] The CAC score also reflects as a beneficial marker for predicting coronary events. As the CAC score increases, it loses sensitivity and gains specificity for predicting CAD. A CAC score of >0 Hounsfield unit (HU) suggests some underlying atherosclerosis, whereas scores ≥100 and ≥400 HU should prompt risk factor modification and further diagnostic evaluation, respectively.[14] Asymptomatic persons without traditional risk factors but with a documented CAC score ≥ 400 Agatston unit (AU) might have a worse cardiovascular prognosis than those with ≥3 risk factors but no CT-detected CAC.[15] The progress of arterial medial calcification is described to be linked with renal failure, hypercalcemia, hyperphosphatemia, and parathyroid hormone abnormalities.[4] Calcified sheets may fracture, leading to the formation of nodular calcification. The nodules extend into the lumen or the media, which is linked with fibrin deposition. The swollen nodules can lead to discontinuity of the



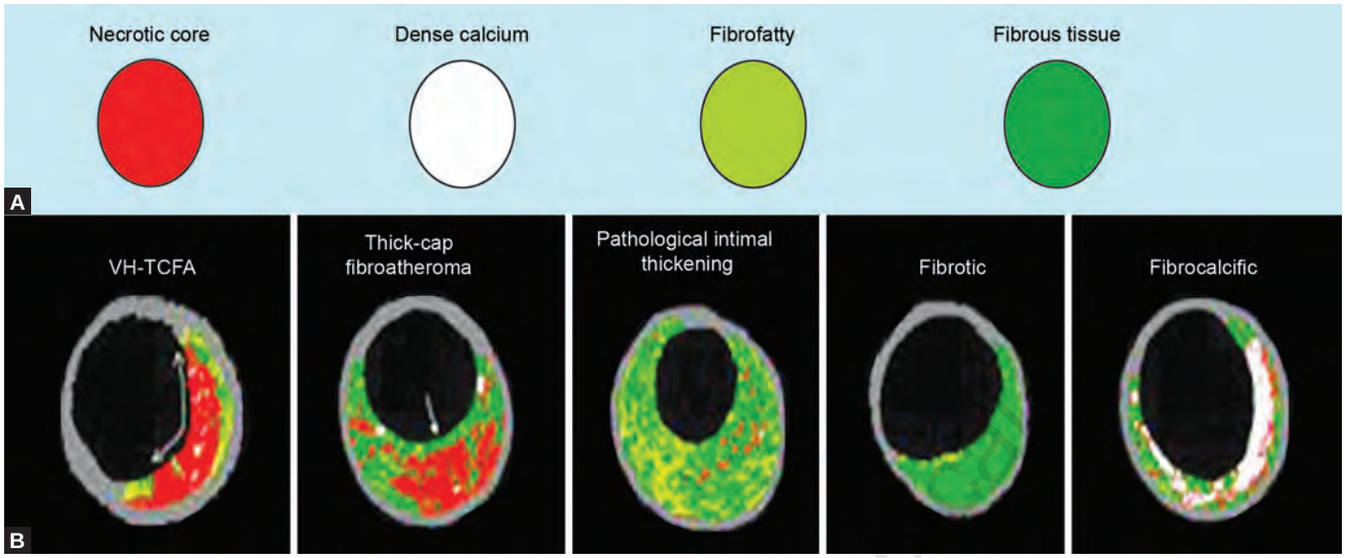
FIGS. 1A TO F: IVUS and OCT images of mild, moderate, and severe calcification. (A to C) IVUS images of mild, moderate, and severe calcification visualized as superficial hyperechoic tissue with acoustic shadowing, delimited by the arc of calcification relative to the center of the lumen (white arrows). (D to F) Corresponding slices obtained by OCT. Calcification by OCT is visualized as a signal poor or heterogeneous region with sharply delineated borders (white arrow in F).[10]

(IVUS: intravascular ultrasound; OCT: optimal coherence tomography)

endothelial lining and underlying collagen matrix, and acute luminal thrombosis. The calcified nodule is the underlying mechanism of acute coronary events in 2–7% of coronary artery thrombosis[16] and 4–14% of carotid artery thrombosis[17] in pathological studies.

GRADING AND RISK STRATIFICATION

Two recognized types of CAC are atherosclerotic and medial artery calcification. Atherosclerotic calcification chiefly occurs in the intima. Inflammatory mediators and elevated lipid content within atherosclerotic lesions induce osteogenic



FIGS. 2A AND B: IVUS virtual histology showing various components of atheromatous plaque.
(IVUS: intravascular ultrasound; VH-TCFA: virtual-histology intravascular ultrasound)

differentiation of VSMCs. Conversely, CAC in the media is associated with advanced age, diabetes, and CKD. Previously thought to be a benign process, medial calcification contributes to arterial stiffness, which increases the risk for adverse cardiovascular events.

The extent of CAC correlates with plaque burden. Microcalcifications in the fibrous cap might promote cavitation-induced plaque rupture. Additionally, calcific nodules might disrupt the fibrous cap, leading to thrombosis. Recurrent plaque rupture and hemorrhage with subsequent healing might result in the development of obstructive fibrocalcific lesions and are frequently found in patients with stable angina and sudden coronary death.

In CT, the extent of CAD is graded according to the CAC score although this correlation is sometimes controversial.

- CAC 0: No evidence of CAD
- CAC 1–10: Minimal evidence of CAD
- CAC 11–100: Mild evidence of CAD
- CAC 101–400: Moderate evidence of CAD
- CAC > 400: Extensive evidence of CAD

The chance of MACE for the next 5 years remains very low in patients with CAC score 0.

A number of risk factors contribute to the development of CAC **(Table 1)**. CAC might be inherited through both common allelic variants (e.g., chromosome 9p21) and rare mutations in phosphate metabolism that have also been associated with myocardial infarction (MI). Certain microribonucleic acids have also been implicated in CAC development, and their dysregulation has been associated with VSMC transition to an osteoblast-like phenotype.

Patients with CKD have greater cardiovascular morbidity and mortality, largely due to the presence of CAC and accelerated atherosclerosis. Hypercalcemia and hyperphosphatemia promote CAC. In addition to affecting the calcium–phosphate solubility equilibrium, phosphate can stimulate osteochondrogenic transformation of VSMCs.

Secondary hyperparathyroidism in CKD is also a risk factor for CAC, and dialysis in younger individuals is associated with similar calcium levels as with advanced age. Interestingly, ingestion of a high-calcium diet has not been associated with CAC, and no relationship has been observed between dietary calcium intake and CAD. These data suggest that CAC is the result of aberrant regulatory mechanisms rather than simple calcium overload. Enhanced understanding of the pathways that contribute to CAC is needed if more effective therapies are to be developed.

REAL-WORLD EVIDENCE AND MEDICAL THERAPY

Table 2 shows medical therapies used for reversing or halting the CAC progression. Statins have resulted in reduced low-density lipoprotein levels but on CAC progression a nonsignificant decline. High-intensity statin causes atherosclerotic plaque regression, resulting in shifting from low-calcium fibrofatty plaque to highly calcific regressed and healed atheroma. Interestingly, chronic high-intensity statin therapy might increase the CAC score with better long-term mortality benefit. Hence, interpretation of CAC score should always be done in the light of clinical background from case-to-case basis. Although selective renin–angiotensin–aldosterone system inhibition does not seem to significantly reduce CAC, no studies have investigated whether modulating the receptor activator of nuclear factor-kappa B or proliferator-activated receptor gamma pathways influences CAC in humans.[10] (10). Calcium channel blockers, hormonal therapy, phosphate binders, and most recently medicinal supplements have all been suggested to reduce CAC progression in small randomized trials and prospective studies. Larger prospective trials are required to definitively evaluate these approaches before they can be recommended.

TABLE 2: Studies of medical therapies for targeting CAC progression.

First author	Year	N	Design	Intervention	Outcomes
Motro and Shemesh[18]	2001	201	RCT	Nifedipine vs. HCTZ/ amiloride	Nifedipine was associated with significantly reduced coronary calcium progression at 3 years in hypertensive patients
Chertow et al.[19]	2002	200	RCT	Sevelamer vs. calcium-based phosphate binder	Sevelamer was associated with significantly lower CAC score progression in hemodialysis patients at 52 weeks
Arad et al.[20]	2005	1,005	RCT	Atorvastatin vs. vitamin C vs. vitamin E vs. placebo	Treatment arms did not have a significant effect on CAC progression
Houslay et al.[21]	2006	102	RCT	Atorvastatin vs. placebo	Statins had no significant effect on the rate of CAC progression
Manson et al.[22]	2007	1,064	RCT	Estrogen vs. placebo	Women treated with estrogen had significantly lower calcified plaque burden
Maahs et al.[23]	2007	478	CS	ACEi/ARB vs. other antihypertensives	Diabetics with albuminuria had nonsignificant reduction in CAC progression with ACEi/ARB treatment
Qunibi et al.[24]	2008	203	RCT	Calcium acetate/atorvastatin vs. sevelamer/atorvastatin	Calcium acetate and sevelamer groups had comparable rates of CAC progression in hemodialysis patients at 1 year
Budoff et al.[25]	2009	65	RCT	Age/vitamins B12 and B6/ folic acid/L-arginine vs. placebo	Treatment group experienced significantly lower rates of CAC progression at 1 year
Zeb et al.[26]	2012	65	RCT	Age/CoQ10 vs. placebo	Age/CoQ10 was associated with significantly lower rates of CAC progression at 1 year

(ACEi: angiotensin-converting enzyme inhibitor; AGE: aged garlic extract; ARB: angiotensin receptor blocker; CAC: coronary artery calcification; Co: coenzyme; CS: case series; HCTZ: hydrochlorothiazide; RCT: randomized controlled trial)

CORONARY INTERVENTION IN THE LIGHT OF CALCIFIED PLAQUE AND CALCIUM NODULE

Coronary calcium possesses significant difficulty during percutaneous transluminal coronary angioplasty (PTCA) as it increases the chance of inadequate bed preparation prior to stent implantation, coronary perforation, and inadequate stent expansion. All of these may lead to both short- and long-term increase in target lesion failure (TLF) and MACE. Interestingly, CAC may remain invisible under fluoroscopy. Hence, intracoronary imaging (IVUS and OCT) has got a significant role to play in planning the complex PTCA in calcified artery. The calcified sheets fracture resulting in the nodular calcification, and the nodules extend into the lumen or the media and cause fibrin deposition. There is discontinuity of the endothelial lining and underlying collagen matrix, and acute luminal thrombosis due to swollen nodules. The calcified nodule is the fundamental mechanism of acute coronary events in 2–7% cases of coronary artery thrombosis[8] and 4–14% cases of carotid artery thrombosis[17] in pathological studies. The ideal way of dealing with calcium nodule during PTCA is still under evaluation, and possibly orbital atherectomy and laser have got a significant role to play in this group. There are innovative devices to improve calcified vessel compliance for better bed preparation so that proper stent expansion can be ensured. Cutting and scoring balloons therapy do not remove calcium. They improve vessel compliance by creating discrete incisions in the atherosclerotic plaque, enable greater lesion expansion, reduce recoil, and also assist in preventing uncontrolled dissections. Rotablation is another prevailing modality that is being used in calcified (effective in intimal calcification only) coronaries for lesion reduction. Intravascular lithotripsy (IVL) is a novel balloon catheter that takes care of all kinds of CAC. It provides pulse ultrasound beams that break down the hard sheets of calcium into concretions, improving the vessel wall compliance. All these novel technologies are to be used on case-to-case basis, depending upon the clinical scenario and angiography findings. Sometimes, even more than one technology may be needed in the same patient depending upon the complexity.

The extent to which CAC contributes to poor outcomes after drug-eluting stent (DES) is controversial **(Table 3)**. Most studies have reported comparable rates of stent thrombosis, MI, and death after percutaneous coronary intervention (PCI) with DES in calcified and noncalcified coronary arteries. However, data with regard to the absolute efficacy of DES in calcified lesions are conflicting. Small-scale studies have suggested that the degree of neointimal hyperplasia is similar in calcified and noncalcified lesions, suggesting that the potency of antiproliferative agents might be independent of CAC. Consistent with these studies are reports showing similar rates of angiographic restenosis and target lesion revascularization in DES-treated calcified and noncalcified lesions. Other studies have reported greater rates of restenosis and repeat revascularization in DES-treated calcified compared with noncalcified lesions. Potential risk factors for restenosis and repeat revascularization include stent underexpansion, damage of DES polymer coats by calcified lesions, or adjunctive use of

TABLE 3: Outcomes of studies comparing DES and BMS in calcified lesions.

First author (ref. #)	Intervention	Follow-up (months)	Restenosis (%)	TLR (%)	MI (%)	Death (%)	MACE (%)
Moussa et al.[27]	PES	12	7.5	5.1	4.1	2.5	11.8
	BMS		18.3	11.9	3.2	0.8	16.8
	p value		0.10	0.09	0.68	0.29	0.27
Seo et al.[28]	SES	6–9	8.8	7.9	0.0	0.0	7.9
	BMS		33.3	19.5	0.0	2.4	24.4
	p value		<0.05	NS	NS	NS	<0.05
Khattab et al.[29*]	DES	9	7.4	7.4	0.0	0.0	7.4
	BMS		52.7	35.2	2.9	2.9	38.2
	p value		0.0008	0.006	0.4	0.4	0.004
Rathore et al.[30*]	DES	6–9	11.0	10.6	–	–	–
	BMS		28.1	25.0	–	–	–
	p value		<0.001	0.001	–	–	–
Bangalore et al.[31*]	DES	12	–	–	5.6	3.9	–
	BMS		–	–	5.8	4.9	–
	p value		–	–	0.90	0.35	–
Schwartz et al.[32*]	DES		–	–	2.7	0.9	3.6
	BMS	In hospital	–	–	0.0	5.3	5.3
	PTCA		–	–	0.0	11.1	14.8
	p value		–	–	1.0	0.0246	0.047

(BMS: bare-metal stent(s); DES: drug-eluting stent(s); MACE: major adverse cardiovascular event(s); MI: myocardial infarction(s); PES: paclitaxel-eluting stent(s); PTCA: percutaneous transluminal coronary angioplasty; SES: sirolimus-eluting stent(s); TLR: target lesion revascularization).

*Used rotational atherectomy.

TABLE 4: Studies of cutting and scoring balloons in calcified coronary lesions.

First author (ref. #)	Year	N	Design	Intervention	Outcomes
Okura et al.[33]	2002	224	RCT	CBA vs. PTCA	CBA was associated with significantly greater lumen cross-sectional area gain than PTCA in calcified lesions. Dissections were more common with CBA
de Ribamar Costa et al.[34]	2007	299	CS	DES vs. SBA/DES vs. semi-compliant balloon/DES	SBA was associated with greater stent expansion compared with direct stenting or stenting with predilation using conventional balloons
Grenadier et al.[35]	2008	521	CS	SBA + PTCA	SBA was associated with high rates of procedural success (97.9%), with low rates of short- and long-term adverse outcomes
Vaquerizo et al.[36]	2010	145	CS	RA ± CBA + DES	Low rates of TLR and ST were observed with CBA alone and RA + CBA in patients receiving DES at 15 ± 11 months

Note: Only studies with ≥100 patients were included.

(CBA: cutting balloon atherotomy; DES: drug-eluting stent(s); PTCA: percutaneous transluminal coronary angioplasty; RA: rotational atherectomy; RCT: randomized controlled trial; SBA: scoring balloon angioplasty; ST: stent thrombosis; TLR: target lesion revascularization)

other devices [e.g., rotational atherectomy (RA)] that might directly promote neointimal hyperplasia. Vaquerizo et al. have more recently reported similar acute- and intermediate-term outcomes (at 15 ± 11 months) in calcified lesions pretreated with cutting balloon atherectomy (CBA) compared with RA before DES implantation. Whether these results apply to the most heavily calcified lesions is uncertain. Finally, predilation with a scoring balloon has been demonstrated to enhance DES expansion. This device might be a useful adjunct to PCI in calcified lesions **(Table 4)**.

FUTURE NEWER INSIGHTS

Coronary artery calcification is also associated with noncardiac diseases. MESA subanalysis showed the association of CAC score above 400 with a higher incidence of cancer, CKD, pneumonia, chronic obstructive pulmonary disease (COPD), deep vein thrombosis/pulmonary embolism (DVT/PE), dementia, and hip fracture. CAC score above 400 is also associated with favorable number needed to treat (NNT) value for aspirin primary prophylaxis. Lipid guidelines look at

CAC score as an additional risk factor for risk stratification of intermediate atherosclerotic cardiovascular disease (ASCVD) risk group. Lee et al. have mentioned in their review new insights into the mechanism of VC wherein the authors have marked that in addition to traditionally established osteogenic signaling, dysfunctional calcium homeostasis is a prerequisite in the development of VC. Moreover, loss of defensive mechanisms by micro-organelle dysfunction, including hyperfragmented mitochondria, mitochondrial oxidative stress, defective autophagy or mitophagy, and endoplasmic reticulum (ER) stress, may all contribute to VC.[37] Ketteler et al. have notified that calcifications can serve to at least partially explain why cardiovascular mortality is dramatically increased in the uremic as compared to a normal population, and why it is not appropriately explained by the traditional Framingham risk factors. One of the mechanisms by which medial VC feeds into cardiovascular mortality may be via the associated increase in aortic pulse wave velocity.[38]

CONCLUSION

Despite a significant amount of research addressing CAC, our understanding of the pathogenesis, clinical implication, and management of CAC remains limited. In terms of pathophysiology of CAC, the governing factors are not fully understood regarding the formation of intimal versus medial calcification, and the clinical significance of these two types of CAC remains to be elucidated. On the other hand, CAC carries prognostic importance. CCTA is an established tool to assess CAC, and a score > 400 is associated with worse clinical outcomes in patients with an intermediate risk of developing CHD and in those with established CHD. Currently, there is no specific medical therapy targeting the reduction of CAC, and whether the treatment strategy limits the progression or enhances the regression of CAC or has prognostic impact needs further clinical studies. On the other hand, in patients with CHD and significant coronary stenosis, which necessitate revascularization therapy, the presence of moderate-to-severe CAC poses a clinical challenge. Specifically, developed PCI strategies have contributed to significantly higher procedure success, though morbidities are usually higher than in those patients without CAC as a result of the increased complexity of the procedures and higher cardiovascular risk profiles. Future studies should focus on the understanding of pathophysiologic mechanisms of CAC, identify targets of potential therapy, and improve interventional strategies.

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CHAPTER 44

Atherogenic Risk of Low Density Lipoprotein and Management Strategies

Kannan Kumaresan, Prabhakar Dorairaj

ABSTRACT

The primary target in the management of dyslipidemia is low-density lipoprotein cholesterol (LDL-C), although the less freely available apolipoprotein B (Apo B) is an all-encompassing and superior measure of all the atherogenic particles. The current concept of LDL-C reduction is "Earlier the Better, Lower the Better, and Longer the Better". The biggest paradigm is a shift in the focus from "high-intensity statin therapy" to "high-intensity lipid lowering therapy". The focus on therapy has also changed from once daily oral therapy to biweekly proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) and now with biannual inclisiran. The last frontier is a permanent gene therapy which is not too far away.

INTRODUCTION

Framingham study first demonstrated a linear relationship between low-density lipoprotein cholesterol (LDL-C) levels and atherosclerosis and an inverse relationship to high-density lipoprotein cholesterol (HDL-C).[1] Since then, atherosclerosis has been described as a lipid-centric disease.

ATHEROGENIC RISK OF LOW-DENSITY LIPOPROTEIN CHOLESTEROL

Lipoprotein molecules are synthesized by the liver and transport cholesterol and endogenous triglycerides (TGs). Very LDL-C (VLDL-C) is synthesized by the liver and transport both cholesterol and TGs. Fat-rich diets and other conditions that release free-fatty acid from adipose tissue (uncontrolled diabetes mellitus and obesity) increase the free-fatty acid in the liver which in turn enhances VLDL-C synthesis. Lipoprotein lipase is activated by apolipoprotein C II which is present in VLDL-C and results in breakdown of TGs into fatty acids and glycerol. As the TGs are hydrolyzed, the VLDL-C becomes intermediate density lipoproteins (IDLs) which contains more cholesterol than TGs. LDL-C is the product of IDL and VLDL metabolism and is the most cholesterol rich lipoprotein. Nearly 40-60% of LDL-C is eliminated by apolipoprotein B (Apo B) mediated LDL receptors in the liver. The remaining LDL-C is eliminated by hepatic and nonhepatic scavenger receptors. LDL receptors can be upregulated by low dietary fat and cholesterol and downregulated by high dietary fat and cholesterol delivered to the liver by chylomicrons. The oxidized circulating LDL is taken up by macrophage scavenger receptors. Foam cells are formed within the atherosclerotic plaques as more LDL-C enters the subendothelial space.[2,3]

Each LDL-C particle has one Apo B moiety. Cholesterol enters the arterial wall when Apo B binds to the vessel wall. There are two types of LDL-C, namely the cholesterol rich and cholesterol depleted. The smaller cholesterol depleted LDL-C has higher affinity to enter the intima and is able to penetrate the vessel wall and binds with the glycosaminoglycans in the subintimal space. These particles are trapped within the subintimal space, promote injury and induce plaque instability. The bigger cholesterol-rich LDL particles enter the vessel through Apo B receptor. These cholesterol-rich particles releases more cholesterol with the vessel and more cholesterol is trapped within the vessel wall. By the higher mass of cholesterol released into the intima, this produces more inflammation. Once the cholesterol is deposited within the vessel, the LDL-C can be released into the circulation. So, both cholesterol rich and cholesterol depleted LDL-C are atherogenic albeit by different mechanisms.[4]

Studies have shown that there is no threshold for clinical benefits defining the concept of "lower the better". Analysis of the Fourier Trial data has shown an incremental benefit of lower levels of LDL-C, even <10 mg/dL.[5] Similar results were noticed when very low LDL-C levels were achieved in the Odyssey Outcomes trial also.[6]

Is low-density lipoprotein C the best measure of atherosclerotic cardiovascular disease risk?

Apolipoprotein B is present in all atherogenic cholesterol particles. There are three major Apo B containing lipoproteins—(i) LDL-C which comprises nearly 80–90% of the Apo B containing particles, (ii) lipoprotein (A), and (iii) triglyceride-rich lipoproteins (TRLs). Less than 70 nm sized TRL particles, the chylomicron remnants, VLDL remnants, and IDLs can enter the endothelium and cause atherosclerosis. Utilizing Apo B as a diagnostic marker and a therapeutic target will encompass treatment of all the atherogenic molecules.

In general, LDL-C levels correlate with the Apo B levels except in diabetes, obesity and low levels of LDL-C.[7] In this situation, non-HDL-C has been used as a poor man's Apo B. However, a recent meta-analysis has shown superiority of Apo B over non-HDL-C in both primary and secondary prevention. In primary prevention, individually Apo B, non-HDL-C and TGs were associated with incident of myocardial infarction. But, when taken together only Apo B was predictive [adjusted hazard ratio (aHR) per 1 SD, 1.27; 95% CI: 1.15–1.40; $p < 0.001$]. In secondary prevention, after adjusting for Apo B, the ratio of TG to LDL-C was not predictive of MI and only Apo B was predictive for MI. The implication of these data is that the risk of MI is best predicted by the number of Apo B containing particles and not the content of lipid like cholesterol or TGs or the type of lipoprotein like LDL rich or TG rich.[8]

CUMULATIVE LOADING OF LOW-DENSITY LIPOPROTEIN CHOLESTEROL

Low-density lipoprotein level and years of exposure is called plaque or LDL burden. The threshold for development ASCVD is >5,000 LDL years.[9]

How early should lipid profile be checked?

Lipid Association of India (LAI) recommends that screening with a non-fasting lipid profile be done at the time of entry into college or around 18 years—for early detection and lifestyle advice. This will reduce overall cumulative plaque burden.

What is the goal of LDL-C in different subsets?

The primary goal for the primary and secondary prevention of ASCVD is LDL-C. Non-HDL-C (Total cholesterol–HDL-C) is a co-primary endpoint.[10] Recent studies have shown that estimation of Apo B levels was a better predictor of ASCVD risk than both LDL-C and Non-HDL-C—in both the primary and secondary prevention categories.[8]

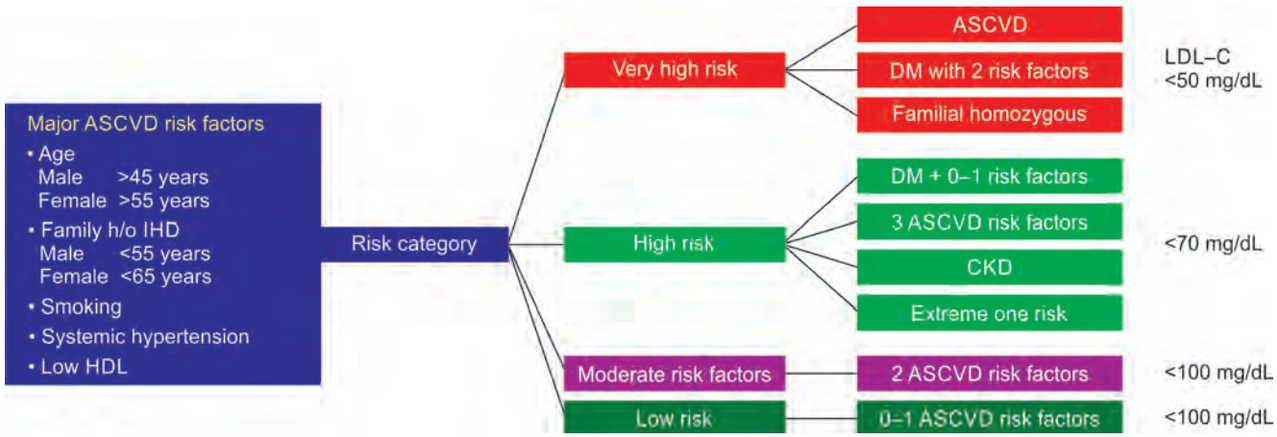
INTERPRETATION OF LOW-DENSITY LIPOPROTEIN CHOLESTEROL

Low-density lipoprotein C is the primary goal in the management of dyslipidemia. Simple algorithm from LAI is given below in **Flowchart 1**.

Extreme risk persons are those with ASCVD and more than one very high factors or recurrent ACS within 1 year after achieving a target LDL ≤ 50 mg/dL. The target LDL-C for extreme risk category is ≤30 mg%. ESC defines a target LDL-C of <40 mg/dL for ASCVD patients on maximally tolerated dose of statin who develop a second ASCVD event (not necessarily the same type) within 2 years **(Table 1)**.

The American College of Cardiology recommends high-intensity statins in ASCVD and high-risk persons with diabetes mellitus, other diabetics aged 40–75 years of age are advised moderate intensity statin therapy **(Table 2)**. In secondary prevention, they also recommend that if a target LDL-C of ≤70 mg/dL is not achieved, sequential addition of ezetimibe and proprotein convertase subtilisin/kexin type 9 serine protease inhibitors (PCSK9i).[13] They do not address the issue of extreme risk category.

Non-HDL-C (total cholesterol–HDL-C) is a co-primary endpoint and the reference values are 30 mg% more than LDL-C.[10] TGs are treated specifically only when ≥500 mg/dL, otherwise intensify statins and target non-HDL-C. HDL-C has inverse relationship to the presence of ASCVD. Pharmacological increase in HDL-C has not translated into clinical benefits, since herein the HDL-C levels increased without increasing the functionality of HDL-C. Currently only physiological increase (exercise, walnuts, etc.) in HDL-C is recommended.



FLOWCHART 1: Major atherosclerotic cardiovascular disease (ASCVD) risk factors: Lipid Association of India.

(ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; DM: diabetes mellitus; HDL: high-density lipoprotein; h/o: history of; IHD: ischemic heart disease)

TABLE 1: Comparison of the ESC and LAI statements on the management of dyslipidemia in adults.

	Low risk	Moderate risk	High risk	Very high risk	Extreme risk	Comments
ESC 2019[11]	≤115	≤100	≤70	≤55	≤40*	
LAI[12]	≤100	≤100	≤70	≤50	≤30	

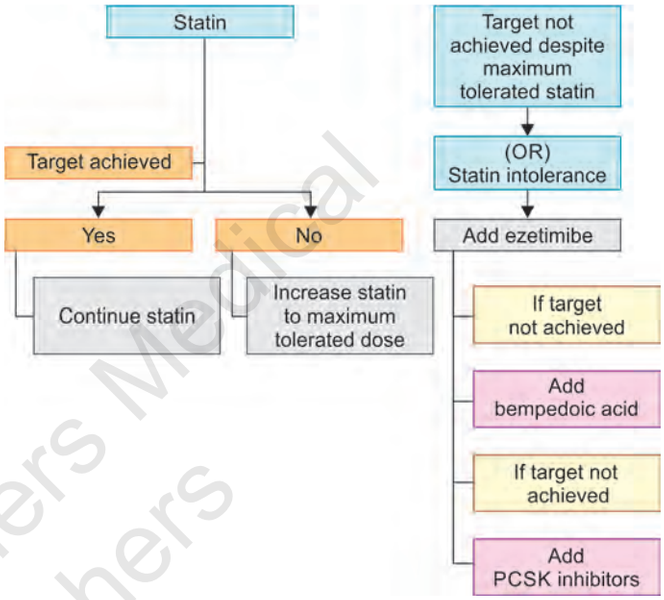
*ASCVD patient on statin developing a second vascular event.

(ESC: European Society of Cardiology; LAI: Lipid Association of India)

TABLE 2: Statins by intensity (available statins).[14]

High-intensity statin	Moderate intensity
Reduce LDL-C by approximately 50%	Reduces LDL-C by approximately 30–50%
• Atorvastatin (40)—80 mg • Rosuvastatin 20 (40) mg	• Atorvastatin 10 (20) mg • Rosuvastatin (5) 10 mg • Simvastatin 20–40 mg • Pravastatin 40 (80) mg • Pitavastatin 2–4 mg

(LDL-C: low-density lipoprotein cholesterol)



FLOWCHART 2: Algorithm for step-wise LDL-C management.

(PCSK: proprotein convertase subtilisin/kexin)

MANAGEMENT OF DYSLIPIDEMIA (FLOWCHART 2)

Lifestyle modification is the first step in the management of dyslipidemia. Statins have been the cornerstone in the reduction of LDL-C. Moderate intensity statins reduce LDL-C by 30% and high-intensity statins reduce the LDL-C by about 50%. Addition of ezetimibe alone further reduced LDL-C by 21%, PCSK9i alone by 57% and both by 69%. The corresponding fall in Apo B levels were 16%, 46%, and 53%, respectively.[15]

Statin therapy failed to achieve the desired LDL-C reduction in several persons. There is substantial interindividual variability in the response to statins. Among those who receive atorvastatin 80 mg daily, 42.5% failed to achieve ≥50% reduction in LDL-C while the corresponding failure with rosuvastatin 40 mg was 26.2%.[16] Statin intolerance is defined as failure to achieve the target LDL-C levels either due to adverse effects of statins or elevation on enzymes (liver enzymes or creatine kinase). Although there is a huge component of drucebo effect (Drucebo effect: a combination of DRUg and plaCEBO or noCEBO effects, used to relate beneficial or adverse effects of a drug, which result from expectation and are not pharmacologically caused by the drug), true statin intolerance is noted in <7% of statin users.[17] Several other alternatives for the reduction of LDL-C have been identified.

TABLE 3: Efficacy of different lipid lowering therapies.

	Percentage LDL reduction
Moderate intensity statins	30–50%
High-intensity statin	~50%
Ezetimibe alone	15–20%
High-intensity statin + Ezetimibe	65%
PCSK9i	50–60%
High-intensity statin + PCSK9i	75%
High-intensity statin + PCSK9i + Ezetimibe	85%

(LDL: low-density lipoprotein; PCSK9i: proprotein convertase subtilisin/kexin type 9 inhibitor)

ALTERNATIVES TO STATIN THERAPY

The IMPROVE-IT trial was the first trial to show that nonstatin therapy is beneficial and can reduce cardiovascular (CV) events. Ezetimibe, in addition to simvastatin, was shown to reduce CV events and is now recommended as the second drug after statins. The Fourier trial (with evolocumab) and Odyssey Outcomes trial (with alirocumab) have shown substantial reduction in LDL-C in both statin taking and statin intolerant patients. But, their parenteral route of administration and price have made the PCSK9i underutilized molecules. The new drugs are discussed separately **(Table 3)**.

Bempedoic Acid

Adenosine triphosphate (ATP) citrate lyase is a cytosolic enzyme which acts before HMG-CoA reductase in de novo synthesis of LDL-C. Bempedoic acid (BA) blocks ATP citrate lyase. The other action of BA is activation of adenosine monophosphate-activated protein kinase (AMPK)—which regulates the phosphorylation of substrates affecting inflammatory signaling and lipid metabolism. BA is a prodrug activated by very long-chain acyl-CoA synthetase-1 to the active drug. This enzyme is present mostly in the liver which minimizes

TABLE 4: Effects of BA on LDL lowering.

	LDL lowering	Comments
BA alone	23.6%	Statin intolerant patients in CLEAR Serenity trial
BA + maximum tolerated lipid therapy	18%	CLEAR Harmony trial
BA + Ezetimibe	38%	
BA + Ezetimibe + Atorvastatin	60.5%	Fixed dose combination
BA + PCSK9 inhibitors	Incremental drop of 25%	

(BA: bempedoic acid; LDL: low-density lipoprotein)

the exposure of the active drug to extrahepatic tissues, especially the muscle. This selective activation minimizes the muscle symptoms despite the action along the same pathway as the statins.

Bempedoic acid reduced LDL-C by 17–25% versus placebo depending on the background use of statins. BA has been studied in primary prevention, secondary prevention, and familial hypercholesterolemia either alone or in combination with statin or ezetimibe. In the CLEAR Harmony trial, addition of BA to maximum tolerated lipid therapy lowered LDL-C by 18%, non-HDL-C by 13.3%, Apo B by 11.9%, and hs-CRT by 21.5%. In the meta-analysis of 4,391 patients in 11 randomized controlled trials (RCTs), there was a reduction in composite CV outcomes and rates of new-onset or worsening diabetes. The extent of LDL lowering of BA alone and in combination is given in **Table 4**.

The incidence of myalgia with BA is comparable to placebo. BA acts on renal organic anion transporter 2 and reduces the excretion of creatinine and uric acid—noted clinically by mild increases in these levels. Mild reversible fall in hemoglobin levels are rare and no mechanism is known. Stimulation of AMPK leads to reduction of gluconeogenesis (maybe the reason for fewer new onset diabetes) and inhibits fatty acid synthesis.

Use maximum tolerated dose of statins, if the target is not achieved, then add ezetimibe. The next step in secondary prevention and familial hypercholesterolemia is the use of PCSK9 inhibitors.

Inclisiran

Inclisiran belongs to a group of molecules called the small interfering RNA (siRNA). This inhibits PCSK9 by binding and degrading the mRNA, thereby preventing its translation into PCSK9. A series of trials called the ORION trials have shown that after baseline injection of 300 mg of inclisiran and the second dose after 3 months. Inclisiran is injected once in 6 months and has shown a sustained reduction in LDL-C of 50%. This has been approved by the Food and Drug Administration (FDA) for familial hypercholesterolemia and ASCVD.[18]

NEWER DRUGS IN THE PIPELINE

Lipoprotein lipase mediated hydrolysis trims TG from the triglyceride-rich lipoproteins (TGRLs) and yields LDL-C, IDLs, and free-fatty acids. Apo C-III (blocked by volanesorsen), angiopoietin-like protein 3 (ANGPTL3) (blocked by evinacumab and volanesorsen), and ANGPTL4 block the action of lipoprotein lipase and increase TGRL levels. The blocking agents are newer therapeutic agents.

Lipoprotein and endothelial lipase are inhibited by ANGPTL3 which is a hepatically secreted protein. Inhibition of ANGPTL3 reduces LDL-C levels through an unknown mechanism. Evinacumab, an Mab that inhibits ANGPTL3, was studied in 65 patients with homozygous familial hypercholesterolemia (HoFH). Patients had to have genetic mutations in LDL receptors, PCSK9, or Apo B with a baseline untreated TC >500 mg/dL and a TG level <300 mg/dL. In addition, patients had to be older than age 12 years with an LDL-C >70 mg/dL on maximally tolerated lipid-lowering therapy. Patients were randomized 2:1 to evinacumab 15 mg/kg IV or placebo every 4 weeks for 24 weeks. Evinacumab decreased LDL-C by 49 ± 8% at 24 weeks. LDL-C was decreased by 50% or greater in 56% of evinacumab patients compared with 4.5% of placebo patients. Genetic mutations in the LDL receptor did not appear to affect response to evinacumab. The overall rate of adverse reactions was less with evinacumab than with placebo, but more serious adverse reactions occurred with evinacumab (4.5%) than with placebo (0%). Evinacumab's unique mechanism of action appears to be independent of LDL-receptor function, which may be particularly valuable in patients with HoFH.[19]

Volanesorsen is an antisense oligonucleotide that targets Apo C-III. It also has proinflammatory effects. In hyperchylomicronemia, volanesorsen reduced TGL by over 70% but almost a quarter of patients had injection site reactions.

Peroxisome proliferator-activated receptor-alpha (PPAR-α) stimulator, fenofibrate raises HDL-C and lowers TGs, but has not demonstrated CV benefits in statin treated patients. Pemafibrate is a selective PPAR-α modulator that lowers TGs, Apo C-III and has been studied in the PROMINENT trial.

How long to continue and how low to go?

Once the target is achieved, then continue. Do not reduce the dose especially in secondary prevention—here reduction in the intensity of statin therapy has been associated with worse outcomes.[20] In recurrent ASCVD events or polyvascular disease, LDL-C target is ≤30 mg%. Long-term safety of LDL-C <15 mg% is not known.

CONCLUSION

The primary target in the management of dyslipidemia is LDL-C, although the less freely available Apo B is an all-encompassing and superior measure of all the atherogenic particles. The current concept of LDL-C reduction is "Earlier the Better, Lower the Better, and Longer the Better". The biggest paradigm is a shift in the focus from "high intensity statin therapy" to "high intensity lipid lowering therapy". The focus on therapy has also changed from once daily oral therapy to biweekly PCSK9i and now with biannual inclisiran. The last frontier is a permanent gene therapy which is not too far away.

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CHAPTER 45

Primary Prevention of Cardiovascular Disease: The Current Approach

G Rajendiran, Puneeth Kumar

ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death across the globe. South Asians have a higher incidence of CVD. Indians develop atherosclerosis at least a decade earlier. With the recent COVID-19 pandemic, CVD is expected to go up manifold. Primary prevention is the key. Western countries have their guidelines incorporating 10-year risk stratification strategies based on large population studies. The guidelines use the traditional risk factors and some nonmodifiable risk factors and predict 10-year CVD risk. This helps the preventive team to decide on further treatment strategies. The guidelines mostly agree on physical activity and dietary recommendations. These risk scores have not been validated in the Indian context and are known to underestimate the risk in the Indian population. This chapter summarizes the salient features of the primary prevention guidelines published in the last 5 years in the Indian context. The chapter recollects the cutoffs for the risk factors prescribed for South Asians settled in the United States and calls for collective changes at the national level.

INTRODUCTION

The Great Influenza epidemic happened in 1918 and that was the only year since 1900 when cardiovascular disease (CVD) was not the leading cause of death in the United States. Now, more than 2 years into the COVID-19 pandemic, CVD continues to top the list, malignancy and COVID-19 being the next two.[1] Moreover, CVD has emerged as a risk factor for COVID-19 related deaths. It is projected that long COVID-19 can affect around 54% of those who have recovered from it as per Nature Reviews 2022.[2] With the pandemic far from over, India is one of the top three countries in both COVID-19 cases and death counts, leading to speculations on the rise in the incidence of CVD in the near future.[3]

The World Health Organization (WHO) estimated that with the current burden of CVD, India would lose $237 billion from losing productivity and spending on healthcare over a 10-year period (2005–2015).[4] The age-standardized CVD death rate of 272 per 100,000 population in India is higher than the global average of 235 per 100,000 population.[5] Similarly, there is an alarming increase in coronary risk factors. The WHO Global Burden of Disease Study has projected an alarming increase in the prevalence of diabetes mellitus (DM) by 151% in the Indian subcontinent from 31.7 to 79.4 million people from 2000 to 2030.

Prevention and early detection of CVD risk factors and subclinical atherosclerosis with the widespread promotion of lifestyle measures (LSM) will remain the key to combating the CVD epidemic.

Atherosclerotic Cardiovascular Disease

Atherosclerotic cardiovascular disease (ASCVD) is caused by plaque buildup in arterial walls and refers to the following conditions:[6]

- Coronary heart disease (CHD), such as myocardial infarction (MI), angina, and coronary artery stenosis >50%
- Cerebrovascular disease, such as transient ischemic attack, ischemic stroke, and carotid artery stenosis >50%
- Peripheral artery disease, such as claudication
- Aortic atherosclerotic disease, such as abdominal aortic aneurysm and descending thoracic aneurysm

Primary Prevention of Cardiovascular Disease

Primary prevention of CVD is defined as preventive measures taken to reduce the risk of developing clinical cardiovascular (CV) events by controlling the major risk factors of CVD such as smoking, hypertension, dyslipidemia, and diabetes, prior to the occurrence of CV events.

Primary prevention measures have been shown to effectively delay or prevent the occurrence of CV events, thereby reducing the morbidity and mortality of the CVD. Studies have shown that 40–70% of decreases in mortality from CVD in Western countries can be attributed to risk factor control. Preventive measures such as a change in diet, physical activity, and smoking cessation decreased mortality due to coronary artery disease by 82% in men and 84% in women in North Karelia, Finland, from 1969 to 2012.[7] Similarly, England and Wales gained 79% life-years in 2 decades by targeting CV risk factors. Scotland had a 30% reduction in CV mortality from 1975 to 1994 by focusing on risk factors.

The United Nations (UN) in 2011 had set a goal of reducing noncommunicable disease (NCD) deaths by 25% by 2025—the Heart of 25 by 25.[8] It is well known that CVD forms the bulk of NCD deaths. More than 1.5 million premature CVD deaths in males and 0.6 million premature CVD deaths in females across the globe can be prevented if set targets for hypertension, diabetes, obesity, and tobacco usage are met. The targets are a 30% relative reduction in tobacco usage, a 25% relative reduction in the prevalence of raised blood pressure (BP), a 30% reduction in mean population intake of sodium/salt, and a 10% relative reduction in the prevalence of insufficient physical activity. This assumes immense significance in the context of the UN's projection that CVD mortality is bound to go up by 56% in South Asian males.

The WHO advocates a clear three-pronged approach to tackle the surging incidence of CVD:[4]

1. *Surveillance*: Map and monitor the epidemic of CVDs.
2. *Prevention*: Reduce exposure to risk factors.
3. *Management*: Equitable health care for people with CVDs

Up to 50% of the people who harbor ASCVD manifest as acute coronary syndrome (ACS). So, identification of the disease in its subclinical stage and tackling the risk factors by LSM are of paramount importance **(Fig. 1)**. What we see as ACS is merely the tip of the iceberg.

Various national and international societies have come out with guidelines to reduce the impact of CVD in their respective populations. The last published consensus statement for prevention in the Indian context was the Lipid Association of India (LAI) in 2020 by Puri et al.,[9] which has not gained any popularity.

Four-step Approach to Prevention

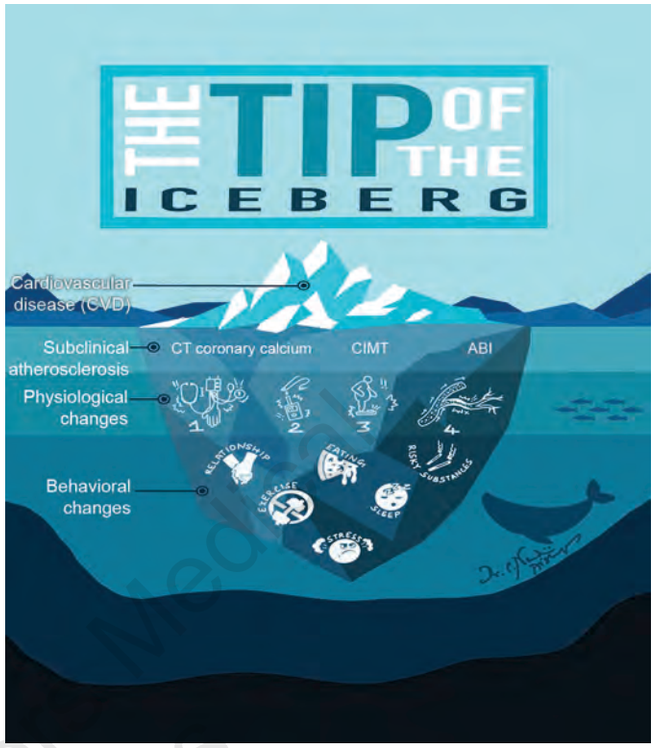
This chapter attempts to bring out the salient features that appeared in the primary prevention guidelines published in the last 5 years **(Box 1)**. All the models use the following four-step approach:

Step 1: Assessment of the individual's modifiable risk factors (hypertension, diabetes, dyslipidemia, smoking, and obesity)

Step 2: Risk stratification score (the above risk factors along with nonmodifiable risk factors such as age and gender), which classifies the participants into various risk categories.

Step 3: Use risk-enhancing factors or risk modifiers such as family history, ethnicity, sleep apnea, and coronary calcium score to deescalate or escalate the risk score in special subsets of patients.

Step 4: Prescription of lifestyle changes along with medications, if indicated, depending on the risk score (absolute risk approach) rather than on individual values (isolated risk approach)



Note: 1. Hypertension; 2. Diabetes mellitus; 3. Obesity; 4. Dyslipidemia

FIG. 1: Acute coronary syndrome as the tip of the iceberg.
(ABI: ankle brachial index; CIMT: carotid intima-media thickness; CT: computed tomography)

Source: By courtesy of Dr C Nandini Aishwarya MD, PSGIMSR.

BOX 1 **Primary prevention guidelines published in the last 5 years.**

- European Society of Cardiology 2021
- British Columbia 2021
- Chinese guidelines 2021
- National Heart Foundation of Australia 2021
- Kaiser Permanente 2020
- Updated recommendations for primary prevention of cardiovascular disease in women 2020
- American Heart Association 2019
- CV risk reduction in high-risk pediatric patients 2019
- Brazilian guidelines 2019
- New Zealand 2018
- Norwegian guidelines 2017
- Malaysian guidelines 2017
- SIGN 2017
- SCCT expert consensus statement 2017

(CV: cardiovascular; SCCT: Society of Cardiovascular Computed Tomography; SIGN: Scottish Intercollegiate Guidelines Network)

GUIDELINES

Let us begin with the two most widely practiced guidelines, namely the European Society of Cardiology (ESC) and the American Heart Association (AHA) guidelines.

European Society of Cardiology (2021) versus American Heart Association (2019)[10,11]

- ESC uses SCORE2 (Systematic COronary Risk Estimation) sex-specific risk model, which includes traditional risk factors: Age, smoking status, systolic BP, total cholesterol, and high-density lipoprotein cholesterol (HDL-C)—for ages between 40 and 69 years, and SCORE2-OP (Systematic COronary Risk Estimation for Older Persons), which gives age-specific and region-specific thresholds for low-, moderate-, high-, and very high-risk categories for people beyond 70 years. AHA uses pooled cohort equation (PCE) and the same thresholds for individuals between 40 and 75 years and classifies them into low, borderline, intermediate, and high-risk individuals.

  In India, nearly one-fourth of the patients presenting with ACS are aged less than 45 years. This means that the screening of the vulnerable should begin at least a decade earlier, making both the above scores invalid in the Indian context.
- ESC addresses population-level threats such as air pollution, noise pollution, and urban planning while AHA is silent on these factors.
- Both the guidelines have considered risk enhancers or modifiers such as ethnicity, family history, chronic kidney disease (CKD), infections, and inflammatory conditions. ESC, in addition, has included some medical conditions such as atrial fibrillation (AF), chronic obstructive pulmonary disease (COPD), migraine, nonalcoholic fatty liver disease (NAFLD), and sleep and stress disorders. ESC specifically provides an ethnic risk multiplier of 1.3 for South Asians from India. ESC also considers socioeconomic determinants and environmental exposure. The frailty of the individual is given weightage while considering treatment options and targets.
- AHA endorses C-reactive protein (CRP), apolipoprotein B, lipoprotein(a) [Lp(a)], coronary artery calcium (CAC) score, and ankle brachial index (ABI) for risk stratification. ESC does not recommend the above and cites CAC as class IIb because of cost and availability concerns.
- *Aspirin*: Both the guidelines do not recommend aspirin for primary prevention, given the high-risk benefit ratio.

Risk Stratification Approach

The risk stratification approach has been designed to maximize the benefits for high-risk people while helping to avoid drug therapy for low-risk individuals. A plethora of risk scores exists, some in electronic format and some in paper form **(Box 2)**. These risk estimators are meant to provide the person's absolute 10-year risk of CV events. They facilitate the planning of preventive and treatment strategies.

Table 1 shows how the two major CV societies calculate the risk.

A case example on how the absolute risk approach better targets therapy is presented in **Table 2**.

Mr Raja is a 65-year-old man, a chronic smoker with a strong family history of CVD but does not have diabetes or known CVD. His BP is 134/80 mm Hg, total cholesterol level is 210 mg/dL, and HDL-C level is 40 mg/dL.

BOX 2 Risk scores.

- Framingham risk score
- ETHRISK tool
- QRISK3
- US-derived PCE
- Reynolds risk score
- JBS2
- Australian absolute CVD risk
- New Zealand absolute CVD risk
- WHO/ISH

(CVD: cardiovascular disease; JBS2: Joint British Societies' guidelines; PCE: pooled cohort equations; WHO/ISH: World Health Organization and the International Society of Hypertension)

TABLE 1: Risk calculation by two major cardiovascular societies.

ESC			AHA/ACC		
Risk category	SCORE2/SCORE2OP	Age (years)	Risk category	PCE	Age
Low to moderate	<2.5	<50	Low	<5%	40–75
	<5%	50–69			
	<7.5	>70			
High	2.5 to <7.5	<50	Borderline	5 to <7.5%	
	5 to <10%	50–69			
	7.5 to 15%	>70			
Very high	≥7.5	<50	Intermediate	7.5–19.9%	
	≥10	50–69			
	≥15	>70			
			High	>20%	

(ACC: American College of Cardiology; AHA: American Heart Association; ESC: European Society of Cardiology; PCE: pooled cohort equation)

TABLE 2: Case example on absolute risk approach.

Patient	Mr Raja	Mrs Rani
Age (years)	65	45
Risk factors	Smoker Strong family history of IHD Normal sugars BP: 134/80 TC: 210 HDL: 40	Nonsmoker No family history of CVD Normal sugars BP: 142/82 TC: 250 HDL: 50
Isolated risk factor approach	Quit smoking/LSM No medications	LSM AHT Statins
Absolute risk (ASCVD)	21.9%	1.7%
Absolute risk approach	Medications + LSM	LSM > medications

(AHT: antihypertensive treatment; ASCVD: atherosclerotic cardiovascular disease; CVD: cardiovascular disease; HDL: high-density lipoprotein; IHD: ischemic heart disease; LSM: lifestyle measures; TC: total cholesterol)

Rani is a 45-year-old woman who does not smoke and does not have diabetes or known CVD. Her BP is 142/82 mm Hg, total cholesterol level is 250 mg/dL, and HDL-C level is 50 mg/dL.

If we go by the conventional method of isolated risk approach, Mr Raja has no elevated individual risk factors that would warrant treatment with medication while Mrs Rani has hypercholesterolemia and hypertension, needing lifelong antihypertensive and lipid-lowering therapy. However, if one adopts the absolute risk approach using the ASCVD risk calculator, Mr Raja's absolute risk is high (21.9%) and Mrs Rani's is low (1.7%). While both need lifestyle modification, it is Mr Raja who requires medication.

The above scenario illustrates the significance of risk stratification. Lipid levels alone should not decide the prescription of statins. It should be based on an absolute CV risk assessment. Unfortunately, no specific risk score is directly applicable to the Indian population. The PCE underestimates the risk for South Asians in the United States. Now, the South Asian ancestry is considered a risk-enhancing factor as per the American College of Cardiology (ACC) and AHA guidelines, which means that the presence of such risk enhancers favors starting on statin even when the PCE risk is between 5 and 7.5% 10-year ASCVD risk. Similarly, the Framingham risk score (FRS) underestimates the risk in South Asians. Young Indians who have had an event before the third decade would not have been categorized as a high-risk category under the FRS system. Risk charts specific for each subregion and country are available with the WHO/International Society of Hypertension (ISH) (https://www.paho.org/hq/dmdocuments/2010/colour_charts_24_Aug_07.pdf). The ETHRISK tool and QRISK3 are the two CV risk prediction tools that account for South Asian ethnicity.

New Zealand Guidelines[12]

The new PREDICT CVDRA equations use 5-year risk prediction over 10 years as the median follow-up of PREDICT cohort is 5 years now and because most randomized controlled trials (RCTs) were based on 5-year treatment.

NICE Guidelines (2019)[13]

The National Institute for Health and Care Excellence (NICE) guidelines recommend the use of non-HDL-C instead of low-density lipoprotein cholesterol (LDL-C). NICE advocates the use of QRISK2 risk assessment for risk stratification up to the age of 84 years. This risk score is not applicable in patients with type 1 diabetes mellitus (T1DM)/CKD or familial hypercholesterolemia. NICE patient decision aid is available to support discussions about statin therapy to reduce CVD risk.

Norwegian Guidelines[14]

Norway developed an age-differentiated Norwegian risk algorithm (NORRISK) in collaboration with the European SCORE project using data from Norwegian patients and also drafted new guidelines for starting medications. By these measures, they aim to become one of the three countries in the world with the highest life expectancy and to achieve the UN's sustainable development goals. They recommend a multiplication factor of 1.5 for South Asian ethnicity.

Scottish Intercollegiate Guidelines Network (2017)[15]

The Scottish intercollegiate guidelines network also recommends the use of the QRISK assessment tool.

Chinese Guideline on the Primary Prevention of Cardiovascular Disease (2020)[16]

"Healthy China 2030" aimed at reducing four major NCDs (CVD, cancer, diabetes, and chronic respiratory disease) by 30% before 2030. Their target population is people of 18 years of age and above. They have a specific risk assessment algorithm for Chinese adults above 18 years of age. Patients with diabetes (age ≥40 years), LDL ≥190 mg/dL, total cholesterol ≥280 mg/dL, or stage 3/4 CKD are straightaway considered high risk. Others go through risk stratification with basic parameters such as blood pressure, lipid levels, smoking history, gender, and age. This risk assessment is to guide statins, hypoglycemic agents, and aspirin. Only the abovesaid conventional risk factors are included in the risk assessment models, making this sort of system suitable for a country like ours. Chinese guidelines do not advocate carotid intimal medial thickness (CIMT), high-sensitivity C-reactive protein (hsCRP), apolipoprotein B, or CAC as additional modalities for further risk stratification. However, when the risks and benefits of treatment are unclear, risk enhancement factors such as cardiac computed tomography scans for coronary calcium (CT CACs), CIMT, ABI, left ventricular hypertrophy (LVH) on electrocardiogram (ECG)/ECHO, Lp(a) levels, and hsCRP are also taken into consideration.

As none of the existing prediction tools has been validated in the Indian population, it is high time an appropriate tool arrives at the earliest by the preventive forums of India. Once the guidelines reach the publication phase, the key messages need to be discussed in national forums with the involvement of social media. Social marketing campaigns need to be encouraged to disseminate the decisions taken.

Multidisciplinary teams should be formed at all levels—administrative, medical, and paramedical.

APPROACH TO INDIVIDUAL TRADITIONAL RISK FACTORS

Framingham Heart Study is deemed as the pioneer in identifying the risk factors and determinants of CVD. Subsequently, the Seven Countries Study, the WHO MONICA project, and the INTERHEART Study provided more insights into the CVD risk factors. The traditional and modifiable risk factors included in most of the guidelines are diabetes, hypertension, dyslipidemia, obesity, and smoking.

Diabetes Mellitus

The diagnostic criteria for diabetes remain uniform across the guidelines. However, the targets differ according to the guideline.

The AHA sets glycosylated hemoglobin of <7% as the target for the entire population, and the ESC provides different targets for different populations **(Table 3)**. Lifestyle changes (dietary and exercise) are advised for each diabetic patient. Metformin remains the first line of treatment in both the guidelines. AHA recommends sodium-glucose cotransporter-2 (SGLT-2) inhibitor or glucagon-like peptide 1 receptor agonist (GLP1RA) for diabetic patients with additional CVD risk factors while ESC recommends SGLT-2 inhibitor for diabetic patients with heart failure with reduced ejection fraction (HFrEF) and CKD.

TABLE 3: AHA and ESC diagnostic criteria for diabetes.

Category of diabetics	Target	
	ESC	AHA
For reduction of CVD risk and microvascular complications of DM of types 1 and 2 in adults	<7	<7%
Long duration of diabetes (>10 years) Old and frail individuals	<8	
At diagnosis, if no CVD/frailty	<6.5	

(AHA: American Heart Association; CVD: cardiovascular disease; DM: diabetes mellitus; ESC: European Society of Cardiology)

Hypertension

The definition of hypertension, classification **(Table 4)**, and treatment targets **(Table 5)** differ in both ESC and AHA guidelines.

The ESC guidelines prescribe a target of <140/90 mm Hg in all patients as the first objective and then to 120–130/80 mm Hg as the target in 18–69 years old. In >70 years old, the target of <140 and then to 130, if tolerated, is recommended. Targets vary according to the target organ damage [e.g., in CKD <140–130 mm Hg; in CAD and cerebrovascular accident (CVA), 120–130 mm Hg] or according to additional risk factors (e.g., in diabetes 120–130 mm Hg).

Both the guidelines emphasize overall risk assessment before considering antihypertensive drug treatment for stage 1 hypertension. This approach may prevent more CVD events than treatment that is based on BP levels alone.

Emphasis is laid on following their regional guidelines in prescribing specific antihypertensives, taking into account the

TABLE 4: AHA and ESC classification of hypertension.

BP	ESC		AHA	
	SBP	DBP	SBP	DBP
Optimal	<120	<80		
Normal	120–129	80–84	<120	<80
High normal	130–139	85–89	120–129	<80
Stage 1	140–159	90–99	130–139	80–89
Stage 2	160–179	100–109	≥140	≥90
Stage 3	≥180	≥110	NA	
ISH	≥140	<90		

(AHA: American Heart Association; BP: blood pressure; DBP: diastolic blood pressure; ESC: European Society of Cardiology; ISH: isolated systolic hypertension; NA: not applicable; SBP: systolic blood pressure)

TABLE 5: AHA and ESC treatment targets of hypertension.

	AHA		ESC			
Treatment goals	<130/80		18–69 years		≥70 years	
			Initial target	Final goal	Initial target	Final goal
			140/90	120–130/80	130–139/80	<130/80, if tolerated
Normal	LSM					
High normal	LSM		LSM			
Stage 1	LSM	10-year CVD risk <10%	Low 10-year risk (<2.5% in 50 years)			
	LSM + medications	10-year CVD risk ≥10%	High 10-year CVD risk (2.5–7.5% in <50 years; 5–10% in 50–69 years; 7.5–15% risk in >70 years) Target organ damage			
Stage 2	LSM + medications					
Stage 3	NA		LSM + medications			

(AHA: American Heart Association; CVD: cardiovascular disease; ESC: European Society of Cardiology; LSM: lifestyle measures; NA: not applicable)

age, race, and presence of other CVD risk factors or target organ damage.

Dyslipidemia

Nonfasting samples are well accepted for lipid measurements unless the patient is known to have high triglyceride levels.

It is worth applying the risk score as well as looking out for evidence of secondary causes before considering statins. Secondary causes include hypothyroidism, alcohol abuse, DM, Cushing syndrome, nephrotic syndrome, and drugs such as corticosteroids. Statins are to be prescribed only after applying the prescribed risk score unless the individual has T1DM, CKD or familial hypercholesterolemia, or coronary calcium.

Both ESC and AHA emphasize LSM and suggest statins based on risk assessment as the mainstay of treatment. Additional use of ezetimibe/proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is recommended if target goals are not met.

Bile acid sequestrants and bempedoic acid are also mentioned as additional agents. AHA considers CAC as an additional risk discriminator. ESC recommends statins for stage 3–5 CKD (class I) and not for dialysis-dependent patients (class III) while AHA merely recognizes CKD as a risk enhancer.

Table 6 summarizes the treatment strategies suggested by AHA and ESC guidelines. **Table 7** will help the reader choose the dose of statins depending on the percentage of LDL reduction needed.

TABLE 6: Treatment strategies suggested by AHA and ESC guidelines.

10-year ASCVD risk		ACC/AHA	ESC
Very high risk	Definition	NA	≥7.5 to ≥15 depending on the age without established ASCVD
	Target	NA	Reduction ≥ 50% from baseline/<55 mg/dL
High risk	Definition	≥20%	2.5–15%
	Target	Reduction ≥50% from baseline	Reduction ≥50% from baseline/<70 mg/dL
Intermediate risk	Definition	7.5 to <20%	NA
	Target	If statin therapy is indicated, reduction of LDL by 30–49%	NA
Borderline risk	Definition	5 to <7.5	NA
	Target	Moderate intensity statin if risk-enhancers present	NA
Low risk	Definition	<5%	NA
	Target	LSM	NA
LDL ≥190 mg/dL		High-intensity statins	FH genetic testing Or Dutch lipid clinic network score
DM 40–75 years without established CVD		Evaluation, stepwise approach	Moderate–high-intensity statins
CKD stage 3–5, nondialysis patients		Utilize as risk enhancer	Statins

(ACC: American College of Cardiology; AHA: American Heart Association; ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; CVD: cardiovascular disease; DM: diabetes mellitus; ESC: European Society of Cardiology; FH: familial hypercholesterolemia; LDL: low-density lipoprotein; LSM: lifestyle measures; NA: not applicable)

TABLE 7: Dose of statins depending on the percentage of LDL reduction needed.

Treatment intensity	Atorvastatin	Rosuvastatin	Simvastatin	LDL reduction (%)
Low			10	30
Medium	10		20	38
Medium	20	5	40	41
High	40	10	80	47
High	80	20		55
Very high		40		63
High + ezetimibe				>65
PCSK				>60
High + PCSK				75
High + PCSK + ezetimibe				85

(LDL: low-density lipoprotein; PCSK: proprotein convertase subtilisin/kexin)

Obesity

While both the guidelines focus on lifestyle modification, ESC advocates medication such as orlistat, naltrexone, bupropion, and high-dose liraglutide or bariatric surgery.

Smoking

Both the guidelines advocate counseling and pharmacotherapy such as nicotine replacement, bupropion, or varenicline. While AHA is against electronic nicotine delivery system (ENDS), ESC says they are less harmful but do not encourage them.

RISK-ENHANCING FACTORS

There is a possibility of underestimating the risk while using the conventional risk factors discussed above in specific populations. Metabolic syndrome, CKD, renal transplantation, chronic inflammatory diseases such as psoriasis and systemic lupus erythematosus (SLE), and human immunodeficiency virus (HIV) will pose additional risks to the individuals. Family history of premature heart disease (males aged <55 and females <65 years), elevated Lp(a), or ABI <9 should be given weightage while considering preventive measures even if the predicted risk is otherwise low. A CT calcium score of more than zero may serve as an indication for starting statins in some individuals **(Table 8)** while a score of zero might avert the use of statins even in the presence of high risk score/high LDL.

Table 9 gives an illustration of this effect. Mr Raja, in routine outpatient services, is likely to end up on statins given his high LDL. But zero calcium score lowers his risk score whereas Mrs Rani ends up on statins as well as aspirin with a much lower LDL level than Mr Raja.

PHYSICAL ACTIVITY

Guidelines share an unequivocal view on exercise. They recommend a detailed physical activity assessment so that a personalized exercise prescription based on the FITT (frequency, intensity, time, and type) principle can be provided to the individuals. 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic exercises per week are the standard recommendation by these guidelines. Specific goal setting, re-evaluation, monitoring of the same, and promoting wearable activity trackers are some of the key measures to increase adherence to physical activity. Equal importance is given to reducing sedentary behavior and promoting resistance and balancing exercises.

NUTRITION

The Mediterranean or a similar diet like a whole-food plant-based diet is recommended. Guidelines focus mainly on increasing the fruits and vegetable intake to a minimum of 4–5 servings, promoting whole grains, plant-based proteins, fiber, and nuts and seeds. Avoidance of saturated fat, trans fat, and sugar-sweetened beverages (SSBs) should be focused on at each dietary counseling. Approximately 16 million (1.0%) disability-adjusted life-years (DALYs) and 1.7 million (2.8%) deaths worldwide are attributable to low fruit and vegetable consumption. Hence, a personalized diet prescription with reinforcement in the portion of food that needs to be taken more (fruits, vegetables, whole grains, fiber, nuts, and seeds), rather than the ones that are to be avoided, will help improve adherence to the prescribed diet. A diet prescription is not a one-time affair and needs to be followed.

TABLE 8: Coronary artery calcium in primary prevention.

	AHA 2019	SCCT expert consensus statement 2017	National Heart Foundation of Australia 2021
When to consider measuring CAC	• In adults 40–75 years of age without diabetes mellitus and with LDL-C 70–189 mg/dL at a 10-year ASCVD risk of 7.5–19.9% • If a decision about statin therapy is uncertain	• In asymptomatic individuals without clinical ASCVD who are 40–75 years of age in the 5–20% 10-year ASCVD risk group • 5% ASCVD group such as those with a family history of premature coronary artery disease	• Moderate absolute cardiovascular risk, as assessed by the NVDPA absolute cardiovascular risk algorithm • Selected people with low absolute CVD risk
Treatment recom-mendations	• *CAC score of 0 AU*: Withhold statin therapy and reassess in 5–10 years, as long as higher risk conditions are absent (e.g., diabetes mellitus, strong family history of premature CHD, cigarette smoking) • *CAC score of 1–99 AU and <75th percentile*: Reasonable to initiate statin therapy for patients >55 years of age • *CAC score of >100 AU and/or >75th percentile*: It is reasonable to initiate statin therapy and aspirin	• *CAC score of 0 AU*: Statin not recommended in the 5–20% ASCVD risk group • *CAC score of 1–99 AU*: Moderate-intensity statin if <75th percentile; moderate-to high-intensity statin if >75th percentile • *CAC score of 100–299 AU*: Moderate-to high-intensity statin 1 ASA 81 mg • *CAC >300*: High-intensity statin 1 ASA 81 mg	• *CAC score of 0 AU*: No statin (Caution in underestimating the risk in the presence of certain risk-enhancing factors, e.g., aboriginal and Torres Strait Islander population, cigarette smoking, diabetes, and a family history of CVD) • *CAC score is 1–99* AU and 99 AU or ≥75th percentile for age and sex could reclassify a person indefinitely to high absolute risk status • *For CAC scores >99 AU or ≥75th percentile*, follow contemporary guidelines for management of absolute CVD risk

(AHA: American Heart Association; ASA: acetylsalicylic acid; ASCVD: atherosclerotic cardiovascular disease; CAC: coronary artery calcium; CHD: coronary heart disease; CVD: cardiovascular disease; LDL: low-density lipoprotein; NVDPA: National Vascular Disease Prevention Alliance; SCCT: Society of Cardiovascular Computed Tomography)

TABLE 9: Case example incorporating CAC.

	Mr Raja	Mrs Rani
Age (years)	65	55
Risk factors	Nonsmoker No family history of IHD Normal sugars BP: 134/80 TC: 240 HDL: 40 LDL: 160	Nonsmoker No family history of CVD Normal sugars Obese, OSA BP: 134/80 TC: 220 HDL: 50 LDL: 110
Traditional treatment	Statins + LSM	LSM
CAC score	0	110
Post CAC	LSM	LSM + statins + aspirin

(CAC: coronary artery calcium; CVD: cardiovascular disease; IHD: ischemic heart disease; LSM: lifestyle measures; OSA: obstructive sleep apnea; TC: total cholesterol)

SPECIAL POPULATIONS

Gender-specific Risk

Cardiovascular disease remains the leading cause of morbidity and mortality for women worldwide. In all, one in three women die from CVD, and 45% of women over the age of 20 years have some form of CVD. The cardiological societies in association with the obstetrics and gynecological bodies have identified CVD risk factors that are unique to women.[17]

Women with a history of adverse pregnancy outcomes (APOs) have a 1.8–4.0% risk of future CVD. The risk is higher when the APO is severe or there is a recurrence of APOs. APOs are likely to be mediated through endothelial dysfunction. It is well known that endothelial dysfunction plays a role in every step of atherosclerosis progression. All women with APOs should undergo CVD risk assessment within 3 months of delivery. Autoimmune diseases are more common in females than males and predispose them to CVD. Premature menopause, hormone replacement therapy (HRT) for menopause, polycystic ovarian disease (PCOD), chemotherapy, and radiation for malignancies also predispose females to CVD. All females with gestational diabetes, intrauterine growth retardation (IUGR), obesity, hypertensive disorders of pregnancy, sleep disorders, and psychosocial stress are recommended to undergo CVD screening. Women with migraine with aura are not to be prescribed oral contraceptive pills (OCPs). While prescribing statins to women of childbearing potential, they should be advised to hold statins 3 months before attempting to conceive till the completion of breastfeeding.

Similarly, men with erectile dysfunction should undergo a CVD risk assessment.

Pediatric Population and Youth

Children provide the window of opportunity to retard the progression of CV risk factors in themselves and CVD in their family members as risk factors take root in the womb, childhood, and youth. An integrated CV health schedule advises a smoke-free home, universal screening for lipids from 9 years of age or earlier if there is a family history of CVD/dyslipidemia or if the child has other CV risk factors, measurement of blood pressure by 3 years of age, and glucose estimation by 9 years of age. Few other conditions such as CKD, cancer treatment, and chronic inflammatory conditions such as SLE predispose youth to early CVD. Cardiac conditions such as coarctation of the aorta (accelerated atherosclerosis/hypertension) and transposition of the great arteries (TGA) with arterial switch (because of reduced coronary flow reserve/proximal intimal thickening) predispose to CAD while cyanotic heart disease and Eisenmenger patients are prone to CVA/peripheral vascular disease (PVD) (secondary erythrocytosis and hyperviscosity syndromes).[18]

INDIAN SCENARIO

Indians experience an early onset of atherosclerosis. Coronary atherosclerosis tends to be diffused with relatively less incidence of traditional risk factors and higher mortality when compared to their western counterparts.

The leading risk factor that contributed to DALYs due to heart disease in India is the dietary risk factor [56.4%, 95% uncertainty interval (UI) 48.5–63.9] followed by high systolic BP (54.6%, 49.0–59.8). Other major contributory factors are air pollution (31.1%), high total cholesterol (29.4%), tobacco use (18.9%) high fasting plasma glucose (16.7%), and high body mass index (BMI) (14.7%).[19]

The largely attributable burden for dietary risk factors such as diets low in fruits, vegetables, whole grains, nuts and seeds, and seafood omega-3 fatty acids surprisingly shares the major risk load when compared to red meat, processed meat, and SSBs.

Underproduction and overpricing of vegetables and fruits, westernization of culture, increasing sedentary life because of mechanization, overreliance on tobacco and alcohol for revenue generation and poorly planned urban expansion, and ever-increasing pollution are the stumbling blocks.

Even in the two most economically prosperous states, Maharashtra and Tamil Nadu, the WHO-recommended consumption of more than five fruits and vegetables daily is only observed among 24% and 1% of people, respectively.

NEED OF THE HOUR

The changes should begin at all levels—home, society, schools and colleges, working places, religious places, health centers, and national level.

National Level

Modeling studies have given the hope that by imposing taxes on tobacco, palm oil, and SSBs in India, substantial gains can be achieved. Smoke-free legislation coupled with tobacco taxation may help avert one-fourth of the CVDs. The national polio eradication program in 2003 effectively used the Indo-Pakistan cricket matches as a source to disseminate or educate the public. The Indian Premier League (IPL) venues could serve

as one in the present era for education on CVD prevention. Medical curriculum should incorporate preventive medicine and nutrition as part of their syllabus and have refresher courses at all levels. It will be worth considering exclusive courses on preventive medicine for medical and paramedical people. All preventive programs should be covered under medical insurance.

Scientific Bodies

Creation of Guidelines and Risk Stratification Tools Exclusively for Indians

Large systematic studies on the prevalence of ischemic heart disease (IHD) are not available in India. Similarly, there is a paucity of data on CVD risk factors. The majority of the data stems from the South Asians who immigrated and settled elsewhere. The population of South Asia is about one-fifth of the entire world. Over 80% of South Asians in the United States (SAUS) are Indians. Amongst all the ethnic groups, South Asians have the highest share of CVD. The INTERHEART and MASALA studies have thrown light on CV risk factors and subclinical atherosclerosis. South Asian ethnicity is regarded as a risk enhancer while considering statins as a preventive measure by both 2016 ESC prevention guidelines and 2018 AHA/ACC multi-society guidelines. The Indian scientific societies such as Indian Council of Medical Research (ICMR), Cardiology Society of India (CSI), Association of Physicians of India (API), Indian Association of Pediatrics (IAP), Indian Psychiatric Society (IPS), Endocrine Society of India (ESI), LAI, Federation of Obstetric and Gynecological Societies of India (FOGSI), and Indian Medical Association should interact and frame the national guidelines and risk stratification tools, disseminate the key messages, and adopt and practice the guidelines.

Adoption of SAUS Cutoffs for Now

The rise in ASCVD in South Asians is akin to what transpired in the early part of the 20th century in the United States. Subsequently, there was a decline in CVD mortality in the last few decades in the United States. However, CVD mortality in South Asians continues to climb. The constellation of conventional risk factors in combination with unhealthy behaviors has placed South Asians at a high risk. Given the alarming CVD burden, it is appropriate to incorporate all three levels of prevention, namely primordial, primary, and secondary prevention, concurrently while the western countries adopted a stepwise approach from secondary to primary to primordial prevention.

The American Diabetes Association (ADA) and WHO have cautioned about a higher prevalence of DM in SAUS at a lower BMI and hence recommend a lower cutoff for metabolic parameters **(Table 10)**.[20] Indian scientific societies should examine and adopt or modify the cutoffs and popularize the same amongst the medical, paramedical staffs, and the public.

Healthcare Centers

Primary prevention should be the focus of all health centers. Primary prevention measures need an interprofessional healthcare team approach involving physicians, nurses, physiotherapists, dieticians, psychologists, clinical pharmacists, public, and patients and their family members.

Preventive medicine should be incorporated into the daily practice of life and medicine. We suggest the six pillars of a healthy life approach for all NCDs with a focus on eating habits, exercise, sleep, stress, risky substances, and relations in every visit to the clinic. These behavioral factors lead to physiological (metabolic) changes, which in turn lead to structural changes (subclinical atherosclerosis). Left alone, these changes lead to the tip of the iceberg, namely CVDs. We propose a modified version of the six-pillar approach adopted by the American College of Lifestyle Medicine (ACLM) for regular clinical follow-up **(Flowchart 1)**.[21]

TABLE 10: Targets of risk reduction.

HbA1c	<6
WC	80 cm in females/90 cm in males
BMI	<23
Lp(a)	<50 mg/dL
TC	<160
LDL	<70 for high risk, <50 very high risk, <30 extreme risk*
HDL	>50 in females, >40 in males
TGL	<150
Non-HDL-C	<100 for high risk, <80 very high risk, <60 extreme risk

*High risk: 20–29% 10-year ASCVD risk; very high-risk: 30–39% 10-year ASCVD risk; extreme-risk: ≥ 40% 10-year ASCVD risk

(ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; HDL-C: high-density lipoprotein cholesterol; LDL: low-density lipoprotein; Lp(a): liproprotein(a); TC: total cholersterol; TGL: triglyceride level; WC: waist circumference)

Pharmaceutical Industry

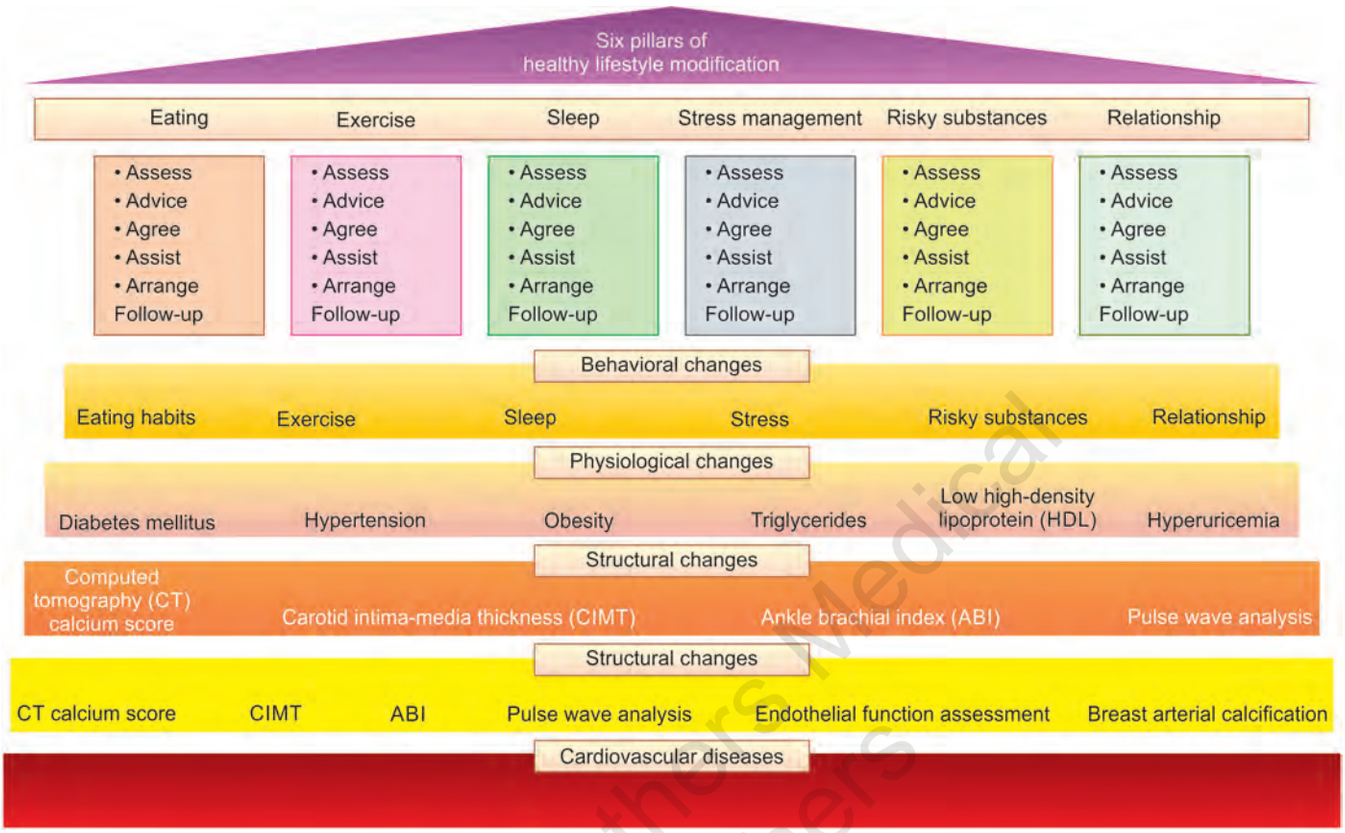
The promotion of polypills by the pharmaceutical industries in consultation with professional bodies will enhance drug compliance. The price regulation measures should be implemented seriously and should be extended to the drugs prescribed for primary prevention.

Community

Community should stick to the traditional culture and encourage traditional food and culturally acceptable physical activities such as local dancing practices and yoga. Organic farming and common kitchen gardens should be encouraged. Community gyms and cycling competitions should get precedence. Communal harmony should prevail. Social media should shoulder the responsibility of spreading the key health information provided by our national bodies and discourage advertisements for unapproved and unhealthy food and food products.

Young Starts, Strong Hearts

Schools and colleges should promote healthy eating habits in their respective cafeteria and canteens. Fruits and vegetables should be promoted. Physical activity should be encouraged.



FLOWCHART 1: Modified version of the six-pillar approach (American College of Lifestyle Medicine) for regular clinical follow-up.

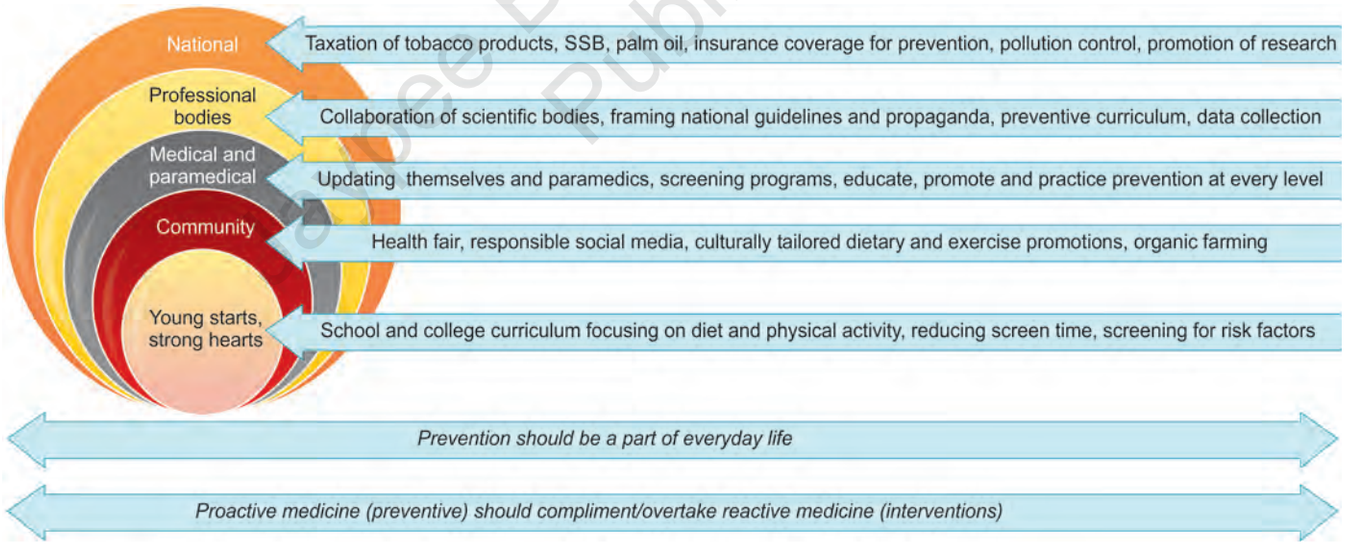


FIG. 2: Changes needed from schools to national level.
(SSB: sugar-sweetened beverages)
Source: By courtesy of Ms Abirami Sakthivel MSW, PSGIMSR.

Kids of cardiac patients and other vulnerable students should be screened for risk factors and should be educated about lifestyle changes. Measures to reduce screen time should be given priority.

Figure 2 summarizes the changes needed from schools to national level.

An empowered community and enlightened policy can together help in effectively quelling the emerging CVD epidemic.

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CHAPTER 46

Use of Biomarkers: Troponin and B-type Natriuretic Peptide—in Cardiovascular Risk Stratification and Disease Prevention

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ABSTRACT

Cardiovascular disease (CVD), which includes coronary heart disease (CHD), stroke, and heart failure (HF), remains the leading cause of morbidity and mortality worldwide and, in addition, causes a significant economic burden. Hence, understanding and identifying risk factors associated with CVD are important so that prevention and treatment strategies can be initiated in a timely manner. Cardiovascular risk prediction models have been developed for estimating the risk of CVD using various modifiable and nonmodifiable risk factors. However, current models, while good, can be improved to identify the highest risk individuals. Along with imaging, biomarkers continue to be explored in helping to identify these at-risk individuals in the general population. Cardiac troponin (cTn) and brain natriuretic peptide (BNP)/N-terminal proBNP (NT-proBNP) are routinely used in the diagnosis and management of acute manifestations of CVD such as myocardial infarction and heart failure. However, with additional research in combination with advances in technology, the value of these biomarkers in predicting incidents of short- and long-term cardiovascular risk including heart failure in the general population has been emerging. Elevated levels of cTn (measured with newer high-sensitivity assays) and BNP/NT-proBNP in individuals at risk for CVD (such as patients with hypertension and diabetes) appear to be a marker of CVD (including heart failure) and mortality and identify the individuals at the highest risk. Hence, elevation of these markers in the general population can be considered as a "silent cry" of the heart for help, given ongoing myocardial injury and neurohormonal stress. Routinely incorporating these biomarkers in CVD risk prediction and whether early initiation of risk-modifying treatment in such individuals will improve outcomes remain to be tested.

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide. CVD includes coronary heart disease (CHD), heart failure (HF), and stroke.[1] Lifetime risk for CVD is approximately 50% after 30 years of age.[2] According to the American Heart Association (AHA), approximately 18.6 million global deaths in 2019 were due to CVD.[3] India and the United States follow similar patterns with respect to CVD.[1,4] In 2017, one in three deaths in the United States was attributed to CVD.[5] In India, the estimated prevalence of CVD was 54.5 million in the general population, accounting for one in four deaths in 2016.[6] The prevalence of CVD increases with age as noted in the Longitudinal Aging Study in India (LASI Wave 1) with prevalence of CVD being 38% in ages >70 years compared to 22% in the 45–54 years age group.[7] Globally, CVD causes significant health and economic burdens. Per AHA reports, CVD-related medical costs and productivity losses are expected to grow from $555 billion in the year 2015 to $1.1 trillion by the year 2035. In addition to being the leading cause of mortality in India, CVD also occurs prematurely with CHD being identified in the Indian population on an average of 10 years earlier than the Western counterparts with the mortality being 20–50% higher.[8] Based on this, the American College of Cardiology (ACC)/AHA has recognized the South Asian ancestry as a risk-enhancing factor for CVD.[9]

On the other hand, between 1980 and 2000, there was a decrease in heart disease mortality in the general population in the United States. Based on the CVD policy model, which is a population-level computer simulation of CVDs, this reduction in mortality was attributed to evidence-based treatments and reductions in major CVD risk factors. However, since 2011, the cardiovascular mortality has been noted to be increasing, especially in population over 65 years of age. This increase is due to increasing rates of diabetes, obesity, and higher rates of HF in adults aged 65 years and older. Although CHD contributes

to the highest total mortality in the overall population, HF is the leading cause of mortality in adults over 65 years, accounting for approximately 80% of all heart disease-related deaths.[10,11] HF prevalence is increasing in this older population due to growing risk factors for HF and longer survival after cardiac events. The prevalence of HF in India ranges from 1.3 to 4.6 million in the general population while prevalence is 2.4% in the United States. In 2012, the total cost for HF was estimated to be $30.7 billion in the United States, with projected increase in costs for care by 127% in 2030.[12]

Biological mechanisms, social determinants, and their complex dynamics continue to lead to increasing risks for CHD and HF worldwide although treatment and prevention strategies have helped. Hence, understanding and identifying these risk factors are important so that prevention and treatment strategies can be initiated in a timely manner. Cardiovascular risk prediction models have been developed for estimating the risk of CVD using various modifiable and nonmodifiable risk factors such as age, diabetes mellitus (DM), gender, total cholesterol, high-density lipoprotein cholesterol (HDL-C), smoking, and systolic blood pressure (SBP) among others. The Framingham CHD risk score was the first risk prediction tool recommended in the 1998 guidelines in the United States. However, it was derived in a predominantly white population and furthermore was developed to predict CHD events only. Several other risk prediction scores were developed including systematic coronary risk evaluation (SCORE), which is used in Europe, QRISK, the Reynolds, atherosclerosis risk in communities (ARIC), and multiethnic study of atherosclerosis risk scores (MESA).[13-16] However, given stroke and CHD share common risk factors, efforts were made to establish a CVD risk model which included CHD and stroke. In 2013 (revised in 2018), the ACC/AHA atherosclerotic cardiovascular disease (ASCVD) risk calculator was developed with endpoints including CHD death, nonfatal myocardial infarction (MI), and fatal/nonfatal stroke, although HF was excluded.[17] This risk score, in addition to including stroke as an outcome, also was developed using multiple cohorts, which included Black Americans and hence was more generalizable. However, even this risk score has limitations in addition to not including HF as an outcome; the population from where the risk score was developed did not include other ethnicities including South Asians. Furthermore, these risk scores do not include other known factors/markers such as family history, lipoprotein(a), and C-reactive protein. Identifying additional risk factors will be important in the given data such as an analysis by Khot et al. who reported that among 122,485 patients recruited in approximately 14 randomized clinical trials, 15% men and 19% women lacked any traditional risk factors during their initial presentation with an acute coronary syndrome.[18] Hence, there is a clear need to improve CVD risk prediction.

Residual CVD risk is the risk for cardiovascular events that remains despite optimal risk factor management. The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY) studies have described the residual CVD risk even after optimal low-density lipoprotein cholesterol (LDL-C) reduction. For example, despite achieving LDL-C levels of approximately 30 mg/dL with the use of medications such as statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), the major adverse CVD event rate in the treatment arms of these studies remained high, around 9.8% over 3 years for FOURIER study and 9.5% over 2.8 years for ODYSSEY study. This suggests that residual risk may involve pathways beyond traditional risk factors such as lipids and include risk factors such as systemic inflammation, metabolic abnormalities, or prothrombotic states that still do not have optimal therapies or yet to be identified risk factors.[19-21]

Hence, identification of risk not captured by traditional risk factor models may help in not only identifying the highest risk individuals but also in identifying novel pathways to target for development of therapies. Along with imaging, biomarkers may provide us with important ways to help improve risk prediction and in the identification of novel pathways. Biomarkers such as troponin and B-type natriuretic peptides (BNPs) have been emerging as important predictors of CVD risk including HF, and we will discuss these markers in detail below.

EVOLUTION OF THE USE OF CARDIAC TROPONIN IN CARDIOVASCULAR DISEASES

In the early years of identifying myocardial injury, various biomarkers were used in the diagnosis of acute myocardial infarction (AMI). In the 1960s, aspartate transaminase (AST) became the first biomarker, followed by lactate dehydrogenase (LDH) and creatinine kinase (CK) in the 1970s. Advancements in electrophoresis were further helpful in detecting cardiac-specific isoenzymes of CK, namely CK-MB.[22] In the 1990s, the advent of more reliable and sensitive immunoassays helped in the identification of troponin, which has over time become the biomarker of choice in the diagnosis of MIs.[23]

Troponin is a complex of three subunit proteins (troponin T, I, and C) that is part of the contractile apparatus within cardiac and skeletal muscles. The troponin complex serves as regulatory proteins that inhibit contraction by blocking actin and myosin interaction. Troponin C acts as the calcium-binding site and is found in skeletal and cardiac muscles. Troponin T attaches the troponin complex to the actin filament and troponin I prevents myosin from binding to actin in a relaxed muscle. Up to 95% of cardiac troponin (cTn) is bound to cardiac sarcomere actin filaments and the remaining 5–8% are free in the myocyte cytoplasm. Unbound cTn is thought to be released promptly following myocyte injury due to various mechanisms and cleared through the kidneys. Structurally bound cTn degrades over several days with gradual troponin release. Immunometric assays are used to identify cardiac myocyte-specific troponins (cTn), namely troponins T and I.[24] Troponin assays have been differentiated into conventional, sensitive, and high-sensitivity cTn assays.[22] Although conventional cTn had a high diagnostic value, the sensitivity was weak.[25] With advances, more sensitive troponin assays with greater precision have been developed, leading to improved care in acute coronary syndromes and its incorporation in the universal definition of MI.[26-30]

In addition to being the biomarker of choice in the setting of clinical symptoms of AMI, elevation of cTn has prognostic implications in hospitalized patients with other medical conditions including congestive heart failure (CHF), arrhythmias, pulmonary embolism, and sepsis.[31,32] For example, in an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE) study, troponin I (positive if >1.0 μg/L) or T (positive if >0.1 μg/L) was measured in 80.5% of patients hospitalized for acute decompensated HF. In these patients, 6.2% were found to have a positive troponin including those with and without a history of coronary artery disease or AMI and a positive cTn was found to be associated with higher in-hospital mortality.[33] Recent emergence of high-sensitivity troponin (HsTn) assays has seen the role of cTn emerge from being only a marker to assess for acute myocardial injury to the one that can identify ongoing myocardial injury/damage in the general population in nonacute settings as well, which we will review later.

EVOLUTION OF NATRIURETIC PEPTIDE SYSTEM

In the 1950s, questions were raised as to whether the heart may also have endocrine properties that could help to maintain stable blood pressure and plasma volume. Experiments in which the left atrium in dogs was artificially expanded elicited diuresis.[34] In 1981, atrial myocyte extracts injected into rats induced brisk diuresis and natriuresis. The active factor was eventually found to have a 28-amino acid peptide and was named atrial natriuretic factor (ANP). In the 1980s, an ANP-like natriuretic peptide was identified in the porcine brain, named brain natriuretic peptide (BNP), and subsequently noted to have peripheral receptors similar to ANP.[35,36] The *BNP* gene encodes for a 108-amino acid prohormone called proBNP. In the circulation, proBNP is split into biologically active BNP and biologically inert N-terminal proBNP (NT-proBNP). Cardiac myocytes in the atria and the ventricles mostly secrete BNP into the circulation from that stored in the cells or through activation of *BNP* genes. BNP has many target organs; it primarily affects the renal arterioles, increasing glomerular filtration, thus playing a role in diuresis, systemic vasodilation, and modulation of renin aldosterone production. Activation of *BNP* gene transcription is more rapid compared to *ANP* gene in response to cardiac stretch.[37] BNP is elevated in various cardiac diseases that cause cardiac muscle stretch. In chronic HF, there is a shift in BNP production from the atria to the ventricles. BNP knockout mice have revealed increased cardiac fibrosis, suggesting that BNP may protect against pathological remodeling that contributes to HF progression.[38] BNP and proBNP levels can be measured using immunoassays and used as biomarkers to identify increased cardiac stress.

Brain natriuretic peptide and NT-proBNP levels can be affected due to various factors and therefore need to be interpreted based on clinical presentation. They increase with age and have been noted to be higher in women and patients with renal failure while obesity has been associated with lower levels.[39,40] BNP levels have been used in acute clinical settings for diagnostic and prognostic purposes. A meta-analysis conducted in 2005 to evaluate the value of circulating BNP levels (ranging from 50 to 250 pg/mL) showed that in a pooled analysis of 11 studies, as the BNP levels increased, the likelihood ratio (LR) of HF also increased (LR 1.7–4.6).[41] In the Breathing Not Properly (BNP) multinational study, 1,586 patients who presented to the emergency room with acute dyspnea were evaluated and patients with HF were found to have higher BNP levels than patients with other causes of dyspnea despite left ventricular (LV) dysfunction. A plasma BNP >100 pg/mL diagnosed HF with a sensitivity, specificity, and predictive accuracy of 90%, 76%, and 83%, respectively.[42] The current ACC/AHA guidelines recommend the use of BNP and NT-proBNP to diagnose HF.[43] BNP levels have also been shown to rise rapidly over the first 24 hours after MI, and when measured between 1 and 7 days can identify patients at risk for LV dysfunction, HF, and death.[44] Similar to acute settings, troponin and BNP have been found in asymptomatic general population and we will review the implications of these levels found in various studies over the past 20 years.

DETECTION AND SIGNIFICANCE OF TROPONIN IN ASYMPTOMATIC GENERAL POPULATION

In 2006, an analysis from the Dallas Heart Study (DHS) examined the prevalence and determinants of cardiac troponin T (cTn-T) elevation (using a traditional assay) in 3,557 subjects aged between 30 and 65 years with a third-generation troponin assay and correlated elevated cTn levels with clinical findings and magnetic resonance imaging (MRI) variables. The authors reported that 1.15% of the study population had detectable levels of cTn correlating with 0.7% population prevalence. In multivariable logistic regression analysis, cTn elevation was independently associated with HF [odds ratio (OR) 5.3; 95% confidence interval (CI) 1.9–14.8], DM (OR 4.6; 95% CI 1.8–11.6), left ventricular hypertrophy (LVH) (OR 5.4; 95% CI 2–14.6), and chronic kidney disease (CKD) (OR 20.4; 95% CI 7.5–55.3).[45] Subsequently, along with DHS, two other large epidemiological studies [the ARIC study and the Cardiovascular Health Study (CHS)] used HsTn assays to identify the prevalence and value of cTn, mainly troponin T (HsTn-T) in the general population, and studied its association with major adverse cardiovascular events. The results from these analyses identified the potential role of HsTn-T in CVD risk prediction and cardiovascular prevention.

In DHS, cTn level measurements were available using standard (as noted previously) and high-sensitivity assays in 3,546 subjects aged 30–65 years (younger age group). Outcomes assessed included MRI measurements of cardiac structure, function, and mortality over a median follow-up of 6.4 years. Prevalence of detectable cTn-T was 25.0% using high-sensitivity assays while it was 0.7% with the standard assay. Prevalence of LVH, LV dysfunction, and CKD increased as the cTn levels increased. After adjustment for traditional risk factors, cTn-T elevation detected with a highly sensitive assay was noted to be independently associated with structural heart disease and all-cause mortality.[46]

The CHS study is a prospective epidemiological study designed to identify CVD risk factors related to the onset of

CHD and stroke in adults aged 65 years or older. Troponin T was measured using a high-sensitivity assay in 4,221 ambulatory patients without pre-existing CHD or HF. In all, 66.2% of the study population had detectable HsTn-T. Over a median follow-up of 11.8 years, participants with the highest HsTn-T concentrations (>0.0129 ng/mL) had an incidence rate of 6.4 for HF (95% CI 5.8–7.2) and 4.8 for cardiovascular death (95% CI 4.3–5.4) compared to the incidence rate of 1.6 for HF (95% CI 1.4–1.8) and 1.1 for cardiovascular death (95% CI 0.9–1.2) in participants with undetectable HsTn-T. The authors also noted that a greater than 50% increase in HsTn-T levels was associated with a greater risk for HF and cardiovascular death. On the other hand, a greater than 50% decrease in HsTn-T levels was associated with lower risk for HF and cardiovascular death.[47] The ARIC study also measured cTn-T with a highly sensitive assay in a middle-aged population (age 54–74 years) of 9,698 subjects and evaluated its association with incident CHD, mortality, and hospitalization for HF. cTn-T was detectable in 66.5% of the study population. Elevated levels of HsTn-T were associated with an increased risk for CHD [hazard ratio (HR) 2.29; 95% CI 1.8–2.89], fatal CHD (HR 7.59; 95% CI 3.78–15.25), total mortality (HR 3.96; 95% CI 3.21–4.88), and HF (HR 5.95; 95% CI 4.47–7.92). Increased risk for mortality and HF ($p < 0.05$) was noted in those with any detectable HsTn-T levels.[48] All three of the above studies were conducted in the general population and were concordant with each other in terms of graded association of cTn-T levels with cardiovascular outcomes and mortality. The strongest associations were noted for HF. Hence, these studies confirmed the notion that cTn was not just a marker of AMI but could have a role in identifying the risk of adverse cardiovascular events in the general population.

Further studies have been done to identify whether measurement of HsTn levels added value to the traditional cardiovascular risk factors. In a cohort substudy of the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54), HsTn testing (troponin I) was added to ASCVD risk estimation to evaluate if it improved risk classification and could guide treatment strategies. The study included 8,635 patients with a mean age of 65 years. Patients were stratified by ACC/AHA cholesterol guidelines-derived risk groups. The primary endpoint was a composite of cardiovascular death, stroke, and MI. Patients were also classified based on HsTn-I levels, with cut points of <2 ng/L being undetectable/low risk and >6 ng/L being high risk. The patients were further jointly classified, combining cholesterol guidelines and HsTn-I levels. In the high-risk ASCVD group, 9% patients with undetectable HsTn-I levels had a 3-year event rate of 2.7% (<1% per year). In the lower-risk ASCVD group, 22.6% of patients with HsTn-I level exceeding 6 ng/L had an event rate of 9.1%, similar to the event rate in very high-risk ASCVD group. Adding HsTn-I to guidelines-based ASCVD risk stratification algorithm reclassified 11.9% of patients into appropriate risk groups and improved risk stratification.[49]

Similarly, HsTn (troponin T) levels were also found to be helpful in risk assessment in patients with hypertension in the Systolic Blood Pressure Intervention Trial (SPRINT). In the SPRINT trial, a multicenter prospective study, a total of 9,361 patients were randomized to receive intensive (<120 mm Hg) versus standard (<140 mm Hg) SBP-lowering therapy and showed that SBP control <120 mm Hg was associated with a reduction in all-cause mortality and HF.[50] In a post hoc analysis of the SPRINT study, HsTn-T and NT-proBNP levels were analyzed to identify individuals with the greatest risk for mortality, HF, and whether these patients obtained the largest benefit associated with intensive SBP reduction. Elevated levels of biomarkers were defined as 14 ng/L or more for HsTn-T and 125 pg/mL or more for NT-proBNP. Out of the 9,361 participants enrolled, 25.6% had elevated HsTn-T, 38.2% had elevated NT-proBNP, and 16.0% had both levels elevated. In the elevated HsTn-T group, randomization to the intensive SBP group led to a 4.9% (95% CI 1.7–7.5%) absolute risk reduction (ARR) in death and HF compared to 1.7% (95% CI 0.7–2.5%) in patients without HsTn-T elevation. In the elevated NT-proBNP group, randomization to the intense SBP group led to ARR of 4.6% (95% CI 2.3–6.5%) versus 1.8% (95% CI 0.9–2.5%) in those without elevated levels. With both biomarkers elevated, ARR for death and HF was found to be 7.8% (95% CI 3.3–11.3%) versus 1.7% (95% CI 0.8–2.3%) when neither biomarkers were elevated. Thus, this post hoc analysis showed that intensive SBP lowering led to large absolute differences in death and HF in patients with abnormal HsTn-T and NT-proBNP and smaller differences when troponin and NT-proBNP were not elevated.[51] An analysis from the ARIC study visit 4 by Pokharel et al. also evaluated the value of HsTn-T levels across SBP groups and studied its association with incident CVD (incident CHD, stroke, and first HF hospitalization). In the 11,191 participants included for the analysis, resting SBP was categorized in 10 mm Hg increments (<120, 120–129, 130–139, 140–149, 150–159, and ≥160 mm Hg) and HsTn-T (<3, 3–5, 6–8, 9–13, and ≥14 ng/L) by previously evaluated categories. Incident rates for HF hospitalization, CHD events, and stroke were 9.9, 19.3, and 4.3/1,000 person-years, respectively, and in every SBP category, increasing HsTn-T levels were associated with increased risk for incident events. Of perhaps even more interest was the finding that subjects with elevated HsTn-T levels but relatively well-controlled SBP (e.g., HsTn-T levels ≥3 ng/L and SBP <140 mm Hg) had higher hazards for adverse cardiovascular events when compared to those with undetectable troponin but elevated SBP (e.g., HsTn-T <3 ng/L and SBP >140–159 mm Hg).[52] This analysis along with the analysis from SPRINT and other analyses suggested the possible use of biomarkers in identifying the highest risk individuals who may benefit the most from intensive blood pressure management and derive the greatest net benefit.

Risk stratification with HsTn has also been shown to be beneficial in the diabetic population. Sodium–glucose cotransporter-2 (SGLT-2) inhibitors have emerged as important cardioprotective medications over the past ~10 years. The CANagliflozin cardioVascular Assessment Study (CANVAS) assessed the effect of canagliflozin therapy in the prevention of major adverse cardiovascular events (MACE) (a composite of cardiovascular death, nonfatal MI, and nonfatal stroke) in patients with type 2 diabetes mellitus (T2DM). This study showed a significant reduction in MACE (event rate in the canagliflozin group was 26.9 per 1,000 patient-years compared to 31.5 per 1,000 patient-years in the placebo group; HR

0.86; 95% CI 0.75–0.97; $p < 0.001$ for noninferiority, $p = 0.02$ for superiority).[53] In a biomarker substudy of CANVAS, a combination of biomarkers including HsTn-T was evaluated for prognostic significance, long-term trajectory, and response to canagliflozin on cardiovascular and renal outcomes. Canagliflozin was found to lower HsTn-T levels over 6 years and patients with higher HsTn-T levels of ≥14 ng/L derived greater relative benefit for reduction in MACE.[54] Elevated biomarkers, hence, may help to identify diabetic individuals who may derive greatest benefit from adding SGLT-2 inhibitor therapy as well.

High-sensitivity troponin (troponin I) was also used to identify mortality and incident CVD in the ARIC study (visit 4). In this analysis, 8,121 participants aged between 54 and 74 years with no prior history of CVD were followed for a median of ~15 years. HsTn-I levels were found to be detectable in 85% of the study population. Outcomes measured include total incident CHD, incident stroke, incident HF hospitalization, incident atherosclerotic CVD, incident global CVD, and all-cause mortality. In comparison to low HsTn-I (HsTn-I ≤1.3 ng/L), elevated HsTn-I (HsTn-I ≥3.8 ng/L) was associated with greater incident CHD (HR 2.20; 95% CI 1.64–2.95), ischemic stroke (HR 2.99; 95% CI 2.01–4.46), ASCVD (HR 2.36; 95% CI 1.86–3.00), HF hospitalization (HR 4.20; 95% CI 3.28–5.37), global CVD (HR 3.01; 95% CI 2.50–3.63), and all-cause mortality (HR 1.83; 95% CI 1.56–2.14). Thus, elevations in HsTn-I, similar to HsTn-T, were noted to be strongly associated with increased global CVD incidence in the general population.[55]

Similar to how troponin augmented risk stratification with blood pressure and diabetes, studies have also evaluated its value in HF (prediction and in those with existing HF). In 2013, Nambi et al. evaluated the association between HsTn-T/NT-proBNP and incident HF and whether these levels could improve HF risk prediction in the ARIC population without prevalent HF. HsTn-T and NT-proBNP were added to age/race ("laboratory report" model) and to the ARIC HF model (which includes age, race, SBP, smoking status, antihypertensive use, DM, body mass index, prevalent CHD, and heart rate). Adding HsTn-T and NT-proBNP to the ARIC HF model improved the area under the receiver operating characteristic curve [area under the curve (AUC)] from 0.779 to 0.836 in men and from 0.776 to 0.817 in women. In all, 38% of men and 32% of women were reclassified with the addition of HsTn-T and NT-proBNP to the ARIC HF model. Additionally, the authors reported that the lab model was as good as the ARIC HF model although the model with the clinical variables and biomarkers performed the best.[56]

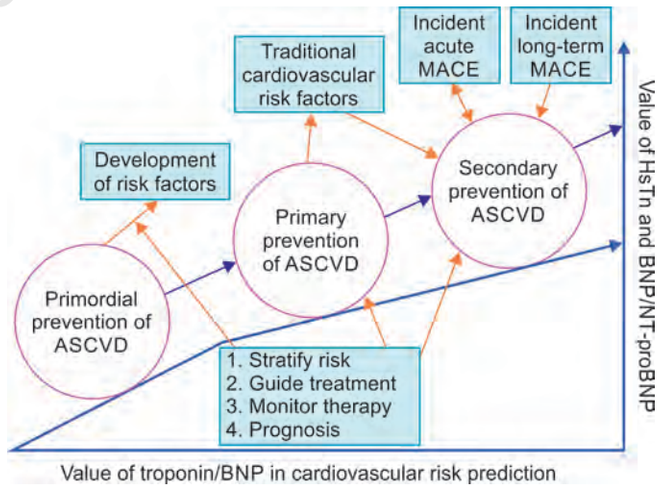
A meta-analysis published in 2018 analyzed data HsTn (T and I) from 16 studies in general population and 6 studies in high-risk patients (high risk defined by stable coronary artery disease, DM, and CKD). Data collected from these studies had 67,063 patients and showed the pooled HR for incident HF, comparing subjects in the top third versus those in the bottom third of HsTn concentration, to be 2.09 (95% CI 1.76–2.48; $p < 0.0001$). The study found a strong association between HsTn levels and the risk of incident HF event in the general and high-risk populations.[57] Troponin was also studied in patients with established HF in a meta-analysis of ~10 studies with 9,289 patients and median follow-up of 2.4 years. HsTn was added to a prognostic model with established risk markers including sex, age, etiology of HF, left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (EGFR), and NT-proBNP. HsTn was found to be independently associated with all-cause mortality, cardiovascular mortality, and hospital admissions for cardiovascular etiology and using HsTn as an additional tool for cardiovascular risk prediction.[58]

Therefore, troponin has progressed from a marker of acute injury to now being a part of risk prediction tools to aid in identifying individuals at the highest risk for cardiovascular outcomes. Use of this biomarker-aided approach to cardiovascular risk assessments may therefore help identify individuals who are at the highest risk and hence perhaps need earlier and more intensive interventions, although such approaches will need to be tested. Similar to troponin, BNP has been found to have value in the general population as well and has an emerging role in risk prediction and cardiovascular prevention, which we will further review **(Fig. 1)**.

SIGNIFICANCE OF MEASURING BNP AND NT-PROBNP IN THE GENERAL POPULATION

Brain natriuretic peptide and NT-proBNP have also been used to predict outcomes and aid in treatment decisions in the general population. In asymptomatic hypertensive patients, elevated BNP levels have been shown to correlate with extracellular matrix alterations, cardiac remodeling, and inflammation.[59]

An analysis from the Framingham study evaluated BNP in 3,346 subjects without HF and demonstrated that BNP



Note:

- *ASCVD*: Atherosclerotic cardiovascular disease; heart failure, coronary artery disease, stroke
- *Risk factors*: Diabetes mellitus, hypertension, smoking, hyperlipidemia, family history, age

FIG. 1: Emergence of HsTn and BNP/NT-proBNP levels: Detection in asymptomatic general population and risk prediction over time.

(ASCVD: atherosclerotic cardiovascular disease; BNP: brain natriuretic peptide; HsTn: high-sensitivity troponin; MACE: major adverse cardiovascular events; NT-proBNP: N-terminal proBNP)

levels above the 80th percentile (20.0 pg/mL for men and 23.3 pg/mL for women) were associated with increased risk for cardiovascular events over a mean follow-up of 5.2 years. The incidence rates of death and cardiovascular events (except for CHD) correlated with increasing BNP levels.[60] Similar results were found by Tsuchida Clinic of Internal Medicine and Cardiology in Japan. BNP levels were measured in 3,123 outpatient subjects from the year 1999 to 2002. Over a median follow-up for 5.5 years, BNP levels of ≥100 pg/mL (when compared to BNP <100 pg/mL) were associated with a HR of 4.6 for cardiovascular events, 18.8 for HF, and 0.6 for CHD events.[61]

In a meta-analysis of 95,617 subjects (mean age 61 years) without prior CVD enrolled in 40 prospective studies from 12 countries, the Natriuretic Peptides Studies Collaboration measured NT-proBNP concentrations from stored samples. There were two primary outcomes that were evaluated: one of the outcomes was the combination of first CHD and stroke and the second outcome was a combination of the first outcome and HF. Risk ratios (top third vs. bottom third of NT-proBNP concentration) were 1.76 (95% CI 1.56–1.98) for the combination of CHD and stroke and 2.00 (95% CI 1.77–2.26) for the combination of CHD, stroke, and HF. Adding NT-proBNP concentration to a model with conventional risk factors was associated with a C-index increase of 0.012 (95% CI 0.010–0.014) for the combination of CHD and stroke and 0.019 (95% CI 0.009–0.015) for the combination of CHD, stroke, and HF. Adding NT-proBNP to conventional risk factors for analysis increased the C-index (95% CI) to >0.7 for the first combined CHD, stroke, and HF. In this population without baseline CVD, NT-proBNP concentration strongly predicted first-onset HF, CHD, and stroke.[62]

Additional analyses from the ARIC study have examined the value of BNP/NT-proBNP in hypertension. ARIC study (visit 4) patients were grouped based on blood pressure categories and the authors examined whether NT-proBNP helps with identifying subjects at higher risk for CVD events. In this analysis, 9,309 participants with a mean age of 62.6 years were followed for a median of 16.7 years. The participants were grouped according to SBP, diastolic blood pressure (DBP), and pulse pressure (PP) categories. They were further stratified by NT-proBNP levels with NT-proBNP categorized as <100, 100 to <300, or 300 pg/mL. The primary outcomes included incident CHD, ischemic stroke, HF hospitalization, CVD, and all-cause mortality. The CVD event rates were the lowest for patients with NT-proBNP <100 and SBP <120 or 120–129 mm Hg. Increase in the levels of NT-proBNP, especially ≥300 pg/mL, had higher HR for HF hospitalization, CVD, and all-cause mortality. Interestingly, the study also found that subjects with stage 1 hypertension (SBP 120–139 mm Hg) and NT pro-BNP ≥300 pg/mL had higher risk for HF hospitalization and cardiovascular mortality compared to subjects with stage 2 hypertension (SBP ≥140–149 mm Hg) and NT-proBNP <100 pg/mL.[63] Therefore, whether adding NT-proBNP information could help identify individuals for intensive SBP control may need to be studied in future clinical trials.

N-terminal proBNP has also been evaluated for its role in risk prediction and treatment decisions in diabetic patients. In the study, NT-proBNP-selected PreventiOn of cardiac evenNts in a populaTion of dIabetic patients without A history of Cardiac disease (PONTIAC), 300 patients without cardiac disease with T2DM and NT-proBNP >125 pg/mL were randomized to an "intensive" treatment group, which included additional visits for up-titration of renin–angiotensin system (RAS) inhibitors and beta blockers or usual care. The primary endpoint was hospitalization or death due to cardiac disease after 2 years. After 12 months, a significant reduction in all-cause hospitalizations and cardiovascular hospitalizations was noted in the group randomized to intensive treatment. Hence, it seemed that NT-proBNP can help identify diabetic patients who may benefit from intensive neuro–hormonal therapy and thereby help prevent hospitalizations or CVD deaths.[64]

In addition, the STOP-HF (St Vincent's Screening to Prevent Heart Failure) study showed that using BNP for screening individuals for cardiology referral helped to reduce rates of combined systolic and diastolic dysfunction and HF. STOP-HF study was a large single-center trial involving 1,374 participants at risk for HF, defined by the presence of diabetes, hypertension, or known vascular disease. Participants were without established LV dysfunction or symptomatic HF and randomized to usual primary care versus referral to collaborative care between primary care and cardiology. Intervention group also received additional blood pressure-lowering medications. The primary endpoint of the study was the development of asymptomatic LV dysfunction with or without new HF and secondary outcome included HF. The primary endpoint, LV dysfunction with or without HF, was reported in 8.7% of the control group and 5.3% of the intervention group (OR 0.55; 95% CI 0.37–0.82). HF occurred in 2.1% of the control group and 1.0% of the intervention group (OR 0.48; 95% CI 0.20–1.20). Hence, BNP-based screening, intervention, and collaborative care including patient education reduced the LV systolic dysfunction, diastolic dysfunction, and HF.[65]

High-sensitivity troponin and BNP/NT-proBNP have been studied in combination for CVD risk stratification and to help with treatment decisions. Incorporation of both these biomarkers into the risk assessment and treatment decisions for hypertension was assessed in an analysis, which pooled data from ARIC, DHS, and MESA. The data included 12,987 subjects with no known CHD, stroke, or HF with a mean age of 55 years. Subjects were categorized based on 2017 ACC/AHA blood pressure guidelines into normal blood pressure (<120/80 mm Hg), elevated blood pressure (120–129/<80 mm Hg), low-risk stage 1 (130–139/80–89 mm Hg), and high-risk stage 1 or stage 2 hypertension (≥140/90 mm Hg). These groups were further stratified based on biomarker elevations; HsTn-T ≥6 ng/L and NT-proBNP levels ≥100 pg/mL were considered as elevated. The primary outcome of interest was an incident cardiovascular event as a composite of ASCVD or HF. In subjects with elevated blood pressure or low-risk hypertension, when HsTn-T or NT-proBNP was added, the 10-year cardiovascular incidence rate was 11.6% for those with elevated markers compared to 4.6% without elevated markers, with a 10-year number needed to treat (NNT) to prevent one event for intensive blood pressure-lowering of 36 and 85, respectively. In patients with high-risk stage 1 or stage 2 hypertension, the 10-year cardiovascular incidence rate was 15.1% with elevated biomarkers, 7.9% without elevated markers, and NNT to prevent one event of 26

and 49, respectively. Thus, cTn and BNP used in concert can aid in risk assessment algorithms and help identify individuals at increased risk for cardiovascular events.[66]

CONCLUSION

Biomarkers such as HsTn (T and I) and BNP/NT-proBNP have been emerging to be important prognostic markers and predictors of cardiovascular risk including HF. As we continue to use HsTn and BNP in the acute care, the value of these two biomarkers in outpatient populations for screening, prevention, prognostic risk stratification, and to guide treatment continue to emerge. Based on the 2022 ACC/AHA guidelines for the management of HF, at-risk patients with increased BNP levels or persistently elevated cTn in the absence of other etiologies have stage B or pre-HF.[43] HsTn-T and NT-proBNP have shown to have significant value in ASCVD and HF risk prediction. Given that these levels can identify the highest risk patients with hypertension and diabetes, their role in the management of these conditions continued to be assessed. Elevation of these markers in general population can be considered as a "silent cry" of the heart for help, given ongoing myocardial injury and stress. These can be added to existing risk prediction tools to identify high-risk individuals. Whether early initiation of risk-modifying treatment in such individuals will improve outcomes remains to be tested.

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CHAPTER 47

Reducing Cardiometabolic Risk Through Diet and Exercise: The Power of Lifestyle Change

Roshani Sanghani

ABSTRACT

The global burden of cardiometabolic disease and obesity is rising. There are many lifestyle contributors to these twin epidemics and clinicians need to know the latest literature to be able to have informed conversation with patients about helpful changes (beyond simply advising "healthy diet and exercise") in their daily practice. The word of the treating doctor still carries the highest weightage in a country like India, and this chapter aims to update and empower the practicing physicians to navigate the complex data and research to arrive at meaningful advice and counsel for their patients. This review brings to light concepts that provide the vocabulary to shift daily conversation from outdated unvalidated misconceptions to the latest evidence on healthy fat, low carbohydrate, and sufficient protein intake in the diet, along with a review of the literature on the relationship between salt intake, blood pressure, and cardiac outcomes. In addition, the impact of exercise (strength, cardio, and combination) and high-intensity interval training and managing sedentariness on improving cardiometabolic health are covered.

INTRODUCTION

The current burden of cardiometabolic syndrome According to 2020 reports, the global burdens of cardiovascular disease and high body-mass index are going up.[1] India ranks second to China in bearing the increasing global burden **(Fig. 1)**.[2]

In parallel with this trend, the report shares another statistic that is either good news or bad news, depending on how you look at it. The total number of disability-adjusted life years (DALY), deaths, years lived with disability (YLD), and years of life lost (YLL) due to dietary risks has also gone up.[3] This is bad news if (1) you have no idea what the relevant dietary risks are or (2) you have no idea on how to guide your patients to meaningfully change these risks. This same statistic can be good news if you consider dietary risk to be modifiable, through teachable and learnable steps. In this scenario, you have the potential to help your patients take their cardiovascular health back in their hands by helping them make meaningful changes in their lifestyle. This chapter aims to help you do just that.

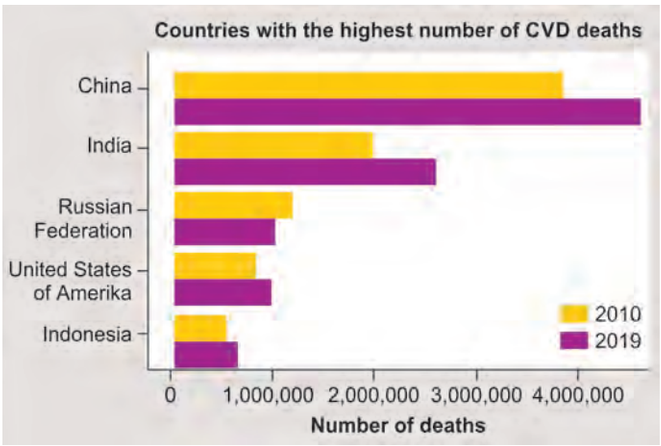
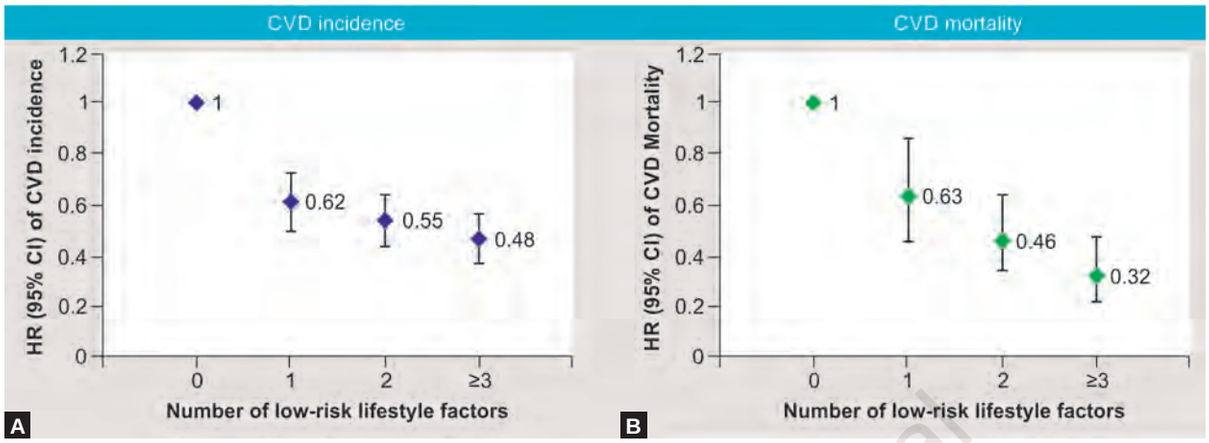


FIG. 1: Countries with highest number of CVD deaths.
(CVD: cardiovascular disease)

The Level of Evidence

The 2019 American College of Cardiology/American Heart Association (ACC/AHA) guidelines clearly state that there is a scarcity of large-scale prospective randomized trials with hard primary outcomes such as cardiovascular morbidity or mortality **(Fig. 2)**. The only randomized controlled trial till date that has demonstrated the power of lifestyle change is the landmark Diabetes Prevention.



FIGS. 2A AND B: (A) CVD incidence; (B) CVD mortality.
Source: Liu G et al. J Am Coll Cardiol. 2018;71(25):2876-76.

Program which showed that lifestyle change including 7% weight loss and 150 minutes of exercise per week were more powerful than metformin in preventing diabetes in 3,234 high-risk people with prediabetes and mean body mass index (BMI) of 34 who were followed for a mean of 2.8 years ($p < 0.001$).[4] Since then, we have not come across any further long-term government-funded head-to-head trial comparing lifestyle to pharmacology in preventing cardiometabolic disease. We can make notes of the lessons learned from the DPP, considering that diabetes is one of the strongest metabolic risk factors for cardiovascular disease. Insulin resistance has been a common link between diabetes and multiple traditional cardiovascular risk factors, and has been proven in mathematical models to possibly be the strongest contributing metabolic factor.[5]

One prospective observational study followed 11,527 participants with type 2 diabetes mellitus (T2DM) (who were free of cardiovascular disease at the start of the study) for an average of 13.3 years. They demonstrated the benefit of adhering to a healthy diet and lifestyle on incident cardiovascular events and mortality. There was a dose-response as well: Having multiple healthy habits gave greater risk reduction.[6]

DIETARY CHANGES TO REDUCE CARDIAC RISK

Healthy Fats

Mediterranean Fats

In Spain, a randomized controlled trial was conducted involving over 7,400 men and women aged 55–80 years who were free of CAD at enrollment but were considered to be high risk for coronary artery disease, because they had T2DM or three or more risk factors. The intervention group received healthy fats as part of the Mediterranean diet protocol (4 tablespoons of extra virgin olive oil or 15 g walnuts, 7.5 g almonds and 7.5 g hazelnuts daily). There was no calorie or fat restriction in the intervention group. The control group received a low-fat diet. In 2018, the corrected study data was published and showed lower hazard ratios in the Mediterranean diet group compared to the low-fat group **(Fig. 3)**.[7]

Dr Aseem Malhotra, a cardiologist based in the UK, has played a role in spreading the message that asking the entire planet to move to a low-fat diet has probably been one of the biggest mistakes in modern medicine,[8,9] and describes the Pioppi diet in his book by the same name inspired by a village in Southern Italy where locals enjoy a long-life expectancy.[10]

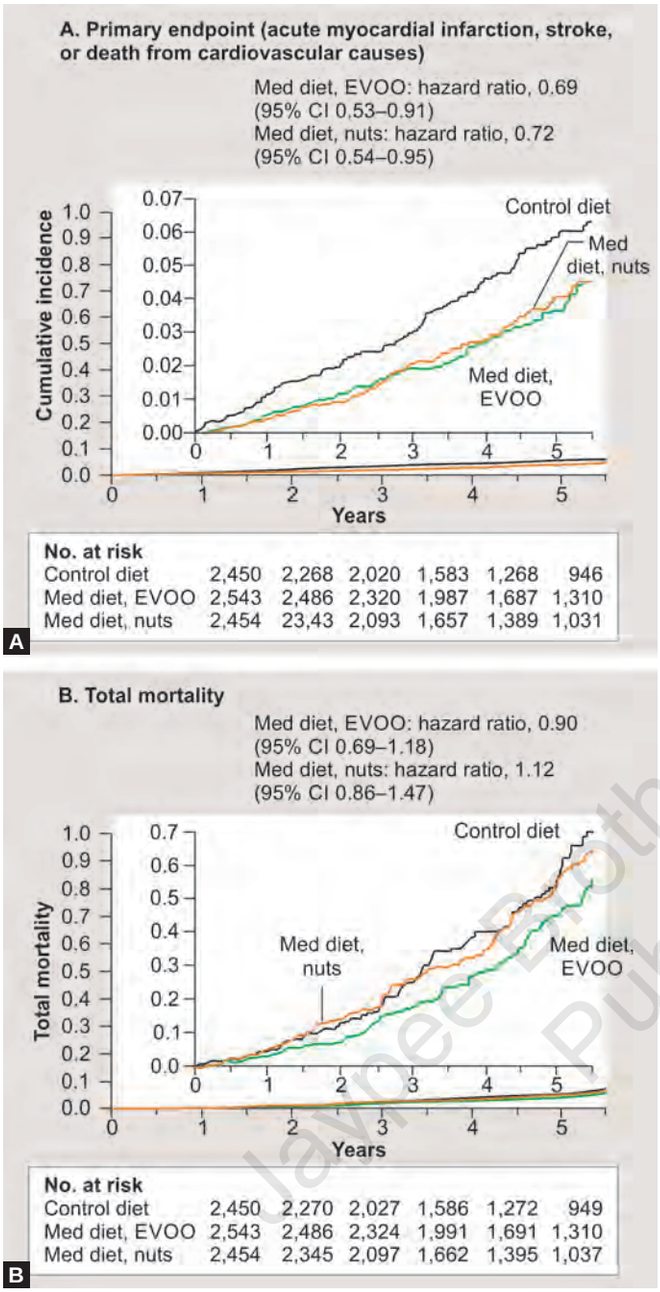
The Diet-heart Hypothesis: Poor Science

In the late 1940's and mid-1950's, scientists were looking for a relationship between diet and increasing cardiovascular mortality rates. The Diet-Heart hypothesis became popular, which suggested that dietary saturated fat might be affecting serum cholesterol, and perhaps these played some role in myocardial infarction. This hypothesis became widely accepted as truth after a controversial study called the Seven Countries Study conducted by Ancel Keys. The statistical methods used in this study would not pass scrutiny in 2022 by any institutional review board and yet its public acceptance in the 1960's and 70's translated globally into guidelines that fear of natural sources of saturated fat. The preferred dietary fat became refined "vegetable oils" rich in the omega-6 polyunsaturated fatty acids (PUFA) linoleic acid. The vegetable oils were, in fact, not derived from vegetables but from highly processed seeds such as soybean, cottonseed, corn, safflower, and canola.[11] Fifty years later, the Diet-Heart hypothesis remains without validation till date from any randomized controlled trials, yet the belief systems remain difficult to shake from popular culture.

Polyunsaturated Fatty Acids versus Saturated Fat

The Minnesota Coronary Experiment

This double-blind randomized controlled trial was conducted from 1968–1973 but the full results were not published at the time, possibly because some people (either the investigators or medical journal editors) were "disappointed"[12] with the results. Subsequent recovery of previously unpublished data made analyzed results available in 2016.[13] The data showed that replacing dietary saturated fat with PUFA (linoleic acid from corn oil) from vegetable oils for over a year in over 2,000



FIGS. 3A AND B: (A) Primary endpoint (acute myocardial infarction, stroke, or death from cardiovascular diseases); (B) Total mortality.
(CI: confidence interval; EVOO: extra virgin olive oil; Med diet: Mediterranean diet)

people from six state mental hospitals and one nursing home did not reduce cardiovascular disease or death. The control group who consumed >18% of their calories from saturated fat did not experience cardiovascular harm. In fact, those with greater reductions in serum cholesterol from the dietary intervention had higher death rates (22% higher risk of death for each lowering of 30 mg/dL, $p < 0.001$ and a 35% higher risk of death in subjects over the age of 65). The 2016 BMJ publication concluded that incomplete publication of the Minnesota Coronary Experiment (MCE) led to misleading study results.[14]

The Sydney Diet Heart Study

This was a single-blind randomized controlled trial to look at secondary prevention, measuring the effect of replacing saturated fat with linoleic acid PUFA (from safflower oil) in 458 men (age 30–59) with a recent coronary event. Although the study took place from 1966–1973, unpublished data was made available, analyzed, and published in the BMJ in 2013. The data showed the intervention group whose diet had safflower oil replacing saturated fat ($n = 221$) had higher rates of death than controls ($n = 237$) [all cause 17.6% vs. 11.8%, hazard ratio 1.62 (95% confidence interval 1.00–2.64), $p = 0.05$; cardiovascular disease 17.2% vs. 11.0%, 1.70 (1.03–2.80), $p = 0.04$; coronary heart disease 16.3% vs. 10.1%, 1.74 (1.04–2.92), $p = 0.04$].[15] The article went on to say that these findings have implications for the worldwide dietary advice that still tells people to substitute saturated fats with omega-6 PUFA oils. Indeed, as clinicians it remains important to stay updated as science evolves so that we are giving our patients advice based on the latest evidence.[16]

Omega 3: Omega 6 Ratio

It is now understood that as the ratio of omega 3: omega 6 reduces, there is a shift toward atherogenic dyslipidemia,[17] with a predominance of small, dense low-density lipoprotein (LDL) particles, 441-6 and intravascular inflammation as dietary linoleic acid increases. A study from India looked at the stability of common cooking oils rich in PUFA after exposure to high cooking temperatures common in Indian kitchens. This study showed PUFA containing oils to be the most unstable and reactive at high temperatures.[18] The high % of monounsaturated fatty acids (MUFA) in olive oil may explain its cardioprotective properties, and due to its low smoke point, it can be considered for use at room temperature or low heat. The most heat-stable fats which seem least likely to generate reactive oxidation species are ghee and coconut oil due to their saturated fat content and lack of available bonding sites (**Table 1**).

Dietary sources of omega-3 fatty acids include walnuts, freshly ground flaxseeds, chia seeds, soybeans and wild caught fatty fish. Increasing these in our diet while reducing PUFA (omega-6 linoleic acid)-rich processed or refined oils can improve the omega-3: omega-6 ratio in our diet.

Keto Diets

A randomized trial done by cardiologist Dr Eric Westman looked at the difference between a ketogenic diet versus a low-fat diet on lipoprotein subclasses and atherogenic particle types on nuclear magnetic resonance (NMR). The study involved people with an average BMI of 34. The intervention group got a ketogenic diet supplemented with fish, borage and flaxseed oil, compared to the standard low-fat low-calorie diet. Six months later, the intervention group showed more large-buoyant LDL and less small dense LDL even though it did not reduce total LDL cholesterol.[19]

TABLE 1: Composition of fats in oils.

Fat	Saturated fatty acids	Monounsaturated acids (MUFA)	Polyunsaturated fatty acids (PUFA)
Olive oil	14%	73%	11%
Coconut oil	86%	12%	2%
Palm oil	49%	42%	9%
Groundnut oil	17%	51%	32%
Sesame oil	14%	44%	42%
Sunflower	10%	24%	66%
Mustard oil	12%	60%	21%
Ghee	65%	32%	3%

Sugar and Carbohydrates

Sugar

One can write an entire textbook on the impact of sugar, sugar substitutes, hidden sugars in processed foods and fructose on insulin resistance and cardiometabolic risk.[20-23] Considering metabolic syndrome and insulin resistance as major drivers or cardiometabolic disease, the less sugar (fructose) we consume, the better.[24,25]

Triglycerides, Atherogenic Dyslipidemia, and Inflammation

More specifically, elevated triglycerides are associated with cardiovascular disease and platelet hyperactivation.[26-28] and the triglyceride-glucose index is associated with coronary artery calcification.[29] Increasing total dietary carbohydrates has been shown to increase triglyceride levels.[30] The triglyceride:HDL ratio is associated with insulin resistance[31] as well as cardiometabolic risk.[32] The TG/HDL ratio has been shown to respond favorably to carbohydrate restriction along with other established cardiac risk markers such as LDL size, LDL particle number, ApoB/ApoA1 ratio, blood pressure, and hs-CRP in people with T2DM **(Fig. 4)**.[33]

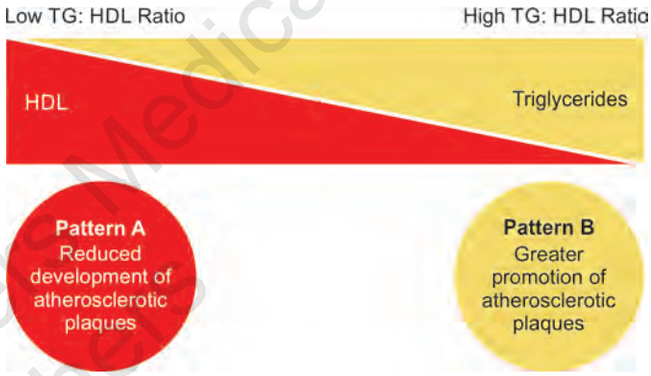


FIG. 4: The TG/HDL ratio.
(HDL: high-density lipoprotein; TG: triglycerides)

Note:
- TG/HDL ratio < 2 = more large-buoyant LDL (pattern A)
- TG/HDL ratio > 2 = more small-dense LDL (pattern B)
- Aim for a ratio closer to 1 or < 1 (HDL higher than TG)

Source: Bikman B. Why We Get Sick?

LABEL READING

It is important to teach people to read nutrition labels because even so called "heart healthy" processed foods often contain highly processed and refined carbohydrates, including many alternate names for sugar. As an example, one can find carbohydrates under names that can easily bypass detection when read by a busy consumer trying to make a quick purchase. It takes a discerning thoughtful well-informed eye to identify these ingredients which are, (possibly by design), difficult to pinpoint at a cursory glance **(Table 2)**.

Low-fat Carbohydrates versus Low Carbohydrates

Now that we have looked individually at the effect of dietary fat and carbohydrates on cardiometabolic risk factors, how do these two macronutrients fare when compared head-to-head? A 2009 study looked at the impact of carbohydrate restriction versus fat restriction in 40 individuals with atherogenic dyslipidemia went through a randomized controlled trial and at the end of 12 weeks, the carbohydrate restricted group showed better improvements in glucose levels, insulin concentration, insulin sensitivity, weight, adiposity, triglycerides, HDL, total cholesterol/HDL ratio, ApoB/ApoA1 ratio and LDL particle distribution.[34]

Another randomized controlled study compared the effect of a low-glycemic diet versus low-fat diet in obese young individuals with a body mass index over 30. Eighteen months later, the low-glycemic group had better weight loss ($p = 0.004$) and body fat percentage ($p = 0.03$) than the low-fat group.[35]

Carbohydrates: We don't need them but we enjoy them
- Proteins are digested into amino acids. We know that there are essential amino acids.
- Fat are digested into fatty acids and glycerol. We know that there are essential fatty acids.
- Carbohydrates are broken down into simple sugars.
- Although glucose is a primary source of energy (ATP) via the Krebs cycle, there are no essential simple sugars thanks to gluconeogenesis. This is the process by which the body is capable of creating glucose from either protein or fats.

TABLE 2: The 98 names for sugar (+ hidden sugar).

Agave	Crystalline fructose	Glucose	Nectar
Agave nectar	Date sugar	Glucose solids	Palm sugar
Anhydrous dextrose	Dehydrated cane juice	Glucose syrup	Pancake syrup
Barbados sugar	Demerara sugar	Golden sugar	Panocha
Barley malt	Dextran	Golden syrup	Powdered sugar
Barley malt syrup	Dextrin	Granulated sugar	Raw sugar
Beet sugar	Dextrose	Grape sugar	Refiner's syrup
Blackstrap molasses	Diastatic malt	Gum syrup	Rice syrup
Brown sugar	Diatase	High-fructose com syrup	Saccharose
Buttered syrup	Dried oat syrup	Honey	Simple syrup
Cane juice	Ethyl maltol	Icing sugar	Sorbitol
Cane juice crystals	Evaporated cane juice crystals	Invert sugar	Sorghum
Cane juice solids	Evaporated cane juice	Invert syrup	Sorghum syrup
Cane sugar	Evaporated cane syrup	King's syrup	Sucanat
Cane syrup	Evaporated sugar cane	Lactose	Sucrose
Caramel	Florida crystals	Malt sugar	Sugar
Carob syrup	Free- flowing brown sugars	Malt syrup	Sugar (granulated)
Castor sugar	Fructose	Maltodextrin	Superfine sugar
Coconut palm sugar	Fructose crystals	Maltol	Sweet sorghum
Coconut sugar	Fruit juice	Maltose	Syrup
Confectioner's sugar	Fruit juice concentrate	Mannose	Treacle
Com sweetener	Fruit juice crystals	Maple sugar	Turbinado sugar
Com syrup	Galactose	Maple syrup	White sugar
Com syrup solids	Glazing sugar	Molasses	Xylose
		Muscovado sugar	Yellow sugar

Carbohydrates are, therefore, not an essential part of our nutritional needs, but as a society, we have come to love them and on an average, people get about half of their daily energy requirements from carbohydrates.

So how do we balance this?

If you must eat carbs, eat them last

A randomized trial looked at the order in which eating nutrients can modify the glycemic impact of dietary carbohydrates.[36] Eating the carbohydrates first showed worse postprandial glucose excursions in people with prediabetes compared to eating the vegetables or protein first. Moving the carbs to be consumed last resulted in stable post meal glucose levels.

Fiber

Fiber can help reduce 24-hour glucose and insulin profiles with better lowering of triglyceride levels in patients with T2DM ($p < 0.02$) when taken in amounts higher than what is recommended in standard guidelines.[37] In a randomized crossover study, people were given 50 g of fiber: Soluble (25 g) and insoluble (25 g). The sources of soluble fiber were melon, grapefruit, orange, papaya, raisins, lima beans, okra, sweet potato, winter squash, zucchini, granola, oat bran, and oatmeal, were used to achieve high-fiber intake. A key point of this study was that the fiber intake was achieved through natural whole unprocessed food, and not fiber supplements.

Carbohydrate Cravings

Most of us find carbohydrates pleasurable and satisfying. It has been known that carbohydrate (particularly sugar) intake is regulated by and has effects on the reward (hedonic) pathway. This has given rise to theories around carbohydrate addiction, in which a person "needs" to take more and more carbohydrate to elicit a dopamine response in the brain.[38] We are wired to experience pleasure from sweet food. Recently however, humans have been found to have a separate taste capacity to sense glucose oligomers (short polymers) that are not sweet, but were reported as tasting "bread-like" and "rice-like".[39] Further research is needed in this area to understand our emotional relationship with carbohydrates, but meanwhile this may help us have more informed conversations with our patients who swear that they have stopped all added sugar and yet struggle with elevated glucose levels and insulin resistance.

What started as whole grain may not be whole anymore?

There is an increasing awareness in society of the benefits of consuming unprocessed wholegrains compared to refined

processed ones as part of a heart healthy diet. The food industry has taken note of the popularity of whole-grain foods and the global market is flooded with breads, biscuits, breakfast cereals, and snack bars. India has seen a rise in labels of whole grain on traditional foods such as khakhra, dosa batter, ready -to-eat upma (just add hot water) and even our beloved atta, or cooking flour. Put simply, most of these contain whole grains that have been turned into a fine powder. There is a concerning discrepancy between processed or ultraprocessed food labels describing items as "whole grain" on the front and what consumers will learn if they actually turn the package around to read the most abundant component listed in the first position of the ingredients list.[40] At the time of this writing, there is a lack of global consensus on what can be truly considered whole grain, and also what health claims can be displayed on products that are not 100% whole grain.[41] Meanwhile, the rampant proclamation of health benefits and attractive labeling are used by processed food marketers to attract customers to make "healthy" choices for themselves and their loved ones.

Salt

Salt Sensitivity

It has been widely proposed that reducing salt intake is good for everyone. When looked at objectively in a scientific trial, investigators found surprising results. They found that 80% of people with normal BP were nor sensitive to salt at all. 75% of people with prehypertension were not salt sensitive. In people with full-blown hypertension, 55% were found to be totally immune to the effects of salt on BP![42]

Do no harm: Salt restriction does not make everyone better

To look at the impact of restricting dietary salt intake in untreated people with hypertension, investigators monitored the BP response in 82 outpatients and 25 inpatients from a metabolic ward. During 10 days of sodium restriction, the mean blood pressure rose at least 5 mm Hg in 17% of OPD and 28% of IPD patients.[43] It is important for us to reconsider giving broad sweeping advice about dietary salt, considering that it may be counterproductive for some.

Salt and insulin resistance

Taking the concept one step further and building on the understanding that hypertension is associated with insulin resistance, investigators looked for links between dietary sodium and insulin sensitivity. Total 13 subjects (8 borderline hypertensive) were enrolled in a randomized, double-blind crossover study. The study showed *worsened insulin resistance* on the low-salt diet in the normotensive and hypertensive group, in parallel with an increase in plasma norepinephrine, without a significant reduction in blood pressure ($p < 0.05$).[44] This forces us to consider that sodium being the most abundant serum electrolyte, remains very tightly regulated, with the body maintaining homeostasis through counterregulatory hormonal responses to dietary sodium restriction.

Weight loss reduces sensitivity of blood pressure to salt.

Are these hormonal responses to salt modifiable? Can they work in our favor? It seems so in certain people. An interesting study looked at 51 obese adolescents to see the impact of high-salt diet versus a low-salt diet on blood pressure.[45] These effects were measured before and after a 20-week weight loss program. In 36 of the 51 participants, the sensitivity of blood pressure to salt was reduced after losing more than 1 kg of weight, so that the blood pressure difference after weight loss when moving from a high-salt diet to low salt was -1 +/- 1mm Hg. The best predictors of blood pressure being salt sensitive were the fasting plasma insulin level and the plasma aldosterone level (during the low-salt diet), the plasma norepinephrine level (during the high-salt diet), and the body fat percentage. This paper elegantly reminded us of the hormonal and counterregulatory mechanisms that connect blood pressure, salt sensitivity and obesity, namely, hyperinsulinemia, hyperaldosteronism, and increased sympathetic activity. Once we understand the hormonal aspects of sodium regulation, we realize that managing blood pressure may not be just a simple matter of salt restriction for all subjects. Although asking people to reduce salt is an easy and quick thing to tell patients in clinical practice, it may not be sufficient advice, and at times may be incomplete or even harmful.

How much salt?

Often the advice to reduce salt intake becomes a blanket statement, lacking quantification. How much is too much? Is there something such as too little? In the PURE study cohort, 101,945 people were followed up in 17 countries (including India) for a mean of 3.7 years, and their sodium intake was estimated based on urinary sodium excretion.[46] When looking at the primary composite outcome of death or major cardiovascular event (MACE), the investigators found an estimated sodium intake of 3–6 g/day (half teaspoon to one teaspoon of salt) to be associated with a lower risk of death and MACE compared to intake <3 g or >6 g/day.

Figure 5 summarizes the various aspects of metabolic regulation[47] that need to be considered as potential tradeoffs before advising everyone to go on a salt restricted diet, in theoretical hopes that it might lower blood pressure. Primum non nocere!

Replacing Carbohydrates with Protein

The third (and perhaps most important) macronutrient to discuss after fats and carbohydrates is protein. A randomized controlled trial looking at high-carbohydrate versus high-protein diet in 24 people (women and men) with obesity and prediabetes showed significant improvement in insulin sensitivity ($p = 0.001$), cardiovascular risk factors ($p = 0.04$), inflammatory cytokines ($p = 0.001$), oxidative stress ($p = 0.001$) and increased lean body mass percentage ($p = 0.001$)[48] at 6 months.

How much is high protein?

What is important to note, however, is the definition of "high protein" versus "high carbohydrate" in this study. The high protein group consumed around 135 g of protein per day. Interestingly, even the high carbohydrate group was consuming around 68 g of protein per day, a number rarely achieved spontaneously by typical vegetarian predominant Indians.

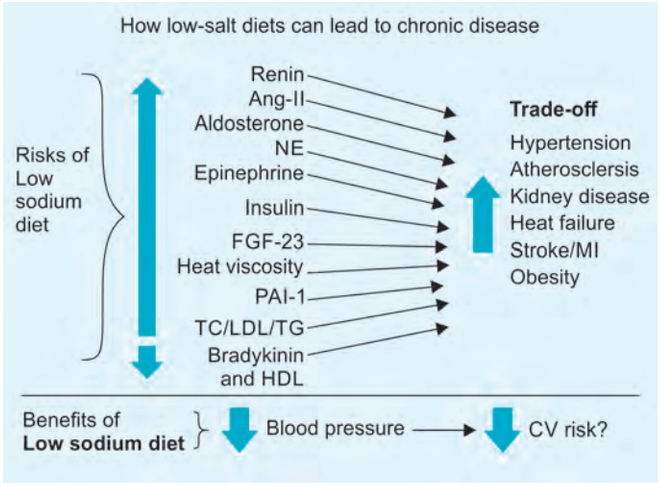


FIG. 5: How low-sodium diet can lead to chronic disease?

Insufficient Protein Intake

There are negative cardiometabolic consequences of protein malnutrition that need to be considered.[49] While India may have overcome caloric malnutrition in many parts of the country, there is reason to be concerned that the caloric supplementation of the malnourished has come mostly through carbohydrates. It is upon us as clinicians to find ways to help people achieve the bare minimum of 0.8 g protein per kg body weight per day in culturally relevant ways. Look for symptoms of a protein-deficient diet in your day-to-day practice:

- Chronic fatigue
- Edema
- Low immunity, recurrent infections
- Constant hunger and cravings
- Poor quality of hair and skin
- Delayed recovery from injury, illness
- Muscle loss (sarcopenia)
- Lack of strength or fitness gains despite regular sincere exercise

EXERCISE

Cardio, Strength, or Both?

A randomized controlled trial answered this by looking at 69 adults (average age 58 years) with hypertension (HTN), overweight or obesity, and a sedentary lifestyle.[50] They were randomized to 8 weeks of three times a week (1) aerobic (cardiovascular) training: 60 min/session, (2) resistance training: 60 min/session or (3) a combination of aerobic 30 min/session plus resistance 30 min/session. Combined training provided significant reductions in peripheral (–4 mm Hg) and central diastolic blood pressure (–4 mm Hg), increase in cardiorespiratory fitness (VO_2 max 4.9 mL/kg/min), increase in upper (4 kg) and lower (11 kg) body strength, and increase in lean body mass (0.8 kg) ($p < 0.05$) compared to either component alone. Further, the composite score of cardiovascular disease risk factors indicated a greater reduction with combination training compared to the control group.

High-intensity Interval Training

There is no clear definition of high-intensity interval training (HIIT), but has been described as "activities with intermittent bouts of activity that were performed at maximal effort, ≥85% VO_2 max, ≥85% heart rate (HR) reserve or the relative intensity of at least 90% HR max"[51] and also described as "vigorous exercise performed at a high intensity for a brief period of time interposed with recovery intervals at low-to-moderate intensity or complete rest."[52]

A literature review on HIIT for cardiometabolic disease prevention concluded that "high-intensity interval training by adults, especially those with overweight and obesity classification, can improve insulin sensitivity, blood pressure, and body composition, comparable to those resulting from moderate-intensity continuous training."[53] It is important for practicing cardiologists today to be familiar with the benefits of HIIT due to its increasing popularity among fitness enthusiasts while also helping patients with exercise prescriptions, customizing their training targets as per target heart rate zones.

Sedentariness

The DPP Study of 2002 showed 150 minutes of exercise per week (roughly 30 minutes, 5 times a week) as part of supervised lifestyle changes resulted in significant prevention of progression from prediabetes to diabetes,[4] outperforming metformin. So, we know that 150 minutes of exercise per week is helpful. With today's modern lifestyles, we need to go a step beyond these findings and examine the impact of treating sedentariness itself.[54]

Alternating Sitting and Standing

Twenty three obese/overweight sedentary office workers went through a randomized controlled trial to look at the effect of alternating standing and sitting during their desk jobs. They used an electric height adjustable workstation to change from sitting-to-standing posture every 30 minutes and were found to have a beneficial effect on postprandial glucose levels.[55]

Interrupting Sedentary Spells

Another study used wearable technology, having participants wear an accelerometer around the trunk during waking hours for 7 consecutive days[56] (a trunk accelerometer was selected presumably to reduce errors that wrist wearables are prone to). These participants were recruited from the AusDiab study, the largest Australian longitudinal, population-based study to examine the natural history of diabetes, pre-diabetes, heart disease, and kidney disease. The findings showed that independent of total sedentary time, moderate-to-vigorous intensity time, and mean intensity of the breaks, *more interruptions* in sedentary time were beneficially associated with metabolic risk variables, particularly adiposity measures (BMI $p = 0.026$, waist circumference $p = 0.027$ and, triglycerides $p = 0.029$). This suggests that even when one is planning to sit at a desk for an extended period, getting up more often and taking a few steps for every 30 minutes of sitting time, may offer an easy protective effect. The authors highlight that these findings suggest that besides counting the amount of sedentary time in

a person's life per day, we may also benefit from looking at how the sedentary time was accumulated.

FROM LITERATURE TO LIFE

The intent behind this chapter is to be able to help clinicians know how to translate study findings into usable information in their day-to-day practice.

- *PRACTICE TIP*: Most doctors (and certainly laypeople) do not know what 80 g of complex unprocessed carbohydrates, 0.8 g/kg body weight of protein or 50 g of dietary fiber from natural sources actually look like in daily life. You can work with your dietitian to establish a visual list of sources to reach these targets with locally preferred foods based on the preferences of your practice population.
- Atta or flour is not whole grain. Instant ready to eat food cannot be whole grain **(Fig. 6)**.
  If a grain has been turned into a powder or fine consistency that is used to make roti, paratha, biscuit, poha, chiwda, instant oats, instant noodles, or even idli or dosa, it is no longer a whole grain. The natural structure of the whole grain has been processed and the impact on plasma insulin/glucose (glycemic index) will be much faster than a true whole grain which actually requires time to chew, digest and absorb into the bloodstream.
- For an 80-kg person achieving the bare minimum protein intake of 0.8 g/kg/day, their daily requirement amounts to 64 g, and yet, on careful review, very few people in India are achieving this level of nutrition in clinical practice!
- This becomes important when handling the psychological reaction from a patient when they are told to increase protein to target of 0.8 g/kg/day, they tend to panic, thinking they are being given a "high-protein" diet.
- There is a mathematical logical difference between high protein (1.6–2 g/kg body weight per day), sufficient protein (0.8–1.2 g/kg body weight per day) and low or insufficient protein (malnutrition: <0.6 g/kg body weight per day).

HOPE FOR THE FUTURE

It has been our experience, both professionally and personally, that lifestyle change starts with the individual. I hope that as you learn the nuances and benefits of lifestyle change, it will help you make changes in food patterns for yourself, your family, and your patients. It can be one of the most rewarding transformations in a person's life, when they are empowered to use their own inner wisdom along with right guidance from their informed healthcare provider, to make meaningful changes in their daily habits, towards better health. It is my deep wish that more healthcare professionals get to enjoy this level of professional satisfaction, when they see their patients reap the benefits of the healing touch of a wise physician's guidance. That is why we all entered healthcare in the first place.

FIG. 6: Whole grain jowar versus jowar flour: See any difference?
Source: https://www.amazon.in/Jinendra-Grocery-Jowar-Sorghum-Powder/dp/B07HVWHSFS

CONCLUSION

Cardiometabolic syndrome is largely a product of unhealthy eating and sedentary, stressful lifestyle. Many large scale population studies have clearly shown the positive impact of dietary modification and exercise on the cardiovascular risk reduction. It is important to understand and implement the lifestyle modifications in addition to various pharmacological measures to successfully reduce the cardiovascular risk, either in primary or secondary prevention.

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SECTION 4

STABLE CORONARY ARTERY DISEASE

CHAPTER 48: **Only Ischemia-guided Percutaneous Coronary Intervention is Appropriate in Stable Coronary Artery Disease, Myth or Truth?**
Ashwin B Mehta, Rahul Chhabria

CHAPTER 49: **Current Status of Exercise Stress Testing vis-à-vis Noninvasive Imaging in Stable Coronary Artery Disease**
Suraj Kumar, Gurpreet S Wander

CHAPTER 50: **FFR–MLA Symbiosis: Is it the Way Forward for Intermediate Lesions?**
Darshan Jhala, Malav Jhala

CHAPTER 51: **Cardiometabolic Syndrome: Approach in the Current Era**
PC Manoria

CHAPTER 52: **Approach to Microvascular Dysfunction Syndromes**
KU Natarajan, Nischal N Hegde

CHAPTER 53: **Aspirin-free Antiplatelet Therapy: Is it the Future?**
Ashish Kumar Jain, RR Mantri

CHAPTER 54: **Approach to Antiplatelet Resistance**
PK Asokan, Anjana AJ

CHAPTER 55: **Coronary Atherosclerosis and Endothelial Dysfunction**
Anindya Mukherjee, Manoranjan Mandal, Ranjan Kumar Sharma

CHAPTER 56: **Myocardial Bridge**
Shibba Takkar Chhabra, Sushil Kumar, Riya Aggarwal

CHAPTER 48

Only Ischemia-guided Percutaneous Coronary Intervention is Appropriate in Stable Coronary Artery Disease, Myth or Truth?

Ashwin B Mehta, Rahul Chhabria

ABSTRACT

In the vast majority of patients, noninvasive evaluation of provocable myocardial ischemia is not done prior to cardiac catheterization. A JAMA-based registry showed that around 50% of patients with stable coronary artery disease fall into this category. Various trials comparing angiographic-guided percutaneous coronary intervention (PCI) versus medical management such as ISCHEMIA, COURAGE, and ORBITA trials had controversial results. However, most of these patients were not subjected to ischemia-guided PCI. On the other hand, most of the trials with physiologically guided PCI such as FAME and FAME 2 showed clear benefits of ischemia-guided PCI. Also deferring patients with insignificant coronary artery disease is safe as proven in 15 years' outcomes of the DEFER trial. Another study comparing angiography and fractional flow reserve (FFR) showed that there was mismatch in almost 57% of the cases and reverse mismatch was seen in another 16% of the cases where one would have missed a significant coronary artery disease on an angiographic basis alone.

INTRODUCTION

As the vast majority of patients are not subjected to noninvasive evaluation of provocable myocardial ischemia, the decision on whether to proceed with revascularization is taken on the catheterization table. Moreover, since the utilization of flow evaluation across a stenosis is performed in <10% of cases, revascularization decisions are made on the basis of the angiographic evaluation of lesion severity alone.[1]

Dr Andreas Gruentzig made initial attempts to record pressures proximal and distal to the target lesions, pre- and post-balloon angioplasty. However, there were three limitations: Firstly, his hardwares were large and resulted in flow obstruction. Secondly, he took an averaged pressure measurement for several beats and at the time, there was no knowledge about hyperemia.

Many bifurcation lesion studies have included lesions of 50–70% severity in their trials. As we know today, lesions of this magnitude may not result in flow limitation and the conclusions drawn may be erroneous. Little was known and understood that revascularizing nonflow-limiting lesions may lead to competitive flow and even graft closure. On the other hand, apparently radiologically, insignificant lesions may have flow-limiting obstruction.

A study on the risk assessment using single-photon emission computed tomography (SPECT) technetium-99m sestamibi imaging in patients with stable coronary syndromes showed that patients with normal SPECT scan results have a very low incidence of myocardial infarction or death **(Fig. 1)**.[2]

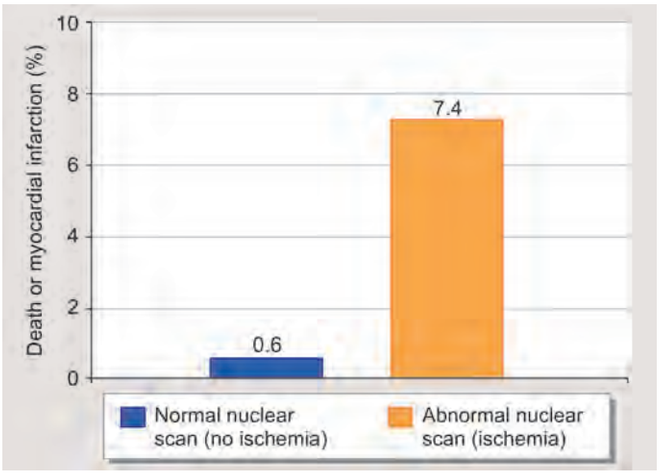


FIG. 1: Correlation of abnormal nuclear scan and incidence of death or myocardial infarction.

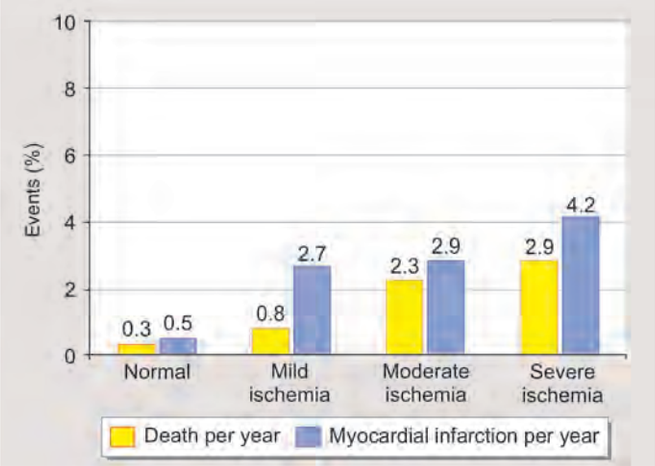


FIG. 2: Correlation of major adverse cardiac events with degree of ischemia.

Determining the degree of ischemia is important to quantify the risk assessment for future cardiac events. As shown in **Figure 2**, myocardial perfusion SPECT yields incremental prognostic information toward the identification of myocardial infarction or death.[3]

PITFALLS OF CORONARY ANGIOGRAPHY

Conventional angiography is considered as the gold standard for the evaluation of coronary artery disease. However, there are certain drawbacks of the procedure, which include the following:

- Limited correlation with physiology
- Angiography evaluation is subjective
- Eccentricity can lead to underestimation
- Vascular remodeling, e.g., Glagov's phenomenon can lead to misjudgment of severity
- Unable to assess unstable plaques
- Does not give information about myocardial viability
- Relative percentage stenosis based on reference segment can lead to an improper assessment of severity, since the reference segment may be diffusely diseased

CONTROVERSIAL OUTCOMES WITH REVASCULARIZATION

A registry-based data published in *JAMA* in 2011 showed that the majority (98.6%) of procedures done for patients with acute coronary syndrome are appropriate, while in patients with chronic stable angina half (49.6%) of the patients undergoing percutaneous coronary intervention (PCI) are inappropriate **(Fig. 3)**.[4]

The COURAGE trial,[5] which was published in 2007, randomized 2,287 patients who had objective evidence of ischemia and significant coronary artery disease to PCI with medical therapy, versus medical therapy alone. It concluded that an initial PCI along with medical therapy did not reduce the risk of death, myocardial infarction, or other major adverse cardiac events (MACE). As shown in **Figure 4**, there was no significant difference in outcomes between the two groups.

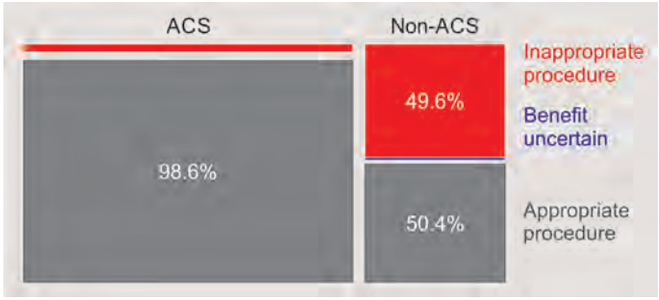


FIG. 3: Registry-based data showing appropriateness of percutaneous coronary intervention.
(ACS: acute coronary syndrome)

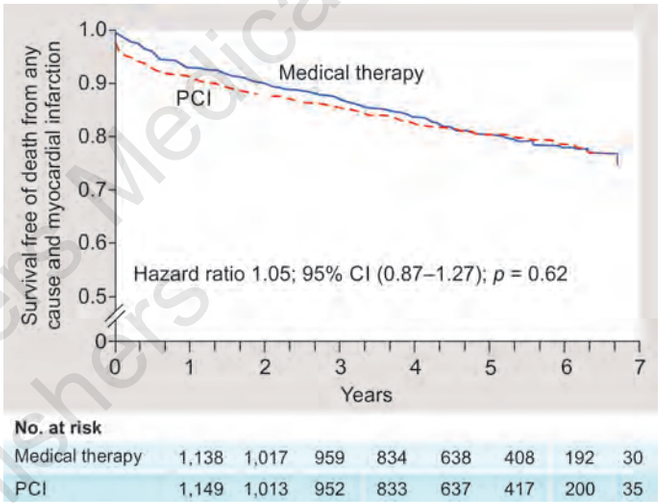


FIG. 4: Outcome of the COURAGE trial showing no significant difference between the two arms.
(CI: confidence interval; PCI: percutaneous coronary intervention)

Shortcomings of the COURAGE trial:

- 13% of the patients underwent plain old balloon angioplasty only.
- The vast majority had received first-generation stent implantation.
- They had remarkable success in controlling the risk factors which is not practical in a real-world scenario.

The trial[6] was another such trial, a randomized controlled trial, to compare an initial invasive strategy with a conservative strategy in patients with moderate or severe ischemia and coronary artery disease. The study concluded that there was no evidence that the initial invasive strategy reduced the risk of ischemic cardiovascular events or death from any cause at a mean follow-up of 3.2 years. Although this trial did not show a reduction in death or myocardial infarction, the results confirmed that an early invasive strategy resulted in a better symptom relief and angina-related quality of life. Among those with daily or weekly angina at the start of the study, 45% of those who were randomized to revascularization and medical therapy were angina free after a year, as compared to 15% of those treated with medical therapy alone. Improvements in angina-related quality of life persisted for 4 years in ISCHEMIA, among those who had at least weekly angina at baseline.

The controversy related to the ISCHEMIA trial arises when compared to overall patients presenting with chronic stable angina; only one-third of the population is reflected in the study. Many of the patients in our clinical practice were excluded from the study. The exclusion criterion included >50% left main stenosis [based on blinded computed tomography (CT) coronary angiography], advanced chronic kidney disease [estimated glomerular filtration rate (eGFR) <30 mL/min], recent myocardial infarction in the preceding 2 months, left ventricular ejection fraction <35%, unacceptable angina at baseline, the New York Heart Association (NYHA) class III–IV heart failure, and prior PCI or coronary artery bypass grafting (CABG) in the last 1 year. Hence, this study does not apply to all the patients with chronic stable angina.

The ORBITA trial,[7] published in 2017, was a double-blind randomized controlled trial comparing 230 patients with angina and severe single-vessel disease (≥70%). These patients were randomized to PCI with current-generation drug-eluting stents (DES) or a placebo procedure after 6 weeks of medical therapy optimization. Evaluation with exercise testing, symptom questionnaires, and dobutamine stress echocardiography were performed before randomization and at 6-week follow-up. There was no significant difference between the two groups in the primary endpoint of exercise time increment [28.4 vs. 11.8 seconds, respectively; the difference in increment between groups 16.6 seconds, 95% confidence interval (CI) 8.9–42 seconds; $p = 0.200$]. Similarly, there were no differences in the rates of other exercise variables or patient-reported angina symptoms. Prior studies have suggested that interventions that improve exercise time by >30 seconds are clinically relevant.

However, there are some shortcomings of the ORBITA trial. First, the patient population studied is highly selective, excluding those with multivessel disease and impaired left ventricular function. The trial recruited participants at five large PCI centers for almost 4 years; only a small minority of patients who planned to undergo PCI were suitable for enrolment. Second, although almost 98% of the patients had Canadian Cardiovascular Society (CCS) II or III angina on enrolment, 23% in the PCI arm and 25% in the placebo arm had CCS 0–I angina by the end of the run-in period. Patients were taking three antianginal medications and had a Seattle Angina Questionnaire physical limitation score of around 70, indicating low-to-moderate limitation. Given the lesser degree of symptoms, it would have been difficult to show an incremental benefit with PCI. Also, the follow-up period was short, which means the long-term beneficial effects of PCI were unclear.

Most of these trials were based on angiography-guided PCI and use of functional assessment was limited. It may be one of the reasons that in the real world if the cases are based on only anatomy, outcomes may be variable as revascularization may not be required in a significant proportion of these patients.

EVALUATING CORONARY PHYSIOLOGY

The very first article on FFR was published in 1996 by Pijls et al. A cut-off value of 0.75 was established in a small sample size. This study proved that if a coronary artery stenosis is not physiologically significant, it does not lead to cardiac events.[8]

Subsequently, the FAME trial was published in 2009, which was a multicenter randomized trial for assessing patients with multivessel coronary artery disease to undergo PCI with stents implantation guided by either angiography alone or FFR measurements.[9] A total of 1,005 patients were randomized and a total of 2,415 stents were placed in the study population. Patients were followed up for a period of 1 year followed by end-point assessment. As shown in **Figures 5A to D**, the FFR-guided arm had better survival: Survival free from MACE, survival free from myocardial infarction, and survival free from repeat revascularization. It was a landmark trial clearly demonstrating the clinical benefits for the physiological significance of the coronary artery disease assessment.

The FAME 2 trial consolidated the important findings of the FAME study. Around 1,220 patients with significant coronary artery disease (FFR ≤ 0.80) were randomized to FFR guided to PCI therapy with the best available medical therapy, compared to medical therapy alone. The recruitment of the trial was prematurely stopped because of higher MACE rates in the medical therapy group (12.7% vs. 4.3%). As depicted in **Figure 6**, there was a statistically significant difference in outcomes of MACE, in the PCI versus the medical therapy alone arm.[10]

This was one of the major trials, which showed a statistically significant improvement in the outcomes with the PCI arm. In conclusion, for patients with physiologically significant coronary artery disease, revascularization improves clinical outcomes as compared to medical therapy alone.

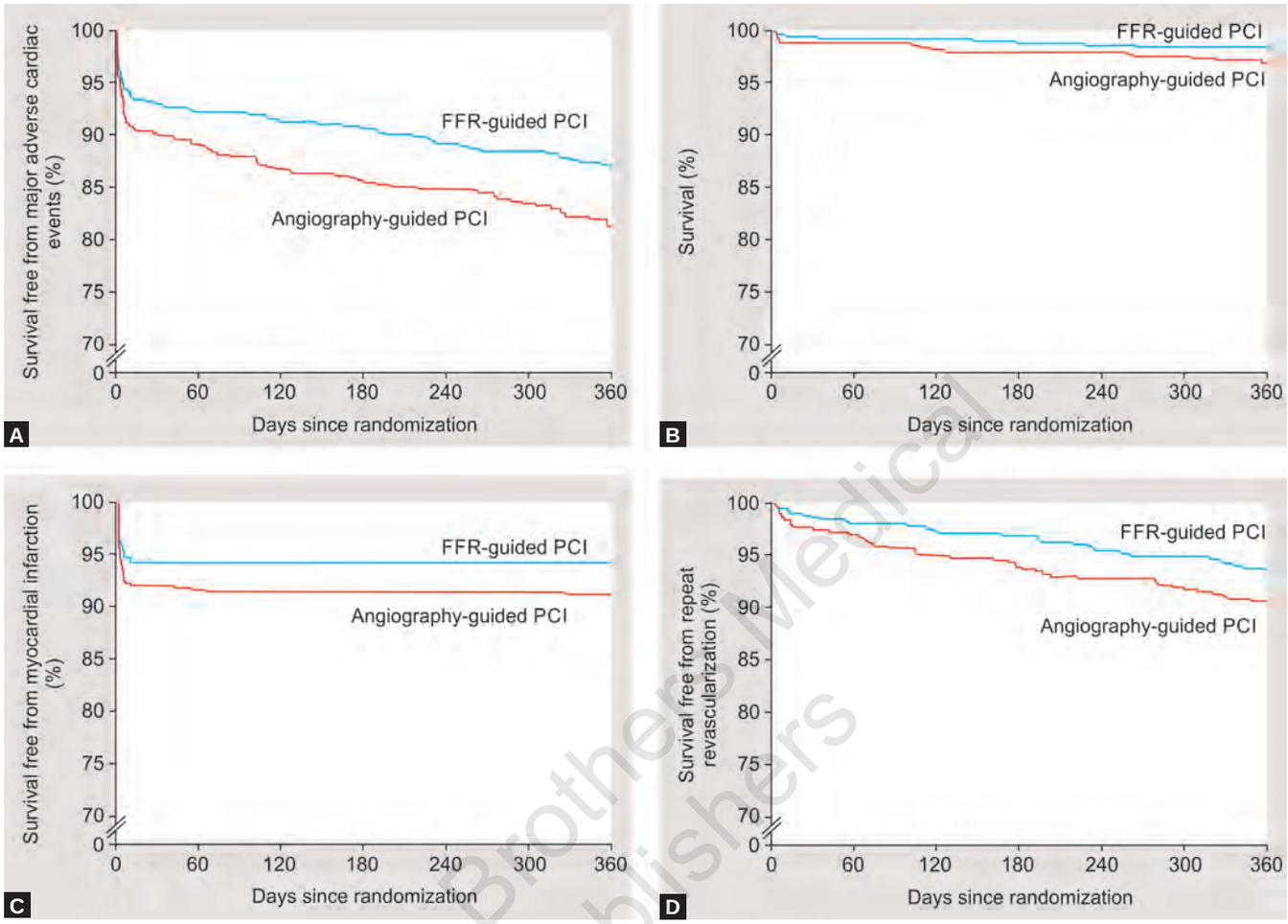
Is deferral safe?

A well-designed randomized controlled trial was conducted in which 325 patients were included with intermediate coronary artery disease. FFR was measured just before the planned intervention. If FFR was ≥0.75, patients were randomly assigned to deferral (DEFER group; $n = 91$) or performance (PERFORM group; $n = 90$) of PCI. If FFR was <0.75, PCI was performed as planned (Reference group; $n = 144$).

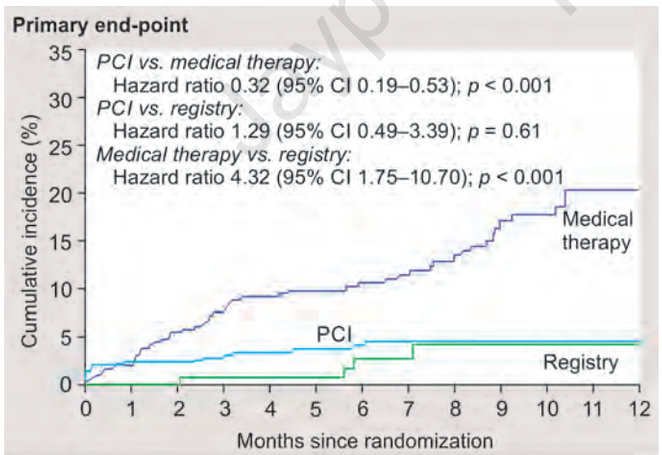
After a follow-up of 15 years, the rate of death was not different among the three groups: 33.0% in the DEFER group, 31.1% in the PERFORM group, and 36.1% in the Reference group [DEFER vs. PERFORM, relative risk (RR) 1.06; 95% CI 0.69–1.62; $p = 0.79$]. However, the rate of myocardial infarction was significantly lower in the DEFER group (2.2%) compared with the PERFORM group (10.0%), RR 0.22; 95% CI 0.05–0.99; $p = 0.03$. This study confirms that if an insignificant coronary artery lesion is revascularized with PCI, the outcomes would be more adverse. There were higher rates of myocardial infarction in the PERFORM group as compared to medical therapy alone **(Fig. 7)**.[11]

ANATOMY VERSUS PHYSIOLOGY

Discrepancies exist between the anatomical and the physiological correlation of coronary artery lesions. Lesions appearing significant on coronary angiography may not be physiologically limiting (mismatch) or lesions which do not appear significant on angiography may be physiologically significant (reverse mismatch). A study published by Park et al. in *JACC* in 2012 showed a comparison of diametric stenosis and FFR **(Fig. 8)**.[12]

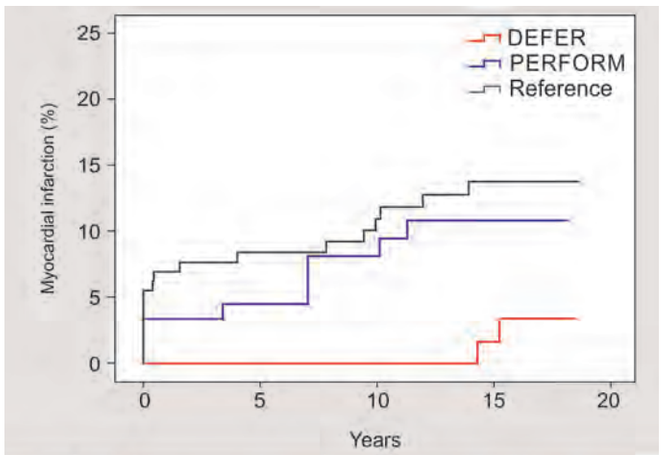


FIGS. 5A TO D: Kaplan–Meier survival curves in the FAME trial showing study outcomes in angiography-guided versus FFR-guided PCI.
(FFR: fractional flow reserve; PCI: percutaneous coronary intervention)



No. at risk													
Medical therapy	441	414	370	322	283	253	220	192	162	127	100	70	37
PCI	447	417	388	351	308	277	243	212	175	155	117	92	53
Registry	166	156	145	133	117	106	93	74	64	52	41	25	13

FIG. 6: Difference between PCI versus medical therapy outcomes in the FAME 2 trial.
(CI: confidence interval; PCI: percutaneous coronary intervention)



No. at risk				
DEFER	91	83	70	56
PERFORM	90	81	68	59
Reference	144	118	102	80

FIG. 7: Outcomes of the DEFER trial with incidence of myocardial infarction in three arms.

The study comprised of 1,000 patients with 1,129 coronary artery lesions. Angiographic FFR mismatch was considered when the angiographic diametric stenosis was >50% and FFR was ≥0.80, whereas reverse mismatch was considered when angiographic diametric stenosis was ≤50% and FFR < 0.8.

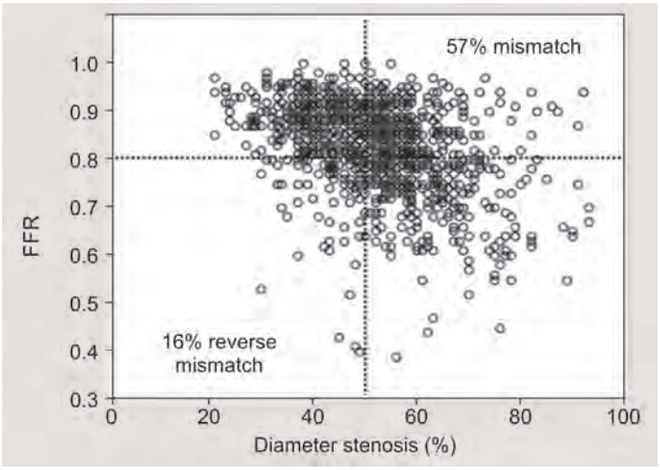


FIG. 8: Mismatch and reverse mismatch while comparing angiography and fractional flow reserve (FFR).

The study showed that 57% of the patients had an angiographic FFR mismatch. Thus, more than half of the patients who would have been considered for revascularization based on angiography alone are inappropriate.

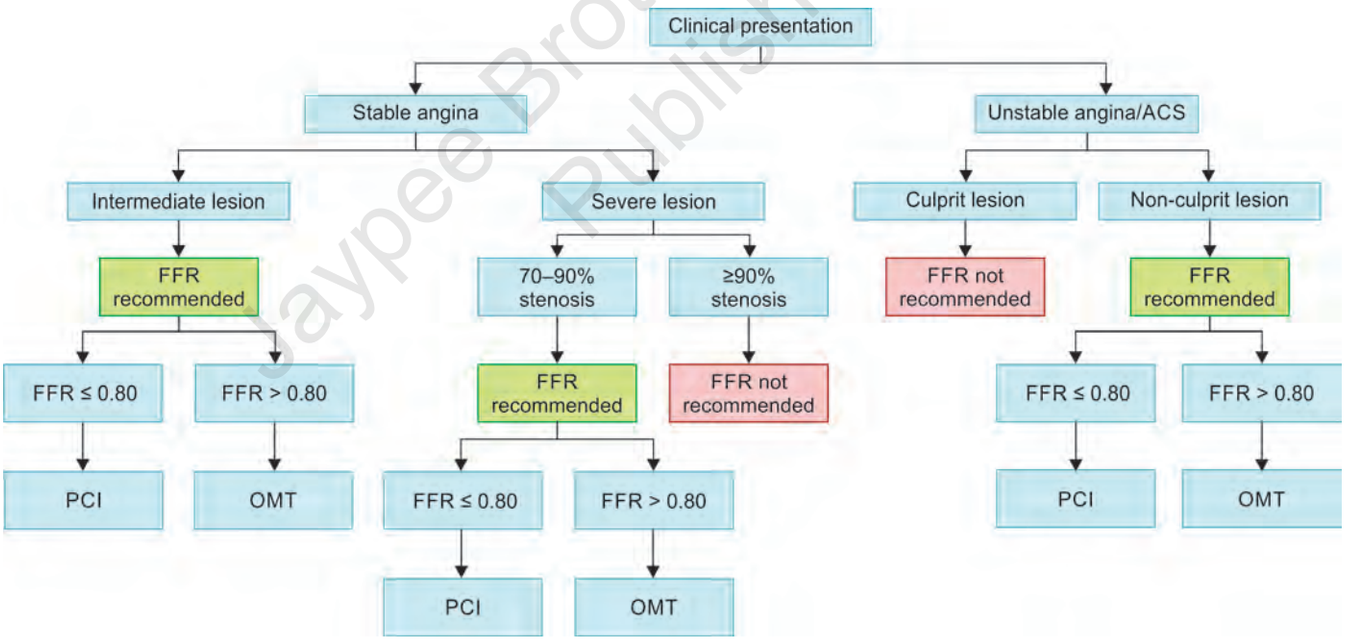
Various reasons for these discrepancies may be eccentrically placed lesions, diffuse lesions, myocardial territory supplied by that particular vessel, overall plaque burden, and characteristics of plaque.

GUIDELINES RECOMMENDATIONS

Based on these, the current American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend the use of FFR-guided PCI as depicted in **Flowchart 1**.[13]

CONCLUSION

Coronary angiography, which is considered as the gold standard, has several limitations. Around 50–70% of times, discrepancies exist in the lesion severity assessed by coronary angiography and its physiological significance assessed by FFR. These differences are more common in patients with intermediate coronary artery stenosis (40–70% severity). Hence, ischemia-guided PCI is a truth and based on these studies, it is strongly recommended by all the major guidelines.



FLOWCHART 1: American Heart Association (AHA) recommendations for use of FFR.

(ACS: acute coronary syndrome; FFR: fractional flow reserve; OMT: optimum medical therapy; PCI: percutaneous coronary intervention)

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CHAPTER 49

Current Status of Exercise Stress Testing vis-à-vis Noninvasive Imaging in Stable Coronary Artery Disease

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ABSTRACT

Exercise stress testing has remained an initial prescription to evaluate chest pain, post myocardial risk stratification, post intervention follow-up and an integral part of cardiac health check-up packages. Theoretically the test appears safe but it's not as safe as believed. The test has serious limitations in presence of abnormal resting electrocardiogram (ECG), poor functional capacity, recent chest pain, left ventricular dysfunction, valvular lesions, and poor quality of ECG tracing during exercise. Apart from all these, the test has lower than expected true positivity and negativity rates. Though American guidelines still endorse this test, the British and European guidelines recommend alternative methods to detect ischemia based on risk status of the patient.

INTRODUCTION

The diagnosis and treatment of coronary artery disease (CAD) have improved significantly in the last two decades. CAD is still a leading cause of death and disability in India. According to the latest guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA) for the management of stable ischemic heart disease, exercise stress electrocardiography is still the initial diagnostic test when the patients have an interpretable resting electrocardiogram (ECG) and are at intermediate pretest risk.[1] However, most patients still undergo stress imaging as the first testing strategy, despite these recommendations. This may be because of a widespread belief that exercise ECG testing has an insufficient diagnostic accuracy to detect CAD.

A good history of the symptoms is the most important first step for the evaluation of patients who present in the outpatient department with chest pain. The pretest probability (PTP) depends very significantly on the history of the patient. The interpretation of all the noninvasive tests depends significantly on the location, character, and precipitating factors of the chest pain **(Table 1)**.

The ability of available methods to diagnose CAD is dependent on the prevalence of the disease in the population studied. When the risk of having the disease is intermediate, diagnostic testing is most beneficial. When the risk of CAD is high in a population, many patients must be evaluated to identify the few people who do not have the illness, and a negative test result may seldom rule out the presence of the condition (i.e., the negative predictive value is low). When the risk of CAD is low, a negative test can rule out the disease. The lower the CAD risk, the higher the chances of a false-positive test. It is, therefore, appropriate to forego diagnostic testing in patients at the extremes of the likelihood range and infer that the patient has or does not have obstructive CAD based only on history, risk factors, and clinical examination. Based on age, sex, and symptoms, a simple predictive model may be used to determine the PTP of CAD **(Table 2)**.

OTHER NONINVASIVE TESTS FOR CORONARY ARTERY DISEASE

Noninvasive Functional Imaging

Stress echocardiography, myocardial perfusion imaging (MPI)-gated single-photon emission computed tomography (SPECT), positron emission tomography (PET), and cardiac magnetic resonance (CMR) are the functional noninvasive imaging techniques for noninvasive diagnosis of CAD. These

TABLE 1: Effect of character of chest pain and its classification on the interpretation of noninvasive tests.

Value of good history taking	
Typical angina	Meets the following three characteristics: • Constricting discomfort in the front of the chest or in the neck, jaw, shoulder, or arm • Precipitated by physical exertion • Relieved by rest or nitrates within 5 minutes
Atypical angina	Meets two of these characteristics
Nonanginal chest pain	Meets only one or none of these characteristics

	Typical		Atypical		Nonanginal		Dyspnea	
Age (years)	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
30–39	3%	5%	4%	3%	1%	1%	0%	3%
40–49	22%	10%	10%	6%	3%	2%	12%	3%
50–59	32%	13%	17%	6%	11%	3%	20%	9%
60–69	44%	16%	26%	11%	22%	6%	27%	14%
70+	52%	27%	34%	19%	24%	10%	32%	12%

TABLE 2: Pretest probabilities of obstructive coronary artery disease (according to age, sex, and the nature of symptoms).

	Typical angina		Atypical chest pain		Nonanginal pain	
Age (years)	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
30–39	Intermediate	Intermediate	Intermediate	Very low	Low	Very low
40–49	High	Intermediate	Intermediate	Low	Intermediate	Very low
50–59	High	Intermediate	Intermediate	Intermediate	Intermediate	Low
60–69	High	High	Intermediate	Intermediate	Intermediate	Intermediate
≥70	High	High	Intermediate	Intermediate	Intermediate	Intermediate

TABLE 3: Various tests for the diagnosis of coronary artery disease.

Diagnostic accuracy of noninvasive tests				
Test	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Exercise electrocardiography	62%	68%	57%	72%
Stress echocardiography	88%	89%	93%	80%
SPECT	84%	80%	80%	81%
Positron emission tomography	90%	86%	94%	79%
Stress CMR imaging	81%	87%	93%	70%
Coronary CT angiography	98%	81%	90%	99%

(CMR: cardiac magnetic resonance; CT: computed tomography; NPV: negative predictive value; PPV: positive predictive value; SPECT: single-photon emission computed tomography)

techniques can detect ischemia by visualization of wall motion abnormalities **(Table 3)**.

Pharmacologic stress testing with imaging is useful for determining the diagnosis and assessing the prognosis in patients who cannot exercise.[2] Stress echocardiography is the most used functional imaging technique since it is the cheapest and widely available.[3,4] However, it is user dependent regarding reliability. MPI is the second most common among these. It is widely available and has been used for a long time. The reliability of picking up wall motion abnormality is better with PET and CMR imaging. However, these are more expensive than stress echo and SPECT-MPI. Although the false positives and false negatives are higher with stress ECG testing as compared to these imaging modalities, it is still suggested as the initial evaluation technique due to the long history, ease of doing it, and cost-effectiveness. In individuals who can walk well, the outcomes are similar to these advanced imaging functional testing modalities.

Noninvasive Anatomical Imaging

Patients with suspected CAD can also be evaluated by computed tomography angiography (CTA) **(Table 3)**. It can effectively exclude obstructive CAD, although it may overestimate the extent of the disease.[5,6] The negative predictive value of CTA is as high as 99%, essentially ruling out obstructive CAD,[6] particularly among patients with low-to-intermediate pretest likelihood of disease. The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial was, therefore, designed to evaluate the differences in clinical outcomes between anatomic testing with CTA and routine functional testing.[7] It was observed that death, myocardial infarction (MI), hospitalization for unstable angina, or a major procedural complication occurred in 3.3% of the patients in

TABLE 4: Parameters to be used for classifying noninvasive tests as high risk when it is positive for coronary artery disease.

Noninvasive testing high-risk for ischemia	
Exercise ECG	Cardiovascular mortality > 3% per year according to Duke Treadmill Score
SPECT or PET perfusion	Area of ischemia ≥10% of the left ventricle myocardium
Stress echocardiography	>3 of 16 segments with stress-induced hypokinesia or akinesia
CMR	≥2 of 16 segments with stress perfusion defects or ≥3 dobutamine-induced dysfunctional segments
Coronary CTA or ICA	Three-vessel disease with proximal stenoses, LM disease, or proximal anterior descending disease
Invasive functional testing	FFR ≤ 0.8, iwFR ≤ 0.89

(CMR: cardiac magnetic resonance; CTA: computed tomography angiography; ECG: electrocardiogram; FFR: fractional flow reserve; ICA: invasive coronary angiography; iwFR: instantaneous wave-free ratio; LM: left main; PET: positron emission tomography; SPECT: single-photon emission computed tomography)

Source: Noninvasive testing high-risk ischemia. European Society of Cardiology (2019).

the CTA group compared with 3.0% in the functional-testing group during 25 months of follow-up. Radiation exposure was, however, greater in the CTA group than in the functional-testing group because nearly one-third of the functional-testing group's patients had not been exposed to radiation. The trial concluded that in symptomatic patients with suspected CAD who required noninvasive testing, an initial strategy of CTA was not associated with better clinical outcomes than functional testing over a median follow-up of 2 years.

The various noninvasive tests for the diagnosis and evaluation of CAD can also risk stratify patients into high risk and low risk. In exercise ECG, it depends on the early appearance of ischemia and ECG parameters suggestive of multivessel disease. In imaging physiological tests, it depends on the area of wall motion abnormalities and CTA on the location and the number of vessels showing CAD **(Table 4)**.

EXERCISE ELECTROCARDIOGRAM TESTING COMPONENTS

One meta-analysis of 24,047 patients in 147 studies found that exercise ECG was 68% sensitive and 77% specific for detecting CAD.[8] Specificity is decreased in the presence of left ventricular (LV) hypertrophy with repolarization changes and digoxin usage, while sensitivity is decreased by mild single-vessel disease. In spite of these confounders, exercise ECG is still generally regarded as diagnostic for patients who can reach 85% of their maximum age-predicted heart rate. The various parameters that we look at in exercise ECG testing for the diagnosis of CAD include ST-segment changes (number of leads and extent of ST change, how early these changes appear and how long these last, downsloping shape of the ST change, exercise capacity, blood pressure response to exercise, and occurrence of angina). Marked ST change of downsloping shape in multiple leads that appears early in exercise is a marker of severe CAD. Similarly, reduced exercise capacity, inadequate blood pressure response, and the occurrence of angina also indicated severe CAD. The significance of some of these parameters is discussed below.

ST-segment Changes

There have been two landmark studies that found the presence and extent of ST-segment depression to be predictive of mortality. In the Duke study, the maximum ST-segment deviation was the strongest predictor of cardiac death and a composite of death and MI.[9] A database analysis by Weiner et al.[10] of the CASS (Coronary Artery Surgery Study) also found that the extent of ST-segment depression was one of the two most powerful prognostic indicators along with the exercise duration. A <1% mortality rate was observed for patients who achieved stage 3 of the Bruce protocol with a <1 mm ST-segment depression. The mortality rate for patients with ST-segment depressions of >1 mm and being unable to complete stage 1 of the Bruce protocol was 5%.

Exercise Capacity

Exercise capacity is another variable that contributes to exercise ECGs diagnostic and prognostic utility. Exercise workload has been correlated with the risk in multiple studies. Compared to patients with >10 metabolic equivalents (METs) exercise capacity, individuals with <7 METs capacity had an 18-fold higher probability of experiencing >10% LV ischemia. For the group with good exercise tolerance (>10 METs), the prevalence of >10% LV ischemia was very low (0.4%). An analysis of the cohort that reached the 10 METs also demonstrated a very low rate of cardiac deaths (0.1%/year) and nonfatal MIs (0.7%/year).[11] A high exercise workload has been shown to be a beneficial diagnostic and prognostic factor in numerous other studies also. In a study of 3,000 patients who underwent MPI with thallium-201, exercise capacity predicted mortality even more accurately than the severity of perfusion defects. High exercise workload is also associated with decreased risk of cardiac deaths, MIs, and revascularization.[11-13] The rate-pressure product, which predicts the likelihood of three-vessel or left main CAD, is another surrogate of exercise capacity that shows diagnostic and prognostic value.[14]

Since ECG changes take time to occur in the ischemic cascade, it is essential to achieve an appropriate level of workload and heart rate. Achieving only 70% of the maximum heart rate leads to a reduction in stress defects from 100 to 47% and angina from 84 to 26%.[15] Further studies have found that ischemia on MPI is reduced regardless of the number of diseased vessels in patients who do not reach the target heart rate. In patients unable to achieve sufficient exercise workload, combinations of exercise protocols with vasodilator administration improve the diagnosis of ischemia significantly.

Additional Findings on Exercise Electrocardiogram

- The recovery time of ST-segment changes following exercise-induced ST-segment depression is a useful

diagnostic and prognostic indicator.[16] Those with a positive treadmill test and a rapid ST-segment recovery show only a 2% rate of confirmed CAD on angiography and a 0.7% rate of cardiovascular death, nonfatal MI, or coronary revascularization.[16]

- The ST/heart rate slope and the ST/heart rate index are additional potential enhancements to the standard ST-segment depression.
- A 1-mm or more ST elevation in lead aVR on exercise ECG is associated with 80% diagnostic accuracy and a 2.6-fold increased posttest probability of an obstructive left main or ostial left anterior descending artery stenosis.

Physiological Markers and Symptoms

Heart rate and blood pressure response to exercise and the presence of symptoms during exercise testing can increase the diagnostic accuracy of the test and help in prognostication.

Coronary artery disease and cardiac events are more likely to occur when the chronotropic response is impaired. Postexercise improvement in heart rate also provides significant diagnostic and prognostic information and is preserved in patients with known CAD.[17] Cole et al. showed that among 2,428 patients with a <12 beats/min drop in heart rate 1 minute postexercise, there was a two-fold increased risk of death.[18]

Changes in blood pressure during exercise are also important, although they are less well validated than changes in heart rate. By 3 minutes postexercise, systolic blood pressure (SBP) typically decreases by 15%. An SBP recovery ratio of >0.9 (SBP at 3 min/SBP at peak exercise) has been found to have diagnostic accuracy like ST-segment depression for the identification of CAD. It also corresponds well with the severity and extent of thallium-201 perfusion defects. When SBP drops by >10 mm Hg during exercise and when late SBP decline postexercise is present, it may be a sign of multivessel or left main disease.[19,20]

The presence of exercise-induced angina along with ST-segment depression increases the sensitivity of diagnosis of CAD. It also indicates more extensive myocardial ischemia and a higher event rate. The risk is more when symptoms are induced at a lower workload.[21]

Duke Treadmill Score

The Duke Treadmill Score (DTS), which combines multiple predictive factors into a single measure, provides additional prognostic information. The DTS employs three exercise measures to evaluate whether patients are at low, middle, or high risk for CAD: exercise duration, ST-segment deviation (depression or elevation), and exertional angina. The usual range is +15 to –25. Patients with a DTS of 5 or higher are considered low risk, while those with a score of –11 or below are deemed high risk. The Duke Treadmill scoring system predicts a 5-year death. The low-risk score individuals have a 97% 5-year survival rate. The intermediate-risk score individuals have a 90% 5-year survival rate, and the high-risk score individuals have a 65% 5-year survival rate. Patients having an intermediate risk assessment should be referred for further risk stratification using imaging modalities **(Table 5)**.

TABLE 5: Duke Treadmill Score for interpretation of exercise electrocardiogram testing.

Duke Treadmill Score	= Exercise duration (min)	– 5 ST (deviation) (mm)	– 4 (angina index) (min)	
Angina index 0—none, 1—typical angina, 2—angina causing test cessation				
Score	**Risk group**	**Stenosis ≥75%**	**Multivessel disease**	**1-year mortality**
≥5	Low	40.1 %	23.7%	0.25%
–10 to 4	Intermediate	67.3%	55.0%	1.25%
≤–11	High	99.6%	93.7%	5.25%

EXERCISE ELECTROCARDIOGRAM IN SPECIAL SITUATIONS

Baseline Electrocardiogram Abnormalities

Exercise ECG is affected by baseline ST-T changes. The presence of resting ST-segment depression increases the sensitivity of exercise ECG but decreases the specificity. The overall diagnostic accuracy does not change.[1] Exercise ECG is not performed in patients with left bundle branch block (LBBB) because of a high false-positive rate and requires stress imaging. For CAD detection in the right bundle branch block (RBBB), Yen et al.[22] observed an increased specificity of 87% but a decreased sensitivity of 27% using leads V_5 and V_6. The ACC/AHA supports the use of exercise ECG in RBBB.[1]

Women

Despite the lower prevalence of CAD in women than in men, the mortality rate from CAD is higher in women. Frequently, women present with atypical symptoms at a later age, which represents a unique challenge. In addition, exercise ECGs are less accurate as diagnostic tools in women. Among 3,721 women recruited from 19 studies, the pooled sensitivity and specificity were 61% and 70%, compared with 68% and 77% in men. It has been suggested that the lower specificity of ST-segment depression among women may be due to digoxin-like estrogen effects, lower ECG voltage, and a higher prevalence of baseline ST-T changes.

Women have a lower prevalence of CAD. So, a positive test has a less predictive value than it has in men. Among women, Baralsky et al. found the positive predictive value to be 47% (vs. 77% in men), while the negative predictive value did not differ statistically (78% vs. 81% for men). Therefore, although an abnormal test result is more likely to be falsely positive in women, a negative study is equally valuable in ruling out disease. Exercise ECG is recommended as the initial study of choice in women at intermediate risk for CAD who are able to exercise owing to its high negative predictive value. DTS has sufficient diagnostic and prognostic power for women.[22] ST-segment depression has not been shown to predict cardiac or all-cause mortality in asymptomatic women.[23]

Myocardial perfusion imaging is preferred by many clinicians because of concerns about the accuracy of exercise ECG testing. This notion was disproved by the WOMEN study in which 824 symptomatic women with good exercise tolerance were randomized to exercise ECG with or without MPI. The group without MPI showed a 48% diagnostic cost savings with no change in major adverse cardiac events during 2 years of follow-up.[24] This study supports a strategy of exercise ECG as the initial type of ischemia evaluation in women who can exercise and with an interpretable ECG.

Diabetes Mellitus

Patients with diabetes mellitus represent a significant subset of patients undergoing stress testing. The occurrence and severity of CAD are increased in individuals with diabetes. Diabetic individuals present with unusual symptoms, and there is a significant frequency of silent ischemia in asymptomatic patients. These considerations have resulted in a high rate of stress testing in diabetic individuals.

Exercise ECG appears to have comparable diagnostic accuracy and prognostic value in diabetic and nondiabetic patients. However, imaging has traditionally been undertaken in this group.[25]

With modern aggressive medical therapy in diabetic patients, the prevalence of ischemia and the risk of future cardiac events may be decreasing. Diabetic individuals who reach greater exercise ECG workloads (10 METs) have a low risk of future cardiac events.[26]

Advanced imaging methods can give further risk stratification in the diabetic population. A nonzero computed tomography (CT) coronary calcium score, undetected myocardial scar by cardiovascular magnetic resonance, and diminished flow reserve by PET-MPI all indicate an increased risk of cardiac events.

The choice to scan diabetic patients must be made on an individual basis. Diabetic individuals with adequate functional capacity who can achieve a high exercise load may benefit from risk stratification based only on exercise ECG. However, for higher-risk diabetic patients, such as those with poor exercise tolerance, LV dysfunction, nephropathy, vascular disease, or an irregular resting ECG and those suspected of having microvascular disease, cardiac imaging may greatly help in risk stratification.

Elderly

Increasing age is not a contraindication for exercise ECG. The functional limitations and comorbidities in the elderly increase the need for pharmacological stress imaging. However, because of the increased prevalence of CAD and cardiac events, they constitute an important subpopulation.

Studies on the elderly confirm the prognostic relevance of exercise capacity. However, in a cohort of 514 senior patients 65 years of age, ST-segment depression did not predict cardiac events. DTS did not have a predictive value in another elderly cohort.[27] However, in the same age group, SPECT perfusion abnormalities were linked to cardiac mortality.[28] In the elderly, abnormal SPECT imaging also predicts nonfatal MI and coronary revascularization. These findings imply that imaging should be considered as the initial workup to detect CAD in the elderly.

Advances in imaging technologies have a significant impact on the aged population. Because elderly individuals have a reduced lifetime attributable risk of cancer, radiation reductions are less of a problem, albeit they are still beneficial. Shorter procedures made feasible by PET imaging and improved SPECT cameras may be beneficial in this group, which has a higher risk of musculoskeletal discomfort and other mechanical restrictions that hinder extended table periods. Decreased exercise capacity and rates of chronotropic incompetence in the elderly lead to insufficient levels of stress. Combined procedures can help to alleviate this problem by enabling the gathering of exercise data followed by vasodilator administration to complete a diagnostic test.

PATIENT-CENTERED APPROACH

Advances in imaging technology have resulted in a diverse set of alternatives for assessing ischemic heart disease, allowing for a more patient-centered approach to ischemia assessment. The array of relevant tests is chosen based on the patient's symptoms, comorbidities, and functional state. Patients are referred for the test that delivers the most clinically relevant information while posing the least risk, expense, and inconvenience.

In many cases, a basic method of exercise ECG without imaging provides appropriate risk classification. In a study evaluating the yield of downstream testing and subsequent cardiac events in 3,656 individuals who had exercise ECG, low rates of referral to MPI (9.0%) and invasive angiography (2.3%) were identified.[16] The risk of cardiac mortality, nonfatal MI, and coronary revascularization was very low in individuals with negative (0.2%) and inconclusive (1.3%) stress tests after a 2.5-year mean follow-up. In the PROMISE trial's functional testing subgroup, individuals who had exercise ECG had the same low rate of the composite endpoint of adverse cardiac events as those who underwent imaging. In suitable individuals, our findings justify an initial strategy of exercise ECG alone.

In patients with a low-risk exercise stress test, a low-risk DTS, or a high rate-pressure product but no ST-segment depression, stress MPI gives limited incremental benefit. Nonetheless, despite the modest risk of events with a negative exercise ECG, imaging tests are still widely used.

CONCLUSION

In intermediate-risk patients with interpretable ECG, exercise ECG remains the recommended initial test. Variables other than ST-segment depression improve the accuracy of the test and provide additional prognostic information. With advances in imaging technology, the amount of radiation and test duration have decreased, shifting the risk–benefit ratio to imaging in patients with higher-risk conditions who are unable to achieve a high workload or reach the target heart rate.

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CHAPTER 50

FFR–MLA Symbiosis: Is it the Way Forward for Intermediate Lesions?

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ABSTRACT

Coronary artery blood flow (CBF) is the common denominator in the spectrum of coronary artery disease (CAD). The lack of a linear correlation between simpler anatomy-based tests such as coronary angiography (CAG) and CBF has led to a search for physiology-based parameters to quantify CBF. Pressure-based indices used for assessing the severity of epicardial stenosis assume that the lower the pressure distal to the stenosis, the lesser is the flow and vice versa. Till recently, as methods to assess coronary flow directly remained beyond the reach of clinicians, pressure-based indices such as fractional flow reserve (FFR), instantaneous wave-free ratio (iFR), and resting full-cycle ratio (RFR) became surrogate "equivalents" to coronary *flow indices albeit with important caveats*. However, with increasing recognition of the importance of microvascular flow in angina syndromes, it became vital to develop flow-based indices to assess coronary microvasculature. We endeavor to provide a concise summary of the pressure as well as flow-based modalities for coronary physiology assessment and also how to meaningfully combine anatomical data from intravascular ultrasound (IVUS) and optical coherence tomography in cases with borderline physiologic parameters.

INTRODUCTION

Among the protean manifestations of myocardial ischemia, the common denominator is coronary artery blood flow (CBF), which is the sole factor determining the health of the myocardium. The lack of a linear correlation between simpler anatomy-based tests such as coronary angiography (CAG) and CBF has led to a search for physiology-based parameters to quantify CBF.

The search for an accurate yet simple test to determine the adequacy of CBF has been the clinician's quest for the "Holy Grail."

With the easy availability of solid-state pressure wires, measuring intracoronary (IC) pressures became very simple. So, can we use coronary pressure as a surrogate for coronary flow?

From *Ohm's law* (*flow* = *pressure*/*resistance*), it was conceived that if *resistance* were to remain *constant*, changes in pressure would represent changes in flow, and hence *pressure* could be used as a *surrogate* for *flow*. In simple terms, a reduction in pressure could be taken as a reduction in flow (e.g., across stenosis) and vice versa.

Pressure-based indices used for assessing the severity of epicardial stenosis assume that the lower the pressure distal to the stenosis, the lesser the flow and vice versa. It is a well-known fact that in any vascular tree having sequential "stenoses," the distalmost stenosis (e.g., microvessels) significantly influences proximal pressures (e.g., epicardial arteries).

Coronary vasculature consists of epicardial vessels (5% of the total vasculature), and microvasculature is made up of arterioles and capillaries (95% of vasculature).[1] Change in diameters (and consequently, resistance) of either, or both, will influence the overall coronary flow with major contribution coming from the microvasculature.

So, if the microvascular resistance were to increase, the pressure difference across the more proximal epicardial stenosis will *decrease*, leading to *underestimation* of the degree of stenosis and vice versa. Pressure-based indices assume that microcirculatory resistance is constant, *which frequently may not be the case, leading to under- or overestimation of epicardial stenosis severity.*

Till recently, since methods to assess coronary flow directly remained beyond the reach of clinicians, pressure-based indices such as fractional flow reserve (FFR), instantaneous wave-free ratio (iFR), and resting full-cycle ratio (RFR) became surrogate "equivalents" to coronary flow indices albeit with important caveats.

However, with increasing recognition of importance of microvascular flow in angina syndromes, it has become necessary to develop flow-based indices to assess the health of coronary microvasculature.[2]

We endeavor to provide a concise summary of the pressure as well as flow-based modalities for coronary physiology assessment as well as a brief account of the current understanding of microvascular dysfunction and the available workup. A brief classification of the coronary physiology indices is illustrated in **Flowchart 1**. This is followed by a description of pressure-based, flow-based, and noninvasive indices. A note on microvascular dysfunction has been added in order to highlight the importance of this entity.

Discussion is limited to currently available *catheter-based invasive* indices in our country, and those which are unavailable have not been discussed. We have not included noninvasive indices such as FFR computed tomography (CT) as these have very limited availability and are not yet fully validated.

INVASIVE HEMODYNAMIC INDICES

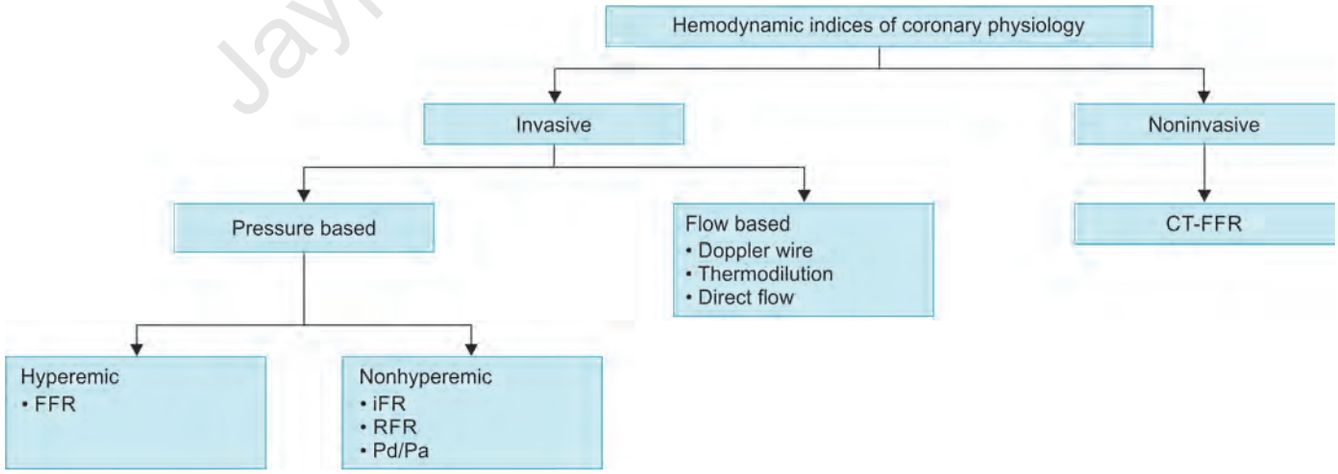
- Currently, only three pressure-based invasive indices (FFR, iFR, and RFR) are available in our country.
- *FFR* and *RFR* are *whole cycle indices* that use proprietary algorithms to assess the mean pressure before the stenosis [aortic pressure (Pa) at coronary ostium] and mean pressure distal to the stenosis.
- *iFR* uses an algorithm to assess pressure during a specific period during *diastole* ("*wave-free period*").
- *Only FFR requires* the study to be done both at rest and during maximal *hyperemia* induced by *intravenous* (*IV*) or *IC* adenosine (hyperemic indices).
- iFR and RFR do not need hyperemia [nonhyperemic pressure ratio (NHPR)].
- Only FFR and iFR have been studied extensively.

INVASIVE HYPEREMIC INDICES (PRESSURE BASED)

Fractional Flow Reserve

Routine measurement of FFR in the cardiac catheterization laboratory involves standard catheters (diagnostic or guiding), a dedicated pressure wire, drugs used during coronary intervention (vasodilator and anticoagulant), and a pharmacological stimulus to produce maximal hyperemia.

- *Catheters*:
  - Although the use of diagnostic catheters is technically feasible, guiding catheters without distal side holes are preferred.
  - Guiding catheters facilitate manipulation of the pressure wire as well as facilitate immediate intervention where indicated (including a rare event of wire injury).
- *Pressure wire*:
  - There are two commercially available pressure wires. Both systems [the Pressure Wire (RadiMedical Systems Inc., Uppsala, Sweden) and the Volcano Wave Wire (Volcano Inc., Rancho Cordova, CA, USA)] measure IC pressure using a dedicated solid-state (electronic) sensor mounted on a 0.014-in (0.33-mm) floppy-tipped guide wire.
  - The sensor is located at the junction between the 3-cm-long radiopaque tip of the wire and the nonradiopaque section of the wire. The cross-sectional area of a sensor guide wire is negligible relative to all but the most critical stenoses, and hence unlikely to influence even the most severe stenosis.
- *Pharmacologically induced maximal hyperemia*:
  - Hyperemia is essential for stenosis assessment.
  - Maximal vasodilatation of the two compartments of the coronary circulation (epicardial and the



FLOWCHART 1: A schematic depicting the various invasive and noninvasive coronary physiology indices in use across the world.

(CT: computed tomography; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; Pa: aortic pressure; Pd: distal coronary pressure; RFR: resting full-cycle ratio)

microvasculature) is required for accurate and reproducible measurements.
  - To abolish epicardial vasoconstrictor tone, an *IC bolus* of *nitroglycerin* (200 µg) should be administered at least 2 minutes before FFR measurement.
  - To obtain maximum microvascular vasodilation and eliminate coronary autoregulation, a *continuous infusion* of *adenosine* through a large-bore cannula in a large vein is preferred over boluses of IC adenosine (at a rate of 140 µg/kg/min) and recommended. It provides steady-state maximum hyperemia within 2 minutes. Continuous adenosine infusion is advocated because it allows for FFR measurement in specific settings (i.e., at aorta-coronary ostial lesions) and permits recording of a pressure pullback curve to differentiate focal from diffuse coronary artery disease (CAD).
  - It is important to note two things: The adenosine dose should include the dose lost in the IV extension line and that the adenosine dose has to be communicated in terms of mL/h to the scrub nurse. For example, a 60 kg male will require a total of 25.2 mg of adenosine for over 3 minutes (i.e., 8.4 × 3 = 25.2 mg). Add to that 15 mg that remains in the IV line. Thus, 40 mg (25 + 15) adenosine (72 mL ampoules) is diluted to make 40 mL solution (1 mg = 1 mL adenosine). This is placed in a 50-mL syringe and infused at 480 mL/h (8.4 × 60 min) for 3 minutes to achieve a steady state. Readymade weight charts are available in high-volume centers for reference.
  - The injection of additional IC boluses of adenosine, in an attempt to stimulate maximal hyperemia, is discouraged because it may provoke artifacts in the FFR tracing due to the injection that may complicate offline analysis. Similarly, other vasodilators such as papaverine and sodium nitroprusside, administered as boluses, are not advocated as steady-state hyperemia may not be achieved reliably.
  - If adenosine FFR has to be performed with IC, a dose of 160–200 µg/bolus in the left system or 60–80 µg/bolus in the right system may be used.

Step-by-step fractional flow reserve

- *Step 1*:
  - Ensure that the pressure transducer is leveled to the heart.
  - Zero the pressure system to the atmosphere.
  - The guiding catheter should be flushed with normal saline during the zeroing steps because contrast medium may dampen the catheter pressure waveform and introduce errors in zeroing.
  - Zero the sensor of the pressure wire ex vivo, following the instructions of the manufacturer.
- *Step 2*:
  - Insert the pressure sensor guide wire into the guide catheter, advance the pressure wire till the pressure sensor is a few millimeters beyond the tip of the guide catheter [for nonostial left main coronary artery (LMCA) or right coronary artery (RCA) lesions], and equalize the two pressures in vivo.
  - For aorto-ostial lesions, this should be performed with the disengaged catheter in the ascending aorta.
  - The introducer needle should be removed from the Y connector during the entire procedure.
- *Step 3*:
  - Advance the pressure wire sensor distal to the region of interest.
  - The sensor should be advanced to the distal two-third part of the coronary artery and at least 2–3 cm distal to the index lesion and its final position was documented angiographically.
  - Ensure that the wire tip is rotating freely, and no resistance is felt when torque is applied.
- *Step 4*: Induce maximal hyperemia
  - Administer adenosine 140 µg/kg/min IV for at least 2 minutes.
  - FFR is then calculated as the ratio of distal coronary pressure (Pd) to Pa at maximal hyperemia.
  - If needed, a pullback curve should be performed to determine the exact location of the lesion most likely responsible for ischemia.
  - The pressure pullback curve may demonstrate either a single (or several) abrupt change(s) in FFR across focal narrowing(s) or a gradual change in the presence of diffuse disease without focal obstructions.
- *Step 5*:
  - Wire pullback to check for signal drift verification of equal pressure signals from the pressure wire and the guiding catheter must be documented at the end of the procedure to check for potential drift.
  - When the difference is minimal (5 mm Hg), it should be considered in the calculation of the final FFR. When the difference is 5 mm Hg, the last measurement must be repeated.

What is the Role of Fractional Flow Reserve in a Coronary Cath Lab?

Moderate (50–70% Luminal Stenosis) Stenosis in Epicardial Coronary Arteries

In landmark studies such as DEFER and FAME, it was noted that stenotic arteries with FFR values >0.8 could be conserved on medical management alone without adverse outcomes.[3] Clinicians now had a scientifically validated tool to decide which borderline lesions to intervene and which ones to conserve.

Serial Lesions in a Single Artery

Identifying lesions that are functionally significant and warrant revascularization versus those that can be deferred is challenging in patients with multiple sequential stenoses or diffuse disease of intermediate severity in the same artery.

In these situations, FFR measurements with pullback pressure recording can be helpful in identifying lesions that are functionally significant. *This is albeit difficult as each proximal lesion will influence the FFR values of more distal downstream lesions*. In a vessel with FFR <0.8 ("apparent" FFR), under steady-state hyperemia, FFR is continuously measured as the pressure wire is slowly withdrawn from the distalmost lesion

toward the coronary ostium and the lesion that causes the largest pressure drop is treated first ("primary" lesion). FFR is measured again ("true" FFR of nonprimary lesion). The value of true FFR is used to decide about stenting of these lesion(s).[4]

This is a safe and proven method for treating serial lesions, validated in real-world practice.

Stepwise approach:

1. Measure FFR past distalmost stenosis.
2. Measure the FFR of all stenoses together under maximal hyperemia
3. If FFR ≤0.80, perform a pressure pullback tracing under maximal hyperemia.
4. Perform percutaneous coronary intervention (PCI) in the lesion with the largest pressure step-up first.
5. Repeat a pressure pullback tracing past the most distal stenosis.
6. Repeat the decision-making process for each stenosis in the series.

Fractional Flow Reserve In Bifurcation Lesions

To reduce complexity without compromising long-term clinical outcomes, it is important to accurately assess the functional significance of bifurcation lesions.

As the flow to the side branch is relatively smaller, side branch FFR is more easily influenced by the main branch lesions.

Large Main Branch with Small Side Branch

After main branch stenting, diverse factors can cause side branch luminal compromise (carina shift, dissection, jailing, etc.), making angiographic assessment difficult.

It is vital to differentiate carinal shift from plaque shift as carinal shift is a condition where there is generally no lumen compromise of the side branch.

Rewiring of the side branch with pressure wire is usually easy and should be done after main branch stenting and FFR measured as usual and intervention of side branch lesion to be done only if FFR <0.8 or if there is angina, electrocardiogram (ECG) changes or compromised thrombolysis in myocardial infarction (TIMI) flow in the side branch.

This is a safe strategy since side branch FFR measured just after main branch stent implantation is reported to be maintained during follow-up as was noted by the works of Koo et al.[5]

Fractional flow reserve is not indicated in small side branches or the branches in which the revascularization is not needed clinically. Benefit of FFR in heavily calcified side branches or diffuse side branch lesions is less, and not indicated.

Fractional Flow Reserve in Left Main Disease

- The ideal modality for estimating the importance of intermediate left main stenosis has always remained a matter of great discussion over the last decade. Intravascular ultrasound (IVUS) is considered to be a gold standard modality to decide about whether to intervene or not. This is definitely the case for distal left main stenosis involving ostia of left anterior descending (LAD) and left circumflex (LCx), where IVUS is the only modality of choice.
- Since considerable variations in minimum lumen area (MLA) estimations occur depending on whether the IVUS catheter is withdrawn from LAD to LMCA or from LCx to LMCA, the use of this modality becomes questionable in borderline lesions involving the ostium or the body of LMCA.
- In such situations, FFR may be used to assess the significance of these borderline lesions.
- In the absence of downstream stenoses, several studies have proposed the use of FFR to guide management in intermediate LMCA disease.[6] These studies, although small, consistently show that deferral of LMCA FFR >0.75 is not associated with an increased risk of future adverse events.
- Animal experiments and meta-analysis of clinical trials have shown that the left main FFR in the *presence of downstream stenosis* (FFRapp) was significantly higher (i.e., *suggestive of less stenosis*) when the non-LMCA epicardial stenosis was proximal and severe.
- In the absence of severe proximal non-LMCA stenosis, LMCA FFR could be reliably used to defer interventions[7] (or vice versa).

Method of Fractional Flow Reserve Testing[8]

- First measure FFR in the least diseased vessel, preferably the LAD, with a pullback. If FFR <0.80, then revascularize. If FFR >0.85, then treat medically.
- If FFR is between 0.80 and 0.85 with significant downstream epicardial disease in the other epicardial vessel, then one can consider IVUS or treat non-LMCA epicardial stenosis and reassess LMCA FFR.
- IV adenosine is the ideal hyperemic agent because it allows time to pull the guide catheter out of the ostium. A physiologic evaluation of the left main disease, compared to an anatomic evaluation alone, is safe and appropriate, just as it is in nonleft main CAD.

Fractional Flow Reserve before and after CTO PCI

- *Chronic total occlusion (CTO) vessel PCI has three major physiological effects*: (1) Effects on the CTO vessel and the dependent myocardium, (2) effects on the donor vessels, and (3) effects on the interaction between the two, i.e., collateral circulation.
- A number of studies have been carried out to evaluate the benefits of using coronary physiological indices for CTO PCI decision-making.[9]
- Three "groups" can be identified: Flow and velocity reserve studies [coronary flow velocity reserve (CFVR)], pressure studies (FFR, iFR), and absolute blood flow and resistance studies.
- While performing an FFR study for CTO PCI, two aspects need to be assessed. One is FFR of the myocardium (FFRmyo) and other is the FFR of the collateral circulation (FFRcoll). Studies that assessed the FFRcoll of the CTO PCI vessel at the time of intervention and at 16 weeks follow-up showed that the increase in FFRmyo happened only over time and was accompanied by a significant reduction in collateral function as expressed by FFRcoll.[10]

- Thus, after successful PCI of a CTO, blood flow in the CTO vessel and microvascular function do not normalize immediately but improve significantly over time. This is reflected by an increase in absolute blood flow and FFR of the CTO artery, decrease in microvascular resistance, and regression of collaterals with decrease in FFRcoll.
- This finding has bearing upon deciding about FFR of an intermediate stenosis in the donor artery with values slightly below the ischemic thresholds before the CTO artery is opened. It should be realized that the donor artery FFR may increase (i.e., become *less* significant) over time, thereby avoiding unnecessary PCI of donor vessel prior to CTO PCI. This may decrease the number of stents and the rate of restenosis over time and improve our knowledge and patient care. This observation is somewhat contrary to current guidelines that recommend intervention of donor vessel soon after PCI of the recipient CTO artery.

Fractional Flow Reserve in Saphenous Venous Graft Lesions

Over the years, saphenous venous graft (SVG) intervention has become a topic of much discussion, especially with the longer survival of coronary artery bypass graft (CABG) candidates and the subsequent improvement in the coronary intervention hardware. However, options to objectively prove the severity and physiological effects of these lesions have been few. Moreover, there are no large-scale randomized controlled trials for studying the use of hemodynamic parameters for assessing SVG lesions. The SVG differs structurally from the native coronary artery; hence, it is difficult to extrapolate the results of coronary physiology assessment trials performed on native coronary vessels.

Various anecdotal reports and single-center studies have used FFR to study the intermediate SVG lesions.[11] Most of these studies have used cardiac single-photon emission computed tomography (SPECT) and positron emission tomography (PET) for comparison. Though many studies used intragraft bolus adenosine in the doses required for the respective native coronary arteries, most of the studies agree that IV adenosine provides a steady-state ideal for correct FFR measurement.[9]

Fractional flow reserve-guided assessment of SVG lesions has an acceptable specificity and negative predictive value for detection of ischemia albeit at lower sensitivity and positive predictive value.

However, the use of FFR to determine the physiological significance of SVG lesions has not been studied.

- *Procedure*:
  - The FFR is measured as the ratio of the mean native coronary artery pressure distal to the SVG touchdown during maximum hyperemia induced by intragraft injection of adenosine.
  - An FFR <0.75 was considered to be indicative of a hemodynamically significant stenosis.
- *Limitations*:
  - Vein grafts are larger in caliber and have different vessel wall constituents compared with native coronary arteries. Thus, the dose of adenosine that produces maximal hyperemia in SVGs might be different from that used in native coronary arteries as well as the vessel wall response to adenosine.
  - The FFR threshold of 0.75 that was derived from native coronary arteries might be different for SVGs.
  - FFR is lesion specific and thus when used to assess SVG lesions, it does not consider lesions in the native artery subtended by the graft unless the pressure wire is placed in the distal native vessel and pullback is performed during hyperemia.
  - The SVG anastomosis can itself cause a pressure drop.
  - Diffuse disease in the bed distal to the SVG anastomosis which occurs in diabetic patients could cause abnormal stress on myocardial perfusion imaging (MPI) results in the face of a normal FFR across the lesion in question. Pullback FFR from the distal native vessel to the proximal SVG might be useful in this instance.

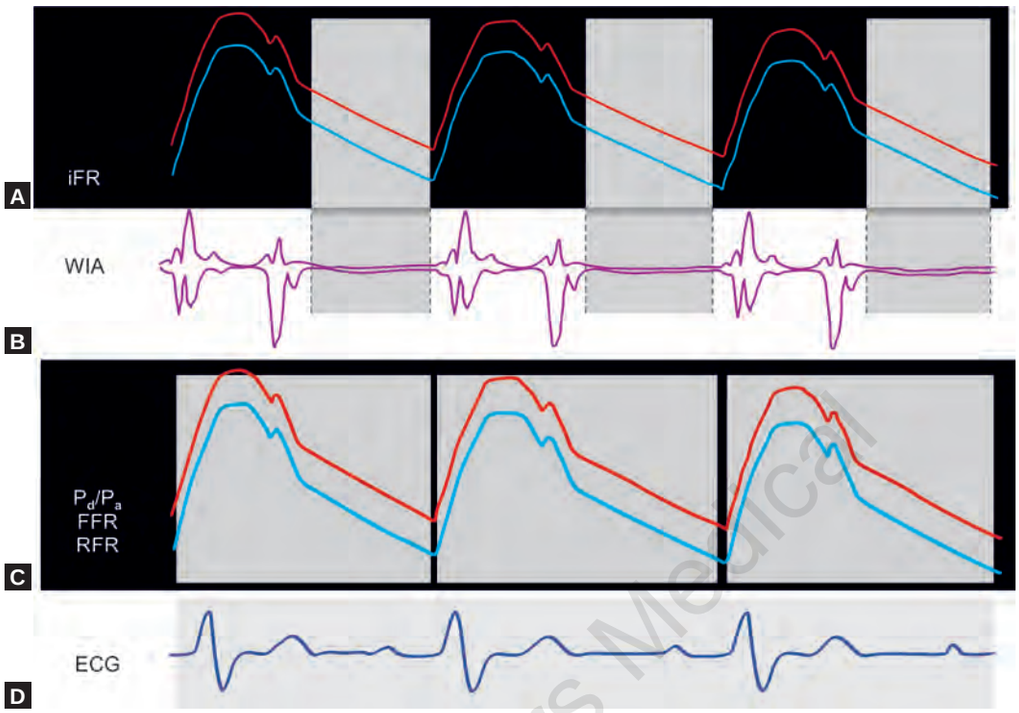
Fractional Flow Reserve in Acute Coronary Syndromes

- Layland et al. quantified index of microvascular resistance (IMR) in *culprit and nonculprit vessels* (a measure of microvascular integrity) in 50 subjects with stable angina, 50 non-ST-elevation myocardial infarction (NSTEMI) subjects, and 50 ST-elevation myocardial infarction (STEMI) subjects.[12]
- IMR in *culprit and nonculprit vessels* was found to be normal in stable angina subjects and NSTEMI subjects suggesting that FFR could reliably be used to assess lesion severity in these subjects.
- IMR was elevated in STEMI subjects, making FFR measurements unreliable. Since microvascular recovery may happen after days or weeks after a myocardial infarction (MI), FFR would be unreliable in the acute phase.
- Current data do not support *routine use* of physiological indices in assessing functional significance of stenoses pertaining to the culprit vessel acute STEMI.
- Nonculprit vessel revascularization in STEMI.
- The DANAMI-3 PRIMULTI trial showed that FFR-guided complete revascularization of nonculprit vessels in acute myocardial infarction (AMI) had significantly better outcomes as compared to culprit vessel-only strategy.
- In summary,
  - FFR in the culprit vessel in STEMI is unreliable.
  - FFR in *nonculprit vessel* in STEMI can be reliable.
  - FFR in *culprit and nonculprit vessels* in NSTEMI is reliable.
  - In chronic phase after acute coronary syndrome (ACS) (STEMI or NSTEMI), FFR at cutoff of 0.75–0.8 is reliable.

INVASIVE NONHYPEREMIC INDICES

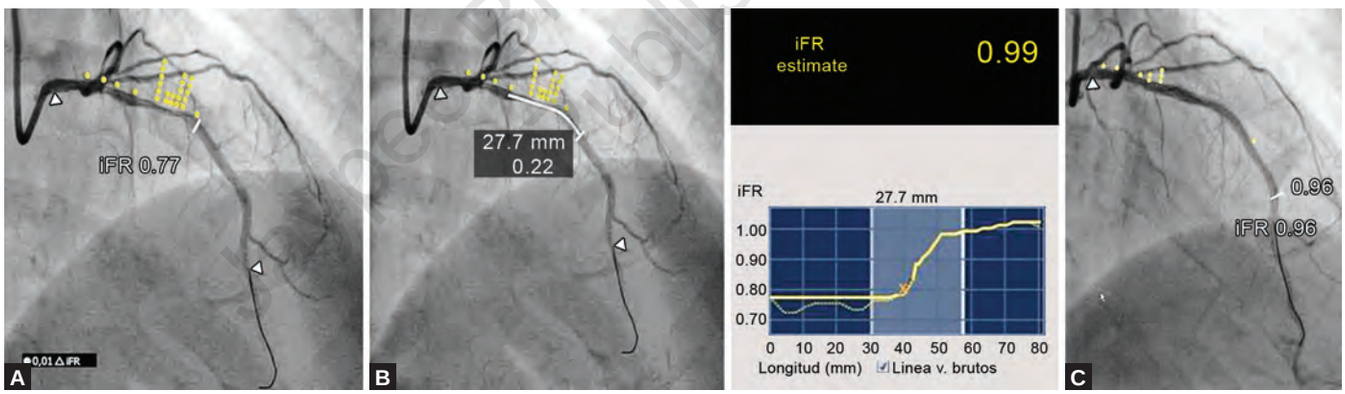
Instantaneous Wave-free Ratio

The iFR is a wire-based NHPR evaluating Pd/Pa during a specific phase of diastole, the wave-free period **(Figs. 1A and B)**.[13] Currently, iFR is the only index alternative to FFR to have been tested in randomized controlled trials. The DEFINE-FLAIR study (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization) is a prospective, multicenter, international trial in which 2,492 patients with intermediate



FIGS. 1A TO D: The figures show the exact area in the cardiac cycle where the respective physiological indices are measured. The gray zones depict the zones of interest for the respective parameter.

(ECG: electrocardiogram; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; RFR: resting full-cycle ratio; Pa: aortic pressure; Pd: distal coronary pressure; WIA: wave intensity analysis)



FIGS. 2A TO C: An instantaneous wave-free ratio (iFR): Coronary angiogram coregistration showing the so-called physiological–anatomical correlation.

coronary stenosis were randomized 1:1 to either iFR- or FFR-guided revascularization.[14] This study showed that iFR-guided management was not inferior to FFR guidance.[8] Similar results were reported in the iFR-SWEDEHEART trial (Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve in Patients With Stable Angina Pectoris or Acute Coronary Syndrome) randomizing 2,037 patients with intermediate coronary stenosis to iFR- or FFR-guided revascularization.[15]

Pros and Cons

- *Pros*:
  - Elimination of hyperemic medications, with the potential for reduction in time, side effects, and cost
  - Software allows for an overlay of the iFR values onto the angiogram during pullback, thereby facilitating physiological angiographic fusion **(Figs. 2A to C)**.

- *Cons*:
  - Smaller gradients than FFR mean more sensitive to noise, hydrostatic effects,[11] and wire drift during pullback.
  - It may be more sensitive to variation in hemodynamic conditions (systemic blood pressure and heart rate) that affect baseline coronary flow as hyperemia is not performed. Hyperemia-induced maximal vasodilation saturates the intrinsic coronary autoregulation making FFR less exposed to these hemodynamic status fluctuations.

Resting Full-cycle Ratio

- The RFR seeks *the lowest instantaneous* Pd/Pa ratio within the entire cardiac cycle **(Figs. 1C and D)**.
- This is what differentiates RFR from iFR.
- RFR can be measured online or calculated offline from each individual waveform with a fully automated software algorithm, using equipment either from Abbott Vascular (Santa Clara, CA, USA) or from Coroventis Research AB (Uppsala, Sweden).
- A minimum of five consecutive heart cycles is needed to determine the RFR.
- The RFR index was derived and validated for the first time in the retrospective VALIDATE-RFR (Validation of a Novel Nonhyperemic Index of Coronary Artery Stenosis Severity: The Resting Full-cycle Ratio) study with an optimal RFR cutoff of 0.89 to predict a positive FFR. RFR was highly correlated with iFR (R^2 = 0.99, $p < 0.001$), with a diagnostic accuracy of 97.4%, sensitivity of 8.2%, specificity of 96.9%, positive predictive value of 94.5%, and negative predictive value of 99.0%. Notably, the RFR was detected outside the diastole in 12.2% of all cardiac cycles and in 32.4% of all cardiac cycles in the RCA.[16]

Pros and Cons

Resting full-cycle ratio offers the same trade-offs as all other NHPRs.

Resting Distal Coronary Pressure/Aortic Pressure Ratio

- The resting Pd/Pa ratio is calculated over the entire cardiac cycle **(Figs. 1C and D)**.
- It equals the ratio of the mean (noninstantaneous) Pd and Pa over the entire cardiac cycle.
- A multitude of studies has shown equivalent diagnostic performance for Pd/Pa versus iFR when using various standards.[17] A cutoff of 0.92 for resting Pd/Pa has most often been identified in clinical studies.

Pros and Cons

- Pd/Pa offers all the same trade-offs as other NHPRs.
- It has a wider applicability since it can be measured with any pressure wire monitoring system.
- The main disadvantages are the lack of unique and validated ischemic threshold, lower reproducibility, and higher susceptibility to hemodynamic variability when compared with FFR,[15] and higher susceptibility to pressure sensor drifts and to pressure curve artifacts when compared with iFR.

FLOW-BASED INVASIVE HYPEREMIC INDICES

Estimating Coronary Flow Directly

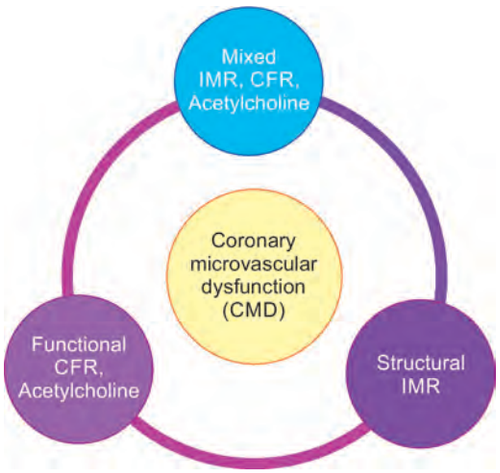
As alluded to earlier, using pressure as a surrogate for flow assessment has caveats, most notable being inability of epicardial flow indices (FFR, iFRa, and RFR) to assess coronary microvascular disease (CMD). Also, FFR assumes that coronary venous pressure is negligible (or zero), which may not be the case in heart failure, thus making FFR unreliable in this condition, which may exist in a significant proportion of patients.

Thus, coronary flow-based indices are the need of the hour that do not rely on any surrogate markers and directly measure coronary flow.

CORONARY MICROVASCULAR DISEASE AND ISCHEMIA IN NONOBSTRUCTIVE CORONARIES

Coronary microvascular disease is a grossly underdiagnosed subset of CAD spectrum. These patients are at a higher risk of major adverse cardiac events (MACEs). Patients with persistent angina, but nonobstructive coronary artery disease (NOCAD) on angiography, are suspected to have CMD.[18]

- A major drawback of pressure-based indices such as FFR and iFR is that CMD cannot be assessed. Unless this entity is recognized and treated aggressively, these may be subjected to recurrent hospitalizations and invasive procedures.
- CMD can be assessed using two physiological indices, namely IMR and coronary flow reserve (CFR). In conjunction with these, acetylcholine (ACh) challenge is performed to evaluate for microvascular spasm [vasospastic angina (VSA)].
- CMD may be defined as functional microvascular impairment (microvascular spasm), reduced CFR, or raised IMR.
- The complex pathophysiological mechanisms involved in CMD and the tests available to assess them are illustrated in **Figure 3**.
- Since proper assessment, diagnosis, and treatment of CMD is the only way to improve outcomes in CMD patients at high risk for MACE, the European Society of Cardiology (ESC) has recommended using a guide wire-based CFR/IMR for symptomatic patients who exhibit no significant evidence of epicardial stenosis for CMD assessment (II/B).[19]
- Entities such as CMD, NOCAD, and ischemia in nonobstructive coronaries (INOCAD) have been a matter of discussion in the recent times. A number of studies are underway to assess the clinical impact of CMD in cardiology practice and the ways to objectively assess CMD, of note being the CorMicA (Coronary Microvascular Angina) study.
- A simplified approach to CMD has been depicted in **Figure 4** for the ease of understanding of the above discussion.



Note: CMD due to fixed structural disorders that may be detected with an endothelial-independent probe (e.g., adenosine). Alternatively, isolated functional disorders affecting the coronary microcirculation can also cause inappropriate vasoconstriction (e.g., microvascular spasm). Microvascular angina due to functional microvascular spasm may be missed without using an endothelial probe such as acetylcholine.

FIG. 3: Complex pathophysiological mechanisms involved in CMD and the tests available to assess them are illustrated in the figure.

(CFR: coronary flow reserve; CMD: coronary microvascular dysfunction; IMR: index of microcirculatory resistance)

- *CorMicA Study*:[20]
  - The CorMicA study, a prospective double-blind randomized controlled trial that studied 151 patients with angina with symptoms and/or signs of ischemia and NOCAD who were randomized to stratified medical therapy guided by an interventional diagnostic procedure versus standard care without an invasive diagnostic procedure, showed that invasive procedure-guided stratified medical treatment leads to marked and sustained angina improvement and better quality of life at 1 year. This study evaluated the microvascular angina (MVA) by using the adenosine hyperemia and pressure wire-based CFR and IMR and VSA using ACh provocation.
  - *Definitions*:
    - *VSA* was defined when significant epicardial vasoconstriction (>90%), reproducible chest pain, and ischemic ECG changes occurred after ACh challenge.
    - *MVA* was defined with clinical symptoms of ischemia, unobstructed coronary arteries, and abnormal CMD indices (CFR < 2.0/IMR >25, coronary spasm on ACh testing).
    - *Microvascular spasm* was defined when ischemic symptoms and ECG changes were provoked with ACh challenge but no epicardial spasm was noted.

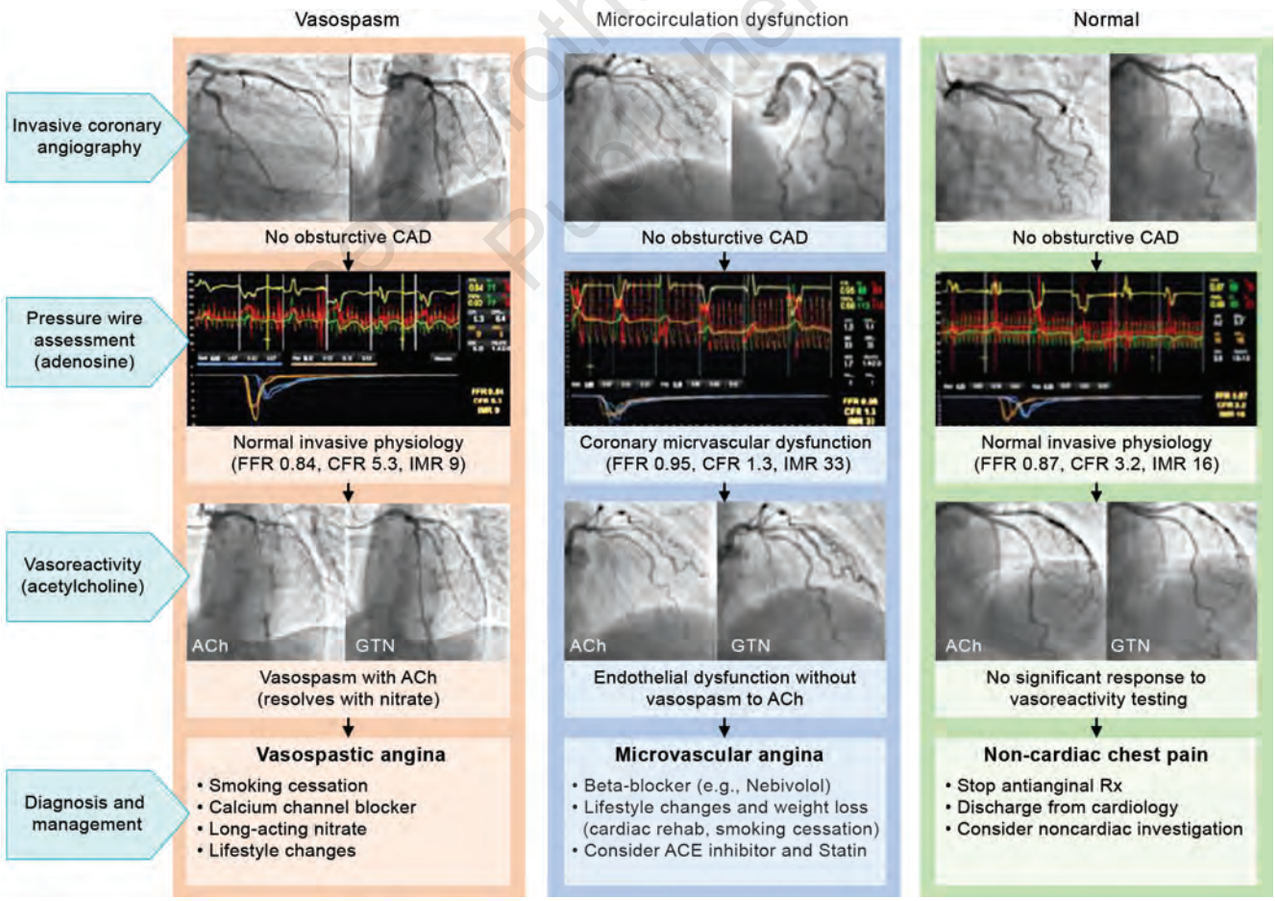


FIG. 4: A simplified approach to coronary microvascular dysfunction.

(ACE: angiotensin-converting enzyme; ACh: acetylcholine; CAD: coronary artery disease; CFR: coronary flow reserve; FFR: fractional flow reserve; GTN: glyceryl trinitrate; IMR: index of microvascular resistance)

- This study showed a *27%* improvement in angina severity and *18%* improvement in quality of life parameters according to the Seattle Angina Questionnaire score.

CORONARY FLOW RESERVE AND INDEX OF MICROVASCULAR RESISTANCE

- These are calculated using the thermodilution technique using the Abbott's PressureWire™ X Guidewire and the Coroventis‡ CoroFlow‡ Cardiovascular System **(Fig. 5)**.
- There are two temperature sensors located in proximal and distal positions on the PressureWire™ X Guidewire. These sensors allow physicians to capture the measurements using thermodilution.

Principle

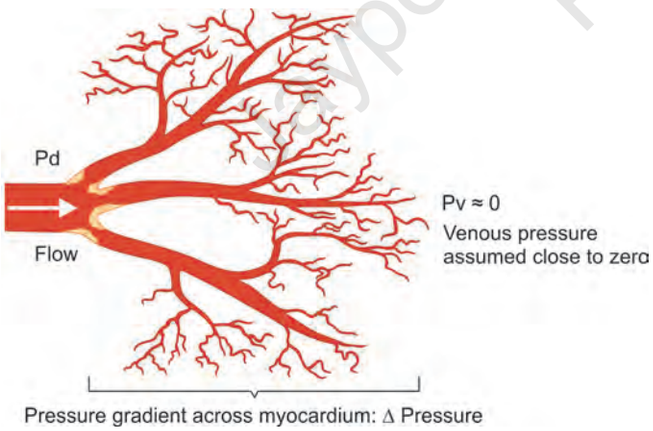
In the thermodilution technique, *CBF* is estimated *inversely* proportional to the *time* it takes for an injected bolus of room temperature saline to travel down the coronary artery system can detect a bolus injection traveling down the artery and calculate the transit mean time: Tmn **(Fig. 6)**.

Formula

The CFR and IMR are calculated by the following formulas:

$$\text{CFR (Coronary flow reserve)} = \frac{\text{Hyperemic flow}}{\text{Resting flow}} = \frac{1/\text{Tmn\_Hyp}}{1/\text{Tmn\_Rest}} = \frac{\text{Tmn\_Rest}}{\text{Tmn\_Hyp}}$$

$$\text{IMR (Index of microcirculatory resistance)} = \frac{\Delta\ \text{Pressure}}{\text{Flow}} = \frac{\text{Pd - Pv}}{1/\text{Tmn}} \approx \text{Pd} \times \text{Tmn (at max hyperemia)}$$



Procedure

- The CFR/IMR measurements are calculated using Abbott's PressureWire™ X Guidewire and the Coroventis‡ CoroFlow‡ Cardiovascular System.
- A total of 3 mL normal saline boluses are administered into the coronary after placing the PressureWire™ X Guidewire in the artery of interest. Then, the saline boluses are repeated after achieving hyperemia with adenosine.

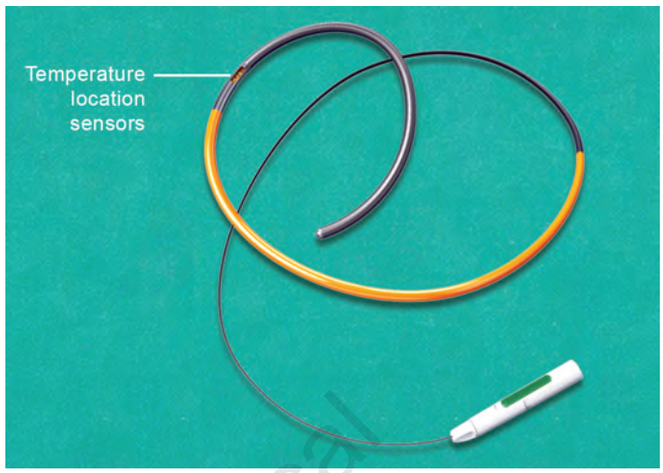


FIG. 5: Abbott's PressureWire™ X Guidewire and the Coroventis‡ CoroFlow‡ Cardiovascular System. Refer to the local regulatory guidelines regarding availability of the product.

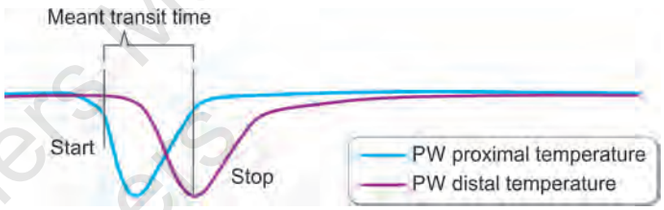


FIG. 6: Thermodilution technique.

- The resting test calculated only the CFR, while the latter test calculated both CFR and IMR.
- The procedure along with end result as seen on the Abbott system is depicted in **Figures 7A and B**.

Normal Values

The CFR and IMR cutoff values are >2 and <25, respectively **(Table 1)**.

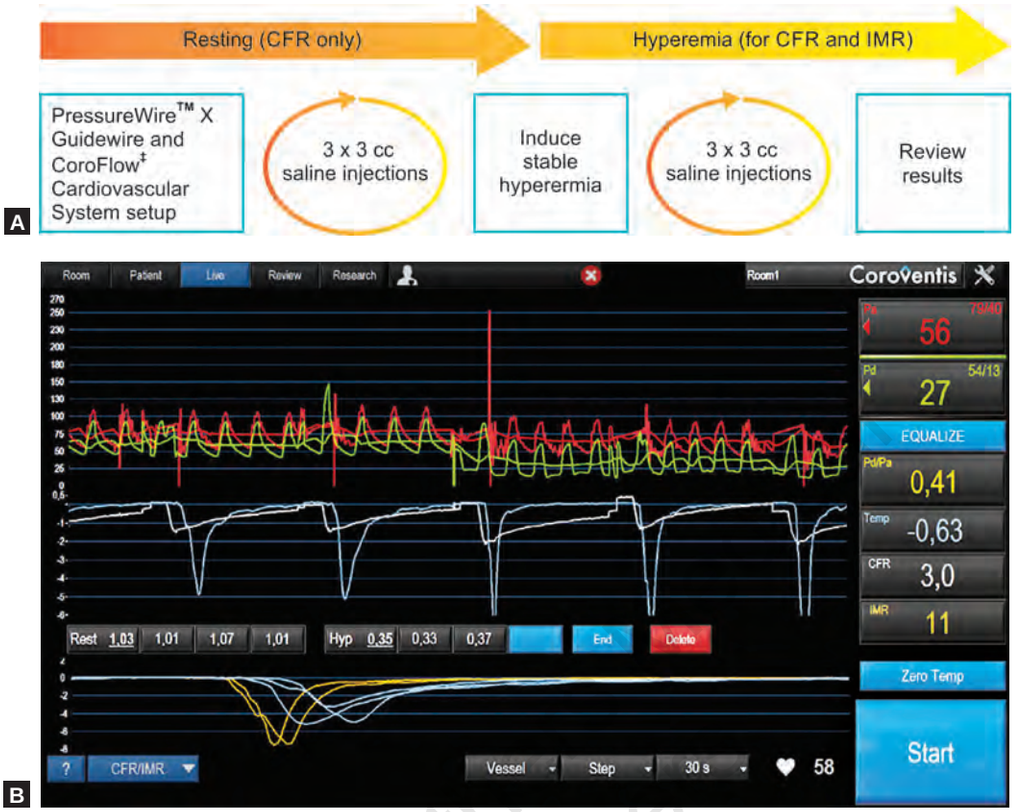
What to do when physiologic parameters are in the "gray zone"?

It is a well-known fact that more coronary events occur in areas where the plaque burden is more, even though these plaques may be nonobstructive; raising the possibility of plaque morphology, composition, and atheroma volume may be as important as degree of stenosis in causing MACE. This is especially true in ACS.

Can we use anatomic metrics to decide about intervention or not in "gray zone" of FFR?

Value of adding coronary anatomic imaging to physiologic assessment: "Surrogating" the surrogates

In a study done by Yang et al.,[21] IVUS characteristics in intermediate coronary lesions with *borderline FFR and intermediate coronary artery stenosis* (40–70% diameter stenosis) were studied. Both IVUS and FFR were performed in a total of 228 LAD arteries and were divided into three groups by FFR value: Ischemic (FFR <0.75), borderline (FFR 0.75 to <0.8), and nonischemic (FFR >0.8). MLA, lesion length, plaque burden,



FIGS. 7A AND B: Procedure of performing coronary flow reserve (CFR) and index of microvascular resistance (IMR) along with the tracings seen on the Coroventis‡ CoroFlow‡ Cardiovascular System.

TABLE 1: Summary of coronary physiology indices along with cutoffs.

Index	Lesion assessed	Cutoff	Hyperemic/Nonhyperemic
Invasive: Pressure			
FFR	Epicardial only	<0.80	Hyperemic
iFR	Epicardial only	<0.90	Nonhyperemic
RFR	Epicardial only	<0.90	Nonhyperemic
Pd/Pa	Epicardial only	<0.92	Nonhyperemic
Invasive: CMD			
CFR	Epicardial and microvascular	<2.0	Hyperemic
IMR	Microvascular only	>25.0	Hyperemic
ACh test	Epicardial vasospasm	>90% stenosis = ST-T changes reversible with i/c GTN	Hyperemic
Noninvasive: CMD			
PET	Epicardial and microvascular	–	
CMR	Epicardial and microvascular	–	

(ACh: acetylcholine; CFR: coronary flow reserve; CMD: coronary microvascular disease; CMR: cardiac magnetic resonance; FFR: fractional flow reserve; GTN: glyceryl trinitrate; iFR: instantaneous wave-free ratio; IMR: index of microvascular resistance; Pa: aortic pressure; Pd: distal coronary pressure; PET: positron emission tomography; RFR: resting full-cycle ratio)

and volumetric analysis were done among the three groups. In the IVUS analysis, the MLA was smaller (2.5 ± 0.6 vs. 2.7 ± 0.7 vs. 3.4 ± 1.2 mm^2, $p < 0.001$), lesion length was longer (23.6 ± 8.4 vs. 23.6 ± 7.4 vs. 17.4 ± 6.8 mm, $p < 0.001$), plaque burden was larger (76.1 ± 9.6 vs. 73.9 ± 7.5 vs. 69.8 ± 9.5%, $p < 0.001$), plaque volume was larger (173.0 ± 78.3 vs. 167.7 ± 75.0 vs. 129.5 ± 79.1 mm^3, $p < 0.01$), and percent atheroma volume was larger (57.9 ± 7.5 vs. 57.6 ± 6.6 vs. 53.9 ± 8.0%, $p < 0.01$) in the *ischemic and borderline FFR groups as compared to nonischemic FFR group.* This suggests that anatomic parameters may be helpful in deciding about intervention in cases with borderline FFR values.

In a similar study, Naganuma et al. tried to correlate IVUS, FFR, and quantitative coronary angiography (QCA) data in 132 intermediate stenoses in 109 patients.[22]

- FFR <0.80 was observed in 39 lesions. Overall, MLA value <2.70 mm^2 had 79.5% sensitivity, 76.3% specificity, 58.5% positive predictive value, 89.9% negative predictive value, and 77.3% accuracy in predicting a positive FFR.
- When the reference diameter was ≥3.0 mm, the MLA cutoff value was 2.84 mm^2 [sensitivity 72.2%, specificity 83.0%, area under curve (AUC) 0.842], whereas in lesions with reference diameter <3.0 mm, the MLA cutoff value was 2.59 mm^2 (sensitivity 90.5%, specificity 69.6%, AUC 0.823).
- The cutoff lesion length predictive of FFR <0.80 was 11.0 mm with a weak correlation between the two.
- Plaque morphology did not significantly affect FFR ($p = 0.485$).
- In multivariable analysis, MLA were independent predictors of FFR <0.80.
- In another study by Johnson et al.,[23] for LMCA stenoses, a minimal lumen diameter (MLD) of <2.8 mm or an MLA of <6 mm^2 suggests a physiologically significant lesion.
- Revascularization may be safely deferred for MLA of >7.5 mm^2, while an MLA between 6 and 7.5 mm^2 requires further physiological assessment.
- Nonleft main stenoses, MLD >2.0 mm and MLA >4.0 mm^2, correlate with low event rates.
- Thus, a modest correlation seems to exist between MLA and FFR.
- Interventionists can confidently conserve intermediate lesions with large MLAs (as mentioned above), given the high negative predictive value of large MLAs while using IVUS only, without incurring additional expense of FFR.

In the COMBINE OCT FFR[24] study, which tried to combine OCT and FFR data to improve prediction of coronary events in a population likely to have a high plaque burden and higher possibility of vulnerable plaques. Up to 500 diabetic patients with indicated angiography and lesions of intermediate severity (40–80%) underwent FFR and OCT and were divided into three groups—Group A: FFR >0.8, no thin-cap fibroatheroma (TCFA); Group B: FFR >0.8 with TCFA; and Group C: FFR <0.8.

All Group C patients underwent intervention. Groups A and B patients were compared for difference in occurrence of primary endpoint [cardiac death, target lesion MI, clinically driven target lesion revascularization (TLR), and hospitalization due to unstable angina] at 1.5 years.

It was noted that 25% of FFR-negative diabetes mellitus (DM) patients had high-risk plaques and had significantly higher percentage of these primary endpoint events as compared to those without TCFA.

Thus, in high-risk populations such as DM, data from imaging modalities such as OCT should be incorporated with coronary physiology data in prognosticating future ischemic events. It is heartening to note that iFR coregistration with OCT and angiography is available, which should be utilized in DM patients.

In the future, with larger studies correlating IVUS/OCT data with FFR, maybe we will be able to dispense with FFR at least for epicardial CAD.

CONCLUSION

- Physiological indices for assessing myocardial ischemic syndromes play an important complimentary role in scientifically allowing the interventionist to decide between intervention and medical treatment alone, especially in "gray zone" intermediate coronary artery stenoses.
- Pressure-based indices still remain the method of choice because of easy availability and fair accuracy.
- Flow-based indices have helped in classifying and scientifically treating coronary microvascular syndromes, which were hitherto being treated inadequately and empirically.
- Anatomic IVUS metrics could be used as an adjunct to decide about intervention in cases with borderline FFR lesions. This may change in favor of IVUS/OCT alone in future.
- It may be relevant to correlate OCT data when interpreting FFR data in diabetic patients with intermediate lesions.
- In the near future, hopefully, these modalities will become a part of routine diagnostic CAG.

ACKNOWLEDGMENTS

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CHAPTER 51

Cardiometabolic Syndrome: Approach in the Current Era

PC Manoria

ABSTRACT

Cardiometabolic diseases (CMD) are rocking the entire universe and creating an ever-increasing burden on the healthcare systems both in terms of morbidity and mortality. Although CMD encompasses a panoply of diseases, obesity, diabetes, hypertension, and atherosclerotic cardiovascular disease (ASCVD) form the major chunk of CMD. Distressingly enough, most of these diseases, commonly coexist and produce multiple comorbidities which are beyond the reach of a physician or a single specialist to comprehensively evaluate and treat them. Therefore, there is an urgent need to build up this new subspecialty of cardiometabolic medicine (CMM) to tackle the suffering afflicted population. The fulfilment of this goal requires a cohesive effort of several specialities like cardiology, diabetology, hepatology, pulmonary medicine, etc. The core concepts of CMM must be included in the medical school curriculum for its better growth and implementation in future.

INTRODUCTION

Cardiometabolic diseases (CMD) such as obesity, diabetes, hypertension, coronary artery disease (CAD), heart failure (HF), etc., are reaching alarming and pandemic proportions and are the leading cause of cardiovascular morbidity and mortality **(Box 1)**. The key driver for rapid transaction from communicable to noncommunicable diseases is environmental influences such as sedentarism, faulty diet, habits such as fast food and addiction like smoking and tobacco abuse. In particular, children, adolescents, and young adults are being rapidly affected by obesity and even diabetes and distressingly enough they are the forerunner of cardiovascular disease (CVD). Chubby children are not healthy children but are the harbingers of atheroma and glycemia and are prime contributors to metabolic syndrome.

Cardiometabolic medicine (CMM) requires cohesive efforts of diverse aspects of medicine such as cardiology, diabetology, hepatology, pulmonary medicine, nephrology, bariatric medicine, nutrition, and rehabilitation medicine **(Fig. 1)**.

The incidence of CVD has been on the decline in the western world during the last few years but the new projections predict an escalation in this disease due to increased prevalence of CMD such as obesity, diabetes, hypertension and metabolic syndrome[1,2] but in India, the CMD continue to progress in alarming and epidemic proportions.

Obesity is a global health problem and is associated with morbidity and mortality. Lifestyle modification is useful but has

BOX 1 Cardiometabolic diseases.

- Obesity
- Diabetes
- Hypertension
- Atherosclerotic cardiovascular disease
- Obstructive sleep apnea
- NAFLD, NASH
- Fatty liver
- Cognitive decline and Alzheimer's disease
- Erectile dysfunction
- Polycystic ovary syndrome
- Osteoporosis

(NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis)

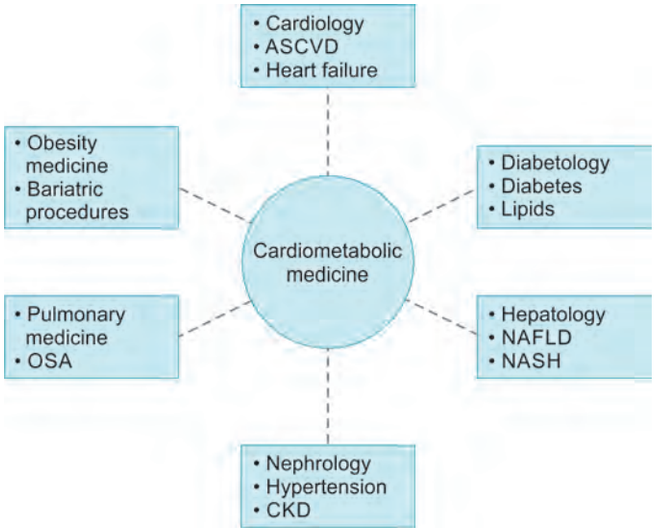

FIG. 1: Conglomeration of specialities required for cardiometabolic medicine.

(ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; OSA: obstructive sleep apnea)

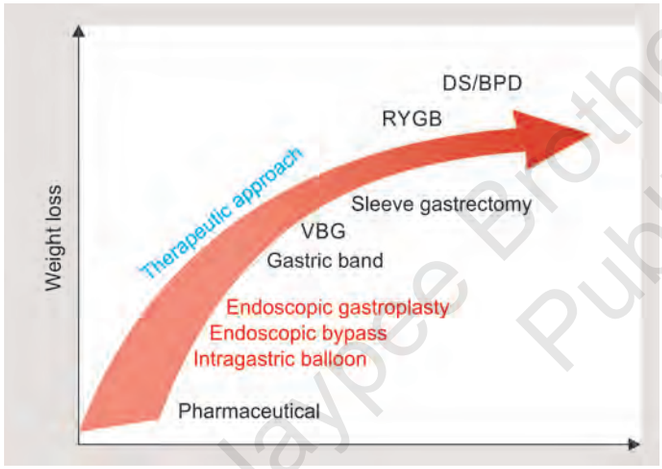

FIG. 2: Therapeutic approaches for obesity management.

(BPD: biliopancreatic diversion; DS: duodenal switch; RYGB: Roux-en-Y gastric bypass; VBG: vertical band gastroplasty)

poor compliance in the long run. Drug therapy only produces a slight decrease in weight.

Bariatric surgical procedures are time-tested modalities of treatment with good results but have a substantial risk and less patient acceptability. However, during the last couple of years, endoscopic bariatric procedures[3] have made great progress and are emerging as the next major breakthrough in the management of obesity. Although they are less effective than bariatric surgery, they are minimally invasive, safe, and have good patient acceptability. The therapeutic approaches for obesity treatment are exhibited in **Figure 2**.

The treatment of diabetes during the last couple of years has undergone a sea change. We have moved from the glycemic control era and glycemic safety era to the current era of CV risk reduction with the availability of sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RAs).

The SGLT-2 inhibitors such as empagliflozin, canagliflozin, and dapagliflozin are panaceas for HF. All three trials, i.e., EMPAREG OUTCOME,[4] CANVAS,[4] and DECLARE TIMI-58[5] have shown a decrease in hospitalization for HF both in patients with atherosclerotic cardiovascular disease (ASCVD) as well as in patients with multiple risk factors. The EMPA-REG OUTCOME in addition also showed a decrease in cardiovascular mortality and all-cause mortality. Based on these trials the guidelines have approved empagliflozin, canagliflozin or dapagliflozin in patients with type 2 diabetes mellitus (T2DM) and CVD or at very high CV risk to reduce CV events. Empagliflozin has also been recommended for reducing the risk of death in patients of T2DM with CVD. The DAPA HF trial[6] and EMPEROR-Reduced trial[7] have shown improved CV outcome of heart failure with reduced ejection fraction (HFrEF) in diabetics as well as nondiabetics. Dapagliflozin has been approved for the treatment of HFrEF and empagliflozin is likely to get approved in future. Trials of SGLT-2 inhibitors in HF with preserved ejection fraction are ongoing such as DELIVER, EMPA PRESERVED, and their results are keenly awaited. SGLT-2 inhibitor also slows down the trajectory of chronic kidney disease (CKD) and postpones dialysis by 10 years or so. The CREDENCE trial[8] showed positive results in diabetic CKD and the DAPA CKD trial[9] has shown improved outcomes in diabetic as well as nondiabetic CKD. The EMPA CKD trial is ongoing.

The GLP-1 RAs have shown a reduction in ASCVD in several trials such as LEADER,[10] SUSTAIN-6,[11] HARMONY OUTCOME,[12] and REWIND[13] trials but have no effect on HF. They, however, have some beneficial effects on CKD. The GLP-1 RAs have been approved for use in patients with ASCVD or those with multiple risk factors. In patients with ASCVD, the current European guidelines have recommended their use even ahead of metformin. The oral semaglutide is already available in six countries in the world and is likely to be available in India in near future. Following its availability, its use and acceptability are likely to increase.

Despite their immense benefits and recommendation by guidelines, these agents are highly underutilized in real-world scenarios. The SGLT-2 inhibitors are utilized in 20% of patients while GLP-1 RAs are utilized in 10% of patients in the western world and in the developed country its use is dismal.

The SGLT-2 inhibitors improve cardiorenal outcomes while the GLP-1 RAs benefit ASCVD and therefore a plea is made to combine both these agents for improving cardiorenal and ASCVD outcomes. The injectable therapy of GLP-1 RA precludes its use in a large number of patients but when the oral form is available both these agents will be used in a larger number of patients.

CONCLUSION

Cardiometabolic disease is posing a great challenge to the medical fraternity throughout the globe. Nurturing this new subspecialty of medicine is an appropriate step in the right

direction for providing the best possible holistic care for patients with CMD. The new emerging epidemic of childhood obesity and childhood diabetes is posing a serious threat to the young generation. If appropriate steps for prevention are not taken on an urgent basis throughout the globe it will ruin their future.

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CHAPTER 52

Approach to Microvascular Dysfunction Syndromes

KU Natarajan, Nischal N Hegde

ABSTRACT

Coronary microvascular dysfunction (CMD) refers to structural and functional impairment of coronary microvasculature. Many patients undergoing coronary angiograms for the evaluation of anginal chest pain are found to have normal epicardial coronaries. CMD is believed to be the cause of chest pain in these patients. CMD today is known to be associated with several conditions such as cardiomyopathies, takotsubo syndrome, heart failure with preserved ejection fraction (HFpEF), obstructive coronary artery disease (CAD), and following revascularization. The mechanism of CMD varies among these conditions. Recognizing the presence of CMD and its mechanism will help us to provide targeted therapy.

INTRODUCTION

In 1988, Cannon and Epstein first coined the term "microvascular angina" in patients who experienced anginal chest discomfort but had angiographically normal epicardial coronary arteries.[1] These patients were believed to have true myocardial ischemia due to coronary microvascular dysfunction (CMD). Over the last 30 years, significant advances made in the field of coronary physiology have led to a better understanding of the structural and functional abnormalities of coronary microcirculation and are now known to be the major cause of myocardial ischemia in various clinical conditions. Depending upon the clinical setting in which it occurs, CMD is classified into four categories **(Table 1)**: (1) CMD in the absence of obstructive coronary artery disease (CAD) and myocardial diseases, (2) CMD in the presence of myocardial diseases, (3) CMD in the presence of obstructive CAD, and (4) iatrogenic CMD.[2] In this chapter, we will describe the current extent of the problem, etiopathogenesis, clinical implications, and approach to CMD syndromes.

EXTENT OF THE PROBLEM

Patients presenting with chest pain syndromes are routinely evaluated with coronary angiography. A number of these patients are found to have angiographically normal coronaries. A study involving 398,978 patients from the American College of Cardiology National Cardiovascular Data Registry found that only 37.6% of the patients undergoing elective coronary

TABLE 1: Classification of coronary microvascular dysfunction.[2]

CMD type	Clinical setting	Main pathogenic mechanism
Type 1: CMD in the absence of myocardial diseases and obstructive CAD	• CVD risk factors • Microvascular angina	• Endothelial dysfunction • SMC dysfunction • Vascular remodeling
Type 2: CMD in myocardial diseases	• HCM • DCM • Anderson–Fabry disease • Amyloidosis • Myocarditis • Aortic stenosis	• Vascular remodeling • SMC dysfunction • Extramural compression • Luminal obstruction
Type 3: CMD in obstructive CAD	• Stable angina • Acute coronary syndrome	• Endothelial dysfunction • SMC dysfunction • Luminal obstruction
Type 4: Iatrogenic CMD	PCI CABG	• Luminal obstruction • Autonomic dysfunction

(CABG: coronary artery bypass grafting; CAD: coronary artery disease; CMD: coronary microvascular dysfunction; CVD: cardiovascular disease; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; PCI: percutaneous coronary intervention; SMC: smooth muscle cell)

angiograms for the evaluation of chest pain syndromes had significant CAD.[3] Moreover, CMD has emerged as the cause of angina in patients with primary and secondary cardiomyopathies, in stable CAD, and following coronary revascularization.[4] In patients with non-ST elevation acute coronary syndrome, CMD plays an important role in determining the severity of myocardial ischemia.[5] In patients presenting with ST-elevation myocardial infarction (STEMI), reperfusion of the infarcted territory following revascularization is highly dependent on the integrity of the microvasculature **(Fig. 1)**.[6,7]

FUNCTIONAL ANATOMY OF CORONARY ARTERIAL SYSTEM

Functionally, the coronary arterial system can be divided into three compartments. Epicardial coronary arteries form the proximal compartment. These arteries have a diameter of 500 μm to 5 mm and offer minimal resistance to the blood flow. The middle compartment is formed by prearterioles. These vessels have a diameter of 100–500 μm, and they offer significant resistance to blood flow as evidenced by pressure drop along their length. Their role is to maintain the pressure at the origin

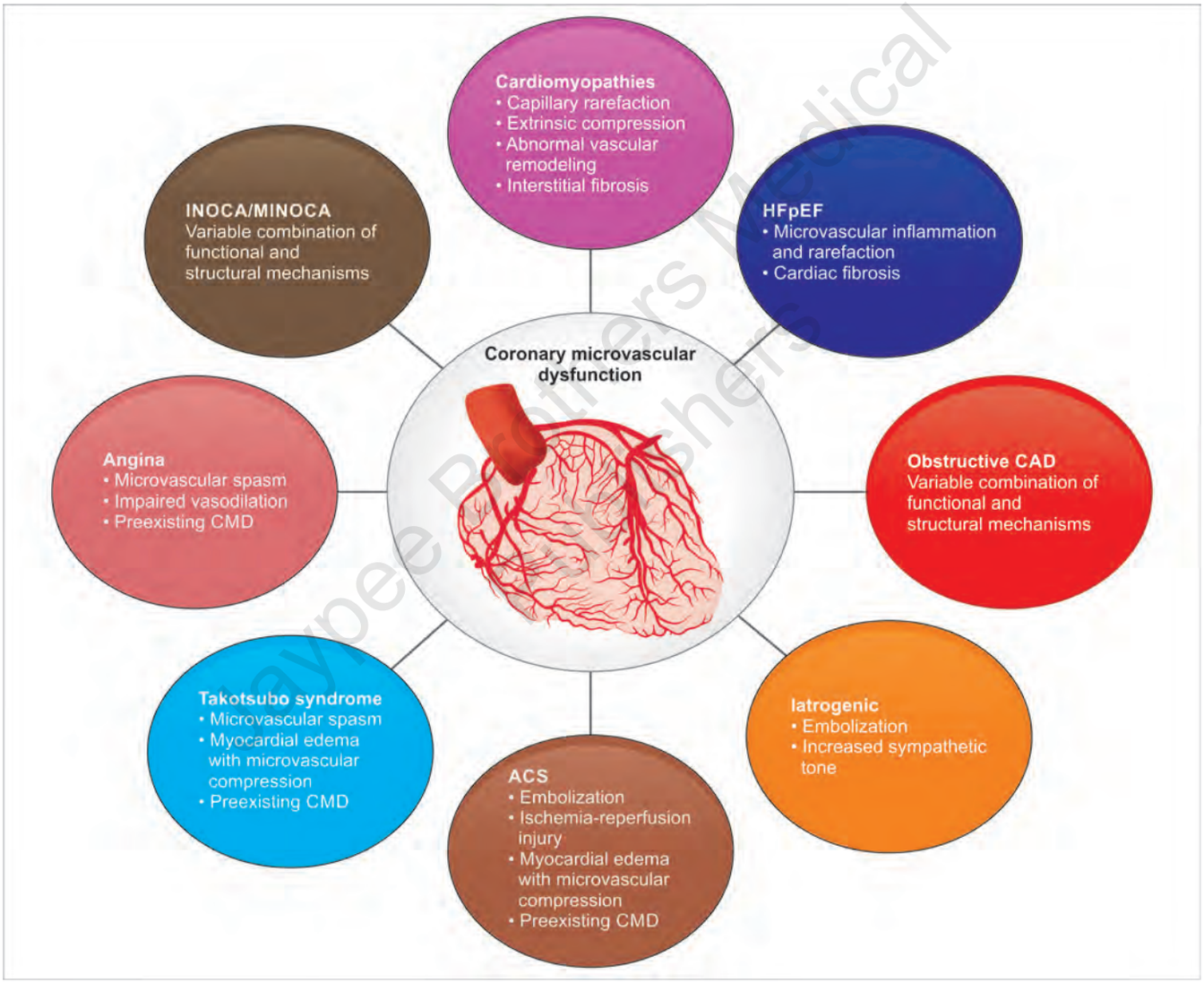
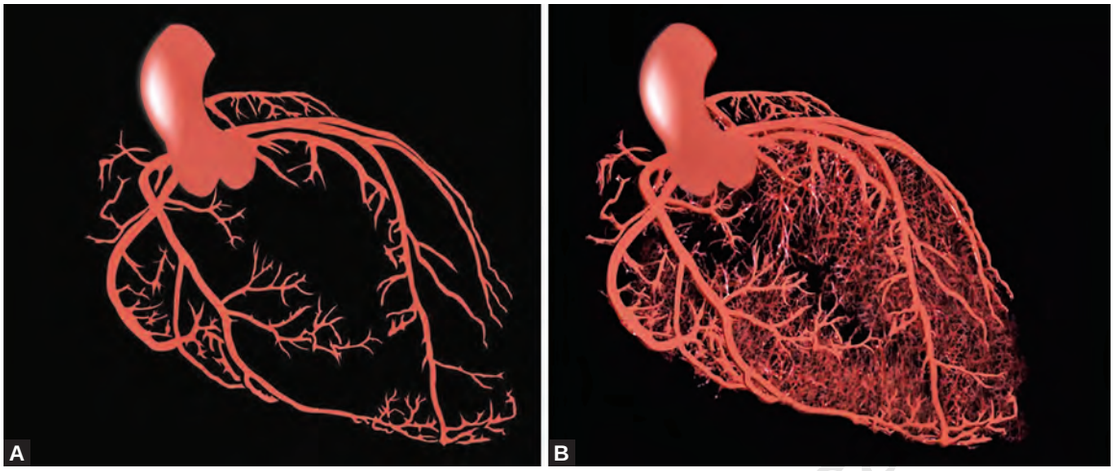


FIG. 1: Extent of coronary microvascular dysfunction.

(ACS: acute coronary syndrome; CAD: coronary artery disease; CMD: coronary microvascular dysfunction; HFpEF: heart failure with preserved ejection fraction; INOCA: ischemia with nonobstructive coronary artery; MINOCA: myocardial infarction with non-obstructive coronary arteries)

Source: Del Buono MG, Montone RA, Camilli M, Carbone S, Narula J, Lavie CJ, et al. Coronary microvascular dysfunction across the spectrum of cardiovascular diseases: JACC state-of-the-art review. J Am Coll Cardiol. 2021;78(13):1352-71.



FIGS. 2A AND B: Coronary arterial system: (A) Macrocirculation; (B) macro- and microcirculation.
Source: Taqueti VR, Di Carli MF. Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC state-of-the-art review. J Am Coll Cardiol. 2018;72(21):2625-41.

of the intramural arterioles within a narrow range. When the aortic pressure increases, the prearterioles constrict to maintain constant pressure in the intramural arterioles and vice versa. The distal compartment comprises the intramural arterioles. The diameter of these vessels is <100 µm. These vessels have a high resting tone and they dilate during increased myocardial oxygen consumption in response to metabolites released from the myocardium **(Figs. 2A and B)**.[8]

PATHOGENESIS

Coronary microvascular dysfunction can occur due to functional or structural abnormalities in the coronary microcirculation or due to the combination of both **(Fig. 3)**.[9]

Functional abnormalities include (1) impaired vasodilatation and/or (2) increased vasoconstriction. Impaired vasodilatation maybe either endothelium dependent or endothelium independent. Endothelium plays an important role in regulating vasomotor tone by releasing nitric oxide (NO; a potent vasodilator) and endothelin-1 (a potent vasoconstrictor). Reactive oxygen species (ROS) overproduction and accumulation promote transformation of NO to peroxynitrite radicals and uncoupling of NO synthase enzyme. This results in increased degradation and decreased production of NO. ROS also causes activation of the RhoA/Rho-kinase pathway. Activation of this pathway causes increased production of endothelin-1 resulting in vasoconstriction.[4] The RhoA/Rho kinase pathway also modulates calcium sensitivity and phosphorylation of contractile myofilaments and is implicated in smooth muscle hypercontraction.[4] Traditional cardiovascular disease (CVD) risk factors such as aging, diabetes, hypertension, and dyslipidemia have been shown to cause endothelial dysfunction.[10] Patients with endothelium-independent impaired vasodilatation show attenuated vasodilator responses to papaverine, adenosine, or dipyridamole due to impaired smooth muscle cell relaxation.[4] Loss of endothelium-mediated vasomotion and alteration of sympathetic innervation cause CMD and "no-flow" following recanalization in patients presenting with STEMI.[2]

Structural alterations are seen in patients with underlying CVD risk factors and cardiomyopathies.[9] Hypertrophic cardiomyopathy (HCM) is associated with medial hypertrophy (due to smooth muscle hypertrophy and collagen deposition) and intimal hyperplasia of the arterioles resulting in marked wall thickening and reduction in luminal diameter.[2] These structural alterations are seen in both the hypertrophied septum and the nonhypertrophied left ventricular (LV) free wall. However, the most severe changes are observed in the septum where the thickness is maximum. In patients with LV hypertrophy (LVH) secondary to aortic stenosis (AS) and systemic hypertension, there is significant decrease in the capillary density proportional to the increase in the volume of myocytes. In addition, increased perivascular fibrosis is seen in both HCM and secondary LVH.[11] In infiltrative heart diseases such as amyloid (mostly AL type), the walls of the intramural arterioles are progressively infiltrated by fibrils resulting in CMD.[12] Microvascular luminal obstruction due to microembolization can occur following recanalization in acute coronary syndrome. Also, ischemia-reperfusion injury with endothelial cell death and myocardial edema causing microvascular compression significantly contribute to the "no-reflow" phenomenon.[2]

TYPE-SPECIFIC CLINICAL IMPLICATIONS

CMD in the Absence of Obstructive CAD and Myocardial Diseases

Patients with angiographically normal coronaries and in the absence of myocardial diseases can present with anginal chest pain, called ischemia with nonobstructive coronary artery (INOCA) disease. The demonstration of ST-segment depression during spontaneous or stress-induced angina in such patients favors ischemia as the cause of angina. The

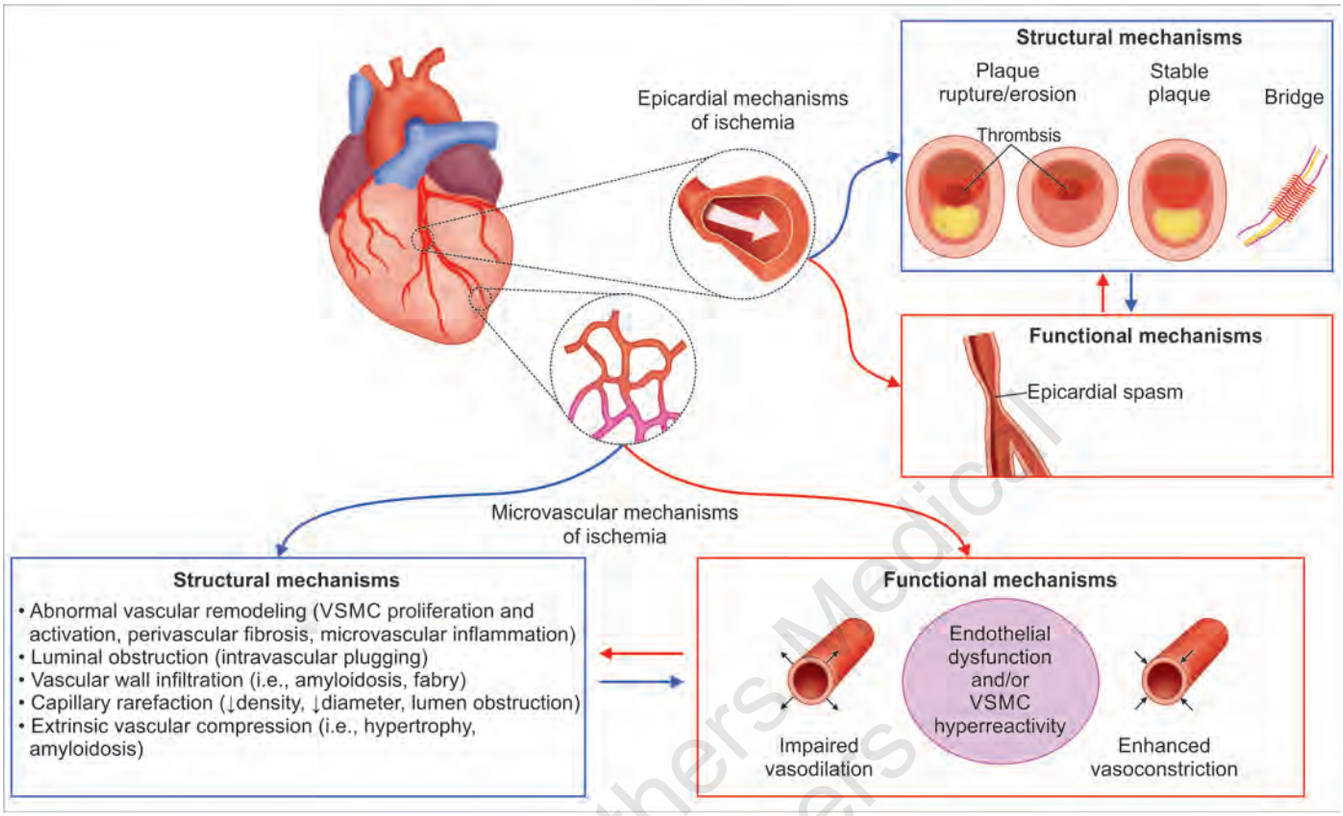


FIG. 3: Structural and functional mechanisms of coronary microvascular dysfunction.

(VSMC: vascular smooth muscle cell)

Source: Del Buono MG, Montone RA, Camilli M, Carbone S, Narula J, Lavie CJ, et al. Coronary microvascular dysfunction across the spectrum of cardiovascular diseases: JACC state-of-the-art review. J Am Coll Cardiol. 2021;78(13):1352-71.

Coronary Vasomotor Disorders International Study Group has proposed a diagnostic criterion for microvascular angina: (1) Presence of symptoms suggestive of myocardial ischemia, (2) objective documentation of myocardial ischemia, (3) absence of obstructive CAD [<50% coronary diameter reduction and/or fractional flow reserve (FFR) >0.80], and (4) confirmation of a reduced coronary blood flow reserve and/or inducible microvascular spasm.[13] Traditional coronary risk factors such as smoking, obesity, hypertension, dyslipidemia, and diabetes have been implicated to cause CMD in this clinical setting.[10] CMD has been demonstrated in smokers with 21% reduction in coronary flow reserve (CFR) as compared to nonsmokers.[10] CMD is prevalent in obesity and increases in severity with the increase in body mass index (BMI).[14] CMD and impaired CFR are seen in patients with dyslipidemia and diabetes.[9] A recent study showed significant impairment of myocardial blood flow (MBF) in response to adenosine infusion and to cold pressor test in young diabetic patients.[9] The Women's Ischemia Syndrome Evaluation (WISE) study demonstrated that, in patients with anginal chest pain and CVD risk factors, lower CFR (<2.32) was associated with an increased risk of major adverse cardiac events (MACE).[9]

CMD in the Presence of Myocardial Diseases

Primary Cardiomyopathies

Hypertrophic Cardiomyopathy

Structural and functional changes in the coronary microvasculature in the presence of increased oxygen demand in patients with HCM result in recurrent ischemia and angina.[11] Myocardial ischemia is responsible for some of the severe complications of HCM, including ventricular arrhythmias and sudden cardiac death (SCD).[2] Recurrent ischemia due to CMD over time can lead to myocyte death and areas of replacement fibrosis.[11] The severity of CMD has been found to be an independent predictor of death from cardiovascular causes.[15] In the subgroup of HCM patients with LV dysfunction and heart failure (HF), CMD has been found to be a critical determinant of clinical deterioration and adverse outcome.[15] In a multivariable analysis, hyperemic MBF of ≤1.1 mL/min/g was the most powerful independent predictor of death and adverse outcome.[4] Patients with the most severe degrees of CMD showed higher risk of progressive LV remodeling and systolic dysfunction including end-stage disease.[15]

Dilated Cardiomyopathy

Patients with dilated cardiomyopathy (DCM) have severely impaired CFR.[2] Like in HCM, in patients with DCM the severity of CMD has been shown to be an independent predictor of MACE and is associated with further progression of HF and increased relative risk of death.[16]

Secondary Cardiomyopathies

Aortic Stenosis

Up to 50% of the patients with AS and normal epicardial coronaries experience anginal chest pain. In patients with AS and LVH, global MBF to LV is increased to meet the increased demand of hypertrophied heart. Hence, there is impaired CFR and reduced hyperemic response of MBF. Low CFR is an independent predictor of future cardiovascular events in AS patients.[17]

Systemic Hypertension

Coronary microvascular dysfunction and impaired CFR in patients with hypertension are not associated with the presence or degree of LVH.[18] Abnormal flow reserve has been demonstrated in patients with essential hypertension with angiographically normal coronaries and the absence of LVH.[19,20] CMD in patients with systemic hypertension can cause myocardial ischemia and angina during conditions requiring high flow.[2]

Infiltrative Heart Diseases

Coronary flow reserve is significantly impaired in patients with Anderson–Fabry disease and amyloidosis.[4] CMD is an important feature of Anderson–Fabry disease-associated cardiomyopathy and is the cause for angina in the absence of obstructive CAD.[4] CMD maybe an early feature of the Anderson–Fabry disease even before the occurrence of hypertrophy which might provide an early window for initiating therapy. Similarly, anginal chest pain maybe the earliest feature of cardiac involvement in patients with systemic amyloidosis.[4] Angina is a frequent symptom of cardiac sarcoidosis.[4]

Takotsubo Cardiomyopathy

Stressful events causing sympathetic overactivity with local myocardial catecholaminergic surge result in vasoconstriction of coronary microcirculation and myocardial stunning. Significantly reduced MBF and CFR have been demonstrated in takotsubo cardiomyopathy (TC) in various studies. CMD associated with TC is reversible and LV function returns to normal within 1 month.[4]

Heart Failure with Preserved Ejection Fraction

Heart failure with preserved ejection fraction (HFpEF) has been reconceptualized as a systemic illness with multiple comorbidities such as obesity, hypertension, diabetes, and chronic obstructive pulmonary disease (COPD) which create a proinflammatory milieu. This causes coronary endothelial microvascular inflammation and dysfunction. The PROMIS-HFpEF study showed that 75% of the patients with HFpEF have CMD. HFpEF patients are found to have low CFR and high index of microcirculatory resistance (IMR). It is not known if ventricular remodeling leads to CMD or if CMD leads to ventricular remodeling and HFpEF.[4]

CMD in the Presence of Obstructive CAD

Stable Coronary Microvascular Dysfunction

In patients with stable angina, the presence of CMD distal to the obstructive lesion enhances myocardial ischemia.[2] In the presence of CMD, FFR may underestimate the severity of an epicardial stenosis.[4] CMD may also be present in regions subtended by angiographically normal coronary arteries.[4] Patients with angiographically successful percutaneous transluminal coronary angioplasty (PTCA) having post-PTCA CFR of <2.5 had an increased risk of recurrence of angina within 1 month.[21]

Acute Coronary Syndrome

In patients with unstable angina, episodes of transient ischemia and angina at rest are associated with a brisk increase in coronary microvascular resistance.[22] In patients with STEMI, the occurrence of CMD is associated with an increased incidence of LV remodeling, HF, and death.[4]

Iatrogenic Coronary Microvascular Dysfunction

Coronary microvascular dysfunction due to either microvascular vasoconstriction or distal embolization can occur following percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). This can result in persistent myocardial ischemia or electrical instability and is associated with increased mortality. CMD is also commonly seen in transplanted hearts and is associated with a higher risk of death **(Fig. 4)**.[4]

DIAGNOSIS

With current methods, direct visualization of coronary microcirculation is not possible. Several noninvasive and invasive methods by quantifying blood flow through the coronary arteries can evaluate the presence of CMD. During the functional assessment of coronary microcirculation, it is important to distinguish if the CMD is due to impaired vasodilation of the coronary microcirculation or due to increased microvascular constriction.

The vasodilator response of the coronary microcirculation is assessed by calculating the CFR as the ratio of maximum hyperemic flow velocity to basal coronary flow velocity. CFR of >2.5 is considered normal.[4] For measuring CFR, an intracoronary Doppler flow wire is placed in the distal part of the coronary artery and flow velocities are measured at rest and during hyperemia. The thermodilution technique can also be used to measure CFR. A temperature sensor–tipped guidewire is placed in the distal coronary artery and 3 mL saline bolus is injected at room temperature and saline bolus transit time is calculated at baseline and during hyperemia. CFR is impaired in both obstructive CAD and CMD; hence, CFR can be used to detect CMD only in patients with unobstructed coronary arteries.[4] IMR uses a pressure wire whose sensor can also act as a thermostat, to selectively test microvascular dilatory function.[23] IMR is quantified by measuring the distal coronary pressure and multiplying it by the mean transit time of the

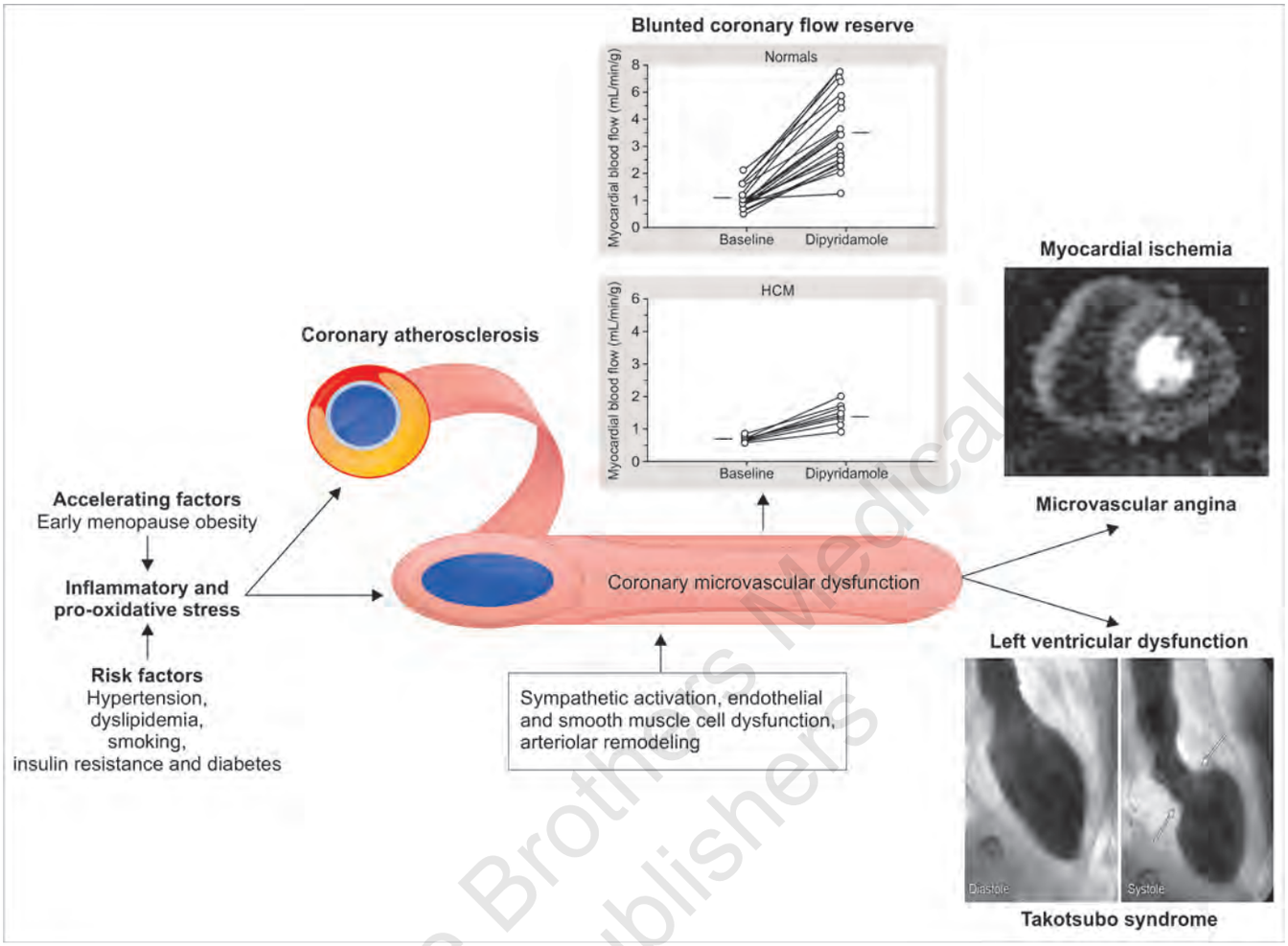


FIG. 4: Causes and consequences of coronary microvascular dysfunction (CMD).
(HCM: hypertrophic cardiomyopathy)
Source: Crea F, Camici PG, Merz CNB. Coronary microvascular dysfunction: an update. Eur Heart J. 2014;35(17):1101-11.

saline bolus during maximum hyperemia.[23] Unlike CFR, IMR is independent of changes in heart rate, blood pressure, and LV contractility.[23] Normal IMR is <25.[23]

Provocative tests (using vasoactive agents such as acetylcholine and ergonovine) are used to diagnose microvascular spasm as the cause of CMD.[24] Ischemic electrocardiogram (ECG) changes with reproduction of typical chest pain without angiographic evidence of epicardial spasm on provocation is needed to confirm microvascular spasm.[4]

Thrombolysis in myocardial infarction (TIMI) myocardial perfusion grade describes the relative "blush," or intensity, of the radiopacity of myocardial tissue achieved with an epicardial coronary injection of contrast medium, and the rapidity with which this enhancement clears. The more intense the myocardial blush of the contrast medium and the faster the clearance, the better the microvascular perfusion.[2]

Noninvasive Methods

Noninvasive methods test only the vasodilatory capacity of the coronary microvasculature and do not directly assess hypercontractility. Moreover, obstructive CAD must be ruled out by computed tomography (CT) angiography or invasive coronary angiography. Transthoracic Doppler echocardiography can be used to measure maximal diastolic flow in the epicardial coronary artery during rest and hyperemia, known as coronary flow velocity ratio (CFVR). CFVR of ≤2–2.5 indicates CMD.[25] Positron emission tomography (PET) allows direct and precise quantification of microvascular function. It calculates the quantity of blood flow per unit mass (in milliliter per minute per gram of tissue) at rest and during hyperemia. Hence, it is possible to calculate myocardial perfusion reserve (MPR) and MBF in all coronary territories at the same time. PET is currently considered the gold standard for the noninvasive assessment of CMD.[2,4] Cardiac magnetic

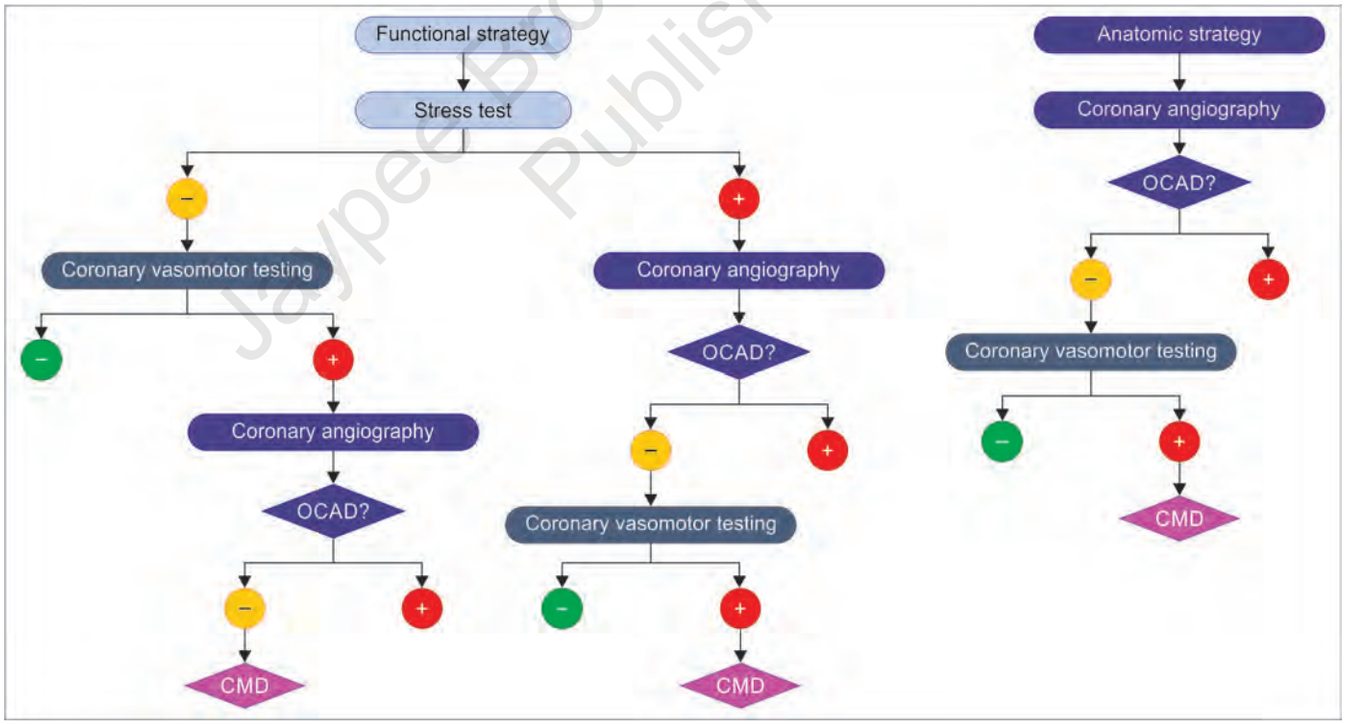
resonance (CMR) also allows quantification of MBF at rest and during hyperemia. MBF and MPR can also be assessed using myocardial first-pass dynamic CT scan but has significant radiation exposure. However, CT allows combination of CT angiography to rule out obstructive CAD and CT perfusion to assess CMD **(Table 2 and Flowchart 1)**.[4]

TABLE 2: Invasive and noninvasive methods to assess coronary microvascular dysfunction (CMD).

Invasive assessment of CMD	
Assessment of both epicardial and microvascular compartments: • CFR (with Doppler or thermodilution technique) • Ratio of coronary blood flow at maximal hyperemia to under-resting condition • Intracoronary provocative testing (acetylcholine) • Assessment of vasoconstriction disorders (epicardial or microvascular spasm)	*Assessment of microvascular compartment*: • IMR (with thermodilution technique) product of the distal coronary pressure and mean transit time of a saline bolus during maximal hyperemia • HMR (with dual Doppler and pressure wire technique) • Pressure distal to a stenosis (or in the absence of a stenosis distal coronary pressure) divided by the distal average peak velocity during maximal hyperemia, during the whole cardiac cycle
Noninvasive assessment of CMD	
Assessment of both epicardial and microvascular compartments: • *CFRV (with Doppler transthoracic echocardiography technique)*: Ratio of coronary blood flow at maximal hyperemia to under-resting condition • *MPR (PET, CMR, CT-scan technique)*: Ratio of myocardial blood flow at peak stress to rest • *MPRI (CMR technique)*: Ratio of myocardial blood flow at hyperemia/rest for the whole myocardium and separately for the 16 segments	

(CFR: coronary flow reserve; CFRV: coronary flow reserve velocity; CMD: coronary microvascular dysfunction; CMR: cardiac magnetic resonance; CT: computed tomography; HMR: hyperemic microvascular resistance; IMR: index of microcirculatory resistance; MPR: myocardial perfusion reserve; MPRI: myocardial perfusion reserve index; PET: positron emission tomography)

Source: Del Buono MG, Montone RA, Camilli M, Carbone S, Narula J, Lavie CJ, et al. Coronary microvascular dysfunction across the spectrum of cardiovascular diseases: JACC state-of-the-art review. J Am Coll Cardiol. 2021;78(13):1352-71.



FLOWCHART 1: Diagnostic testing strategy for CMD.

(CMD: coronary microvascular dysfunction; OCAD: obstructive coronary artery disease)

Source: Taqueti VR, Di Carli MF. Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC state-of-the-art review. J Am Coll Cardiol. 2018;72(21):2625-41.

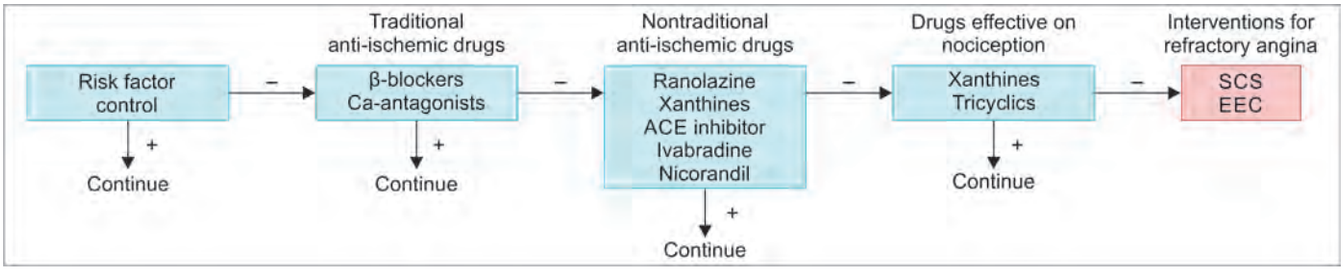


FIG. 5: Treatment algorithm for patients with microvascular angina.

(ACE: angiotensin-converting enzyme; EEC: enhanced external counterpulsation; SCS: spinal cord stimulation)

Source: Crea F, Camici PG, Merz CNB. Coronary microvascular dysfunction: an update. *Eur Heart J.* 2014;35(17):1101-11.

TYPE-SPECIFIC MANAGEMENT

Treatment of CMD mainly involves treating the risk factors, smoking cessation, lifestyle modification, physical training, and intentional weight loss in obese patients. These measures have been shown to increase CFR, exercise capacity, cardiorespiratory fitness, and CVD outcomes in all clinical types of CMD.[4]

CMD in the Absence of Myocardial Diseases and Obstructive CAD

In patients with microvascular angina, an improvement in PET-derived MBF and CFR has been demonstrated after 6 months of treatment with perindopril and indapamide, suggesting reverse remodeling of coronary arterioles. β-blockers are effective in improving chest pain symptoms. Statins and angiotensin-converting enzyme (ACE) inhibitors improve endothelial dysfunction in patients with INOCA.[26]

Calcium channel blockers (CCBs) did not improve CFR and had inconsistent effects on chest pain.[26] CCBs were effective only in patients with microvascular angina triggered by vasospasm **(Fig. 5)**.[4] The efficacy of sublingual nitrates is less consistent in CMD than in patients with obstructive CAD.[26] Xanthines were found to have beneficial effects in microvascular angina.[17] Xanthines inhibit the arteriolar dilator effects of adenosine and thus favor cerebral blood flow (CBF) redistribution toward myocardial areas with CMD. Xanthines also exhibit an analgesic effect by antagonizing the effect of adenosine on cardiac nerve fibers. Nicorandil improved peak exercise capacity but failed to improve exercise-induced ST-T changes.[17] Fasudil, the rho-kinase inhibitor, can prevent acetylcholine-induced ischemia.[26] Imipramine has anticholinergic and alpha-antagonist effects and improves symptoms in patients with chest pain and angiographically normal coronaries. Phosphodiesterase-5-inhibitors, such as sildenafil, have demonstrated significant improvement in CFR in patients with CMD.[4] Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have shown promise in CMD by restoring the beneficial effects of coronary microvascular endothelium.[4] Spinal cord stimulation and enhanced external counterpulsation have also been used in patients refractory to the above measures.[26]

CMD in Myocardial Diseases

In HCM, alcohol septal ablation improved CFR and septal endocardial-to-epicardial MBF.[27] CCB, ACE inhibitor, and disopyramide failed to improve myocardial perfusion.[14,26] In DCM, nebivolol and carvedilol improved CFR and CMD symptoms but not CCB or ACE inhibitors.[26] Allopurinol had some favorable effects on CMD in some studies.[26] In patients with AS, drugs that increase diastolic time help in relieving myocardial ischemia and angina.[17] In patients with Anderson–Fabry disease, enzyme replacement with alpha-galactosidase A reduced LV mass and improved cardiac function as well as clinical outcome, but it does not improve CMD.[4,26]

CMD in Obstructive CAD

In patients undergoing primary PCI, intracoronary adenosine given immediately after thrombus aspiration was associated with a lower rate of microvascular obstruction when compared to placebo.[28] Gene therapy, to stimulate and enhance microcirculation and collateral growth in refractory angina, has been disappointing in randomized trials. Ischemic preconditioning cells to ischemic injury and thus it has been shown to improve angina.[29] Preconditioning has been found to be associated with fewer ventricular arrhythmias and fewer need for inotropic support.[30]

Iatrogenic CMD

Mechanical prevention of distal embolization by filters during PCI of obstructed saphenous grafts using loading doses of aspirin and clopidogrel even in patients on maintenance treatment, glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, and statins has been shown to reduce periprocedural infarction. Pretreatment with α_1-adrenergic antagonist doxazosin restored CFR immediately after PCI.[4]

CONCLUSION

Coronary microvascular dysfunction is commonly underdiagnosed in current clinical practice. In patients with CVD risk factors and typical anginal symptoms, when found to have normal epicardial coronaries on angiography, CMD should be suspected as the cause of angina. CMD is also associated with several conditions such as cardiomyopathies, takotsubo syndrome, HFpEF, obstructive CAD, and following revascularization. Diagnosis of CMD can be made by quantifying blood flow through the coronary arteries. Depending upon the clinical setting in which it occurs, type-specific treatment can help ameliorate symptoms and improve the quality of life in such patients.

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CHAPTER 53

Aspirin-free Antiplatelet Therapy: Is it the Future?

Ashish Kumar Jain, RR Mantri

ABSTRACT

The use of aspirin in primary prevention is debated for a long-time and after results of ASCEND, ASPREE, and ARRIVE trial guidelines do not support the use of aspirin in primary prevention of cardiovascular diseases. P2Y12 inhibitor monotherapy for chronic secondary prevention was associated with a lower risk of major adverse cardiovascular outcomes without significant difference in stroke and major bleeding. Recent studies also raised a question about the duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) with a drug-eluting stent (DES) and also the possibility of monotherapy with only P2Y12 inhibitor after a brief duration of DAPT. Bleeding events while taking DAPT is an important predictor of adverse clinical outcomes. This chapter will outline recently published major trials that support the use of aspirin-free single antiplatelet therapy with P2Y12 inhibitor after a brief duration of DAPT in patients who underwent PCI with current-generation DES.

INTRODUCTION

Dual antiplatelet therapy (DAPT) using aspirin and P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel) has been the standard of care post procedure regimen since the advent of intracoronary stent implantation. However, stent thrombosis (ST), usually subacute and sometimes late or very late, has been a dreaded complication leading to significant mortality and morbidity. In some of the cases, the reason for ST has been the premature withdrawal of antiplatelet therapy. For patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS), the standard treatment has been 12 months of DAPT with aspirin and P2Y12 inhibitor followed by aspirin monotherapy. For chronic coronary syndrome (CCS), the standard treatment has been 6 months of DAPT. However, DAPT is associated with an increased risk of bleeding mainly attributed to aspirin. Recent developments in stent design, polymer technology (biocompatible or polymerless), and the use of intracoronary imaging (to optimize stent implantation and identification and treatment of implant-related complications) have significantly improved post PCI outcomes. Recent studies have thus raised questions about the duration of DAPT and also the possibility of monotherapy with only a P2Y12 inhibitor after shortened or brief duration of DAPT. But bleeding events while taking DAPT still continue to be an important predictor of adverse clinical outcomes.[1,2] There has been an adequate number of trials, which suggest the potential benefits of short DAPT followed by "aspirin-free" strategies to reduce bleeding events without increasing major ischemic events.

EVIDENCE SUPPORTING SHORTENED DURATION OF DUAL ANTIPLATELET THERAPY

No Dual Antiplatelet Therapy after Index Procedure

ASET Pilot Study

All patients of CCS with baseline syntax score less than 23 underwent PCI with platinum–chromium everolimus-eluting stent. All participants were on standard DAPT at the time of index PCI. Aspirin was discontinued on the day of the index procedure after loading dose prior to the procedure, prasugrel was administered in the catheterization laboratory immediately after the successful procedure, and only prasugrel was continued from that moment. Patients were treated solely with prasugrel

for 3 months. Aspirin-free prasugrel monotherapy following successful PCI demonstrated feasibility and safety without any ST in selected low-risk patients with CCS after 3 months.

Limitations

- These were CCS cases; no ACS case was enrolled.
- This was a nonrandomized study without any comparator.
- Patients with high-risk features for PCI (left main disease, chronic total occlusion, bifurcation lesion, saphenous or arterial graft lesion, and severely calcified lesion requiring the use of the rotablation) were excluded from the study.[3]

Trials Neutral for 1 Month Dual Antiplatelet Therapy

Global Leaders

Patients undergoing PCI for CCS (53%) or unstable coronary disease [unstable angina (USA) 12.6%, non-ST-elevation myocardial infarction (NSTEMI) 21.1%, ST-elevation myocardial infarction (STEMI) 13.3%] were randomized to DAPT of aspirin/ticagrelor for 1 month, followed by ticagrelor for 23 months versus DAPT for 12 months (aspirin/clopidogrel for CCS and aspirin/ticagrelor for unstable coronary disease), followed by aspirin for 12 months. All patients underwent PCI with a biolimus-eluting stent. The result of this trial showed that ticagrelor in combination with aspirin for 1 month followed by ticagrelor alone for 23 months was noninferior but not superior to 12 months of standard DAPT at preventing death, myocardial infarction (MI), stroke, or urgent target vessel revascularization. 1 month of DAPT also failed to reduce major bleeding events compared with 12 months of DAPT. Rates of definite or probable ST were similar between the groups included in the study patients.

Limitation

It was an open-label trial, and thus participants and investigators were not masked to the components of the treatment strategy.[4]

STOPDAPT-2

Patients undergoing PCI for CCS (62.3%), USA (12.9%), NSTEMI (5.4%), and STEMI (19.4%) were randomized to 1 month of DAPT followed by clopidogrel monotherapy for 5 years versus 12 months of DAPT followed by aspirin monotherapy for 5 years. For DAPT treatment during month 1, the selected P2Y12 receptor blocker was clopidogrel (75 mg/day) in 62% of the patients and prasugrel (3.75 mg/day) in 38% of the patients. All patients underwent PCI with an everolimus-eluting cobalt–chromium stent. The primary outcome, death, MI, ST, stroke, thrombolysis in myocardial infarction (TIMI), and major/minor bleeding at 1 year occurred in 2.4% of the 1 month DAPT group compared with 3.7% of the 12-month DAPT group (p for superiority = 0.04).

Limitations

- A composite endpoint assessing both cardiovascular and bleeding events was used as the primary endpoint to evaluate the net clinical benefit.
- This study could not assess the risk of ST with very short DAPT.
- The lower-than-expected actual event rate for the primary endpoint reduced the statistical power of this noninferiority study.
- The majority of enrolled patients had low or intermediate ischemic risk.
- Japanese patients with coronary artery disease have lower ischemic risk compared with the US and European patients.
- The majority of patients in this particular study underwent PCI that was guided by intracoronary imaging devices.[5]

Onyx ONE Trial

The goal of the trial was to compare the safety and efficacy of 1 month of DAPT following PCI with either the resolute Onyx drug-eluting stent (DES) or the BioFreedom drug-coated stent (DCS) among patients at high bleeding risk. Patients received DAPT for 1 month. After 1 month, patients were given a prescription for single antiplatelet therapy (either aspirin or a P2Y12 inhibitor) at the discretion of the physician. The presentation was with ACS in 51% of the patients. The primary safety outcome of cardiac death/MI/ST for resolute versus BioFreedom was 17.1% versus 16.9% (p for noninferiority = 0.011; p for superiority = 0.84).

Limitations

- This study was not powered for the assessment of low-frequency events, such as ST.
- It is a single-arm study investigating a selected patient population with low-risk features.[6]

MASTER Dual Antiplatelet Therapy Trial

This is a randomized controlled trial (RCT) that investigated patients at high bleeding risk to discontinue DAPT after 1 month of PCI (abbreviated therapy) or to continue it for at least two additional months (standard therapy) who underwent PCI with a biodegradable polymer sirolimus-eluting stent (Ultimaster, Terumo). The study included patients with stable angina (40%), silent ischemia (11%), NSTEMI (26%), and STEMI (12%).

Primary Outcomes

- Net adverse clinical events (all-cause mortality, MI, stroke, or major bleeding): 7.5% in the abbreviated therapy group compared with 7.7% in the standard arm ($p < 0.001$ for noninferiority)
- Major adverse cardiac and cerebrovascular events [(MACCE); all-cause mortality, MI, or stroke] were found to be 6.1% in the abbreviated therapy group compared with 5.9% in the standard arm ($p = 0.001$ for noninferiority)
- Major or clinically relevant nonmajor bleeding: 6.5% in the abbreviated therapy group compared with 9.4% in the standard therapy group ($p < 0.001$ for superiority)

Limitations

- Patients with in-stent restenosis (ISR) and ST were excluded.
- The incidence of MACCE was lower than expected.
- The duration of DAPT was heterogeneous in the standard treatment group.[7]

Trials Supporting 3-month Dual Antiplatelet Therapy

TWILIGHT Trial

This trial showed the safety and efficacy of DAPT for 3 months followed by ticagrelor monotherapy compared with longer duration DAPT (12 months) among patients with PCI with a DES and with ≥1 high-risk feature of ischemia or bleeding. This trial included patients with previous MI: 29%, previous PCI: 42%, and USA/NSTEMI: 64%.

- The primary outcome of Bleeding Academic Research Consortium (BARC) two, three, or five bleeding at 12 months, for ticagrelor monotherapy versus aspirin + ticagrelor, was 4.0 versus 7.1% ($p < 0.001$).
- Ticagrelor monotherapy versus aspirin + ticagrelor: Secondary outcomes
  - ST, definite + probable: 0.4 versus 0.6% ($p < 0.05$)
  - Ischemic stroke: 0.5 versus 0.2% ($p > 0.05$)

Limitations

- STEMI and cardiogenic shock patients were excluded.
- Six percent of total enrollees who underwent PCI were totally asymptomatic.
- Everyone in the standard DAPT arm received 12 months of DAPT including CCS patients.
- The endpoint was overall major adverse cardiac events (MACE) but was underpowered to detect differences in important clinical events (MI, ST).[8]

TICO Trial

- This trial evaluated ticagrelor monotherapy after 3 months of DAPT compared with 12 months of DAPT after PCI for ACS. This trial included patients with USA 29%, NSTEMI 35%, and STEMI 36%. Patients were treated with the ultrathin bioresorbable polymer sirolimus-eluting stent (Orsiro).
- This trial differs from the TWILIGHT trial because this trial excluded the patients with high bleeding risk and included patients with STEMI.
- The primary outcome, net adverse clinical events (death, MI, ST, stroke, target vessel revascularization, or TIMI major bleeding) at 12 months, occurred in 3.9% of the ticagrelor monotherapy after 3 months of therapy with DAPT group compared with 5.9% of the treatment with the standard therapy group ($p = 0.01$).

Limitations

- It was an open-label trial and drug adherence was not monitored.
- Patients at high risk of bleeding, which generally account for approximately 40% of patients undergoing PCI in a real-world setting, were excluded.[9]

SMART-CHOICE Trial

This trial evaluated the safety and efficacy of DAPT for 3 months compared with longer duration DAPT for 12 months among patients undergoing PCI. Patients presenting with ACS were 58%. The use of intravascular imaging was done in 26% of the patients. Clopidogrel was used in 76.9% of the P2Y12 inhibitor monotherapy group and 77.6% in the DAPT group. Potent P2Y12 inhibitors, prasugrel or ticagrelor, were used in 23.1% of the P2Y12 inhibitor monotherapy group and 22.4% in the DAPT group.

The primary outcome, MACE (all-cause death, MI, or stroke) at 12 months, for 3 months versus 12 months of DAPT, was 2.9% versus 2.5%, p for noninferiority = 0.007; p for superiority = 0.46.

- *All-cause death*: 1.4% versus 1.2%, $p = 0.61$
- *MI*: 0.8% versus 1.2%; $p = 0.28$

Secondary outcomes for 3 months versus 12 months of DAPT:

- *ST*: 0.2% versus 0.1%; $p = 0.65$
- *BARC 2–5*: 2.0% versus 3.4%; $p = 0.02$

Limitation

About 10% of patients in the short-duration DAPT arm were still on aspirin at 12 months.[10]

META-ANALYSIS SUPPORTING SHORT-TERM DUAL ANTIPLATELET THERAPY

Recently published meta-analysis of short-term DAPT RCTs showed that short-term DAPT after current-generation DES implantation is associated with lower major bleeding **(Fig. 1)**, but the incidence of ST **(Fig. 2)**, all-cause death, MI, and stroke remains the same as compared with prolonged DAPT.[11]

TRIAL ON CHRONIC MAINTENANCE THERAPY WITH P2Y12 INHIBITOR

HOST-EXAM Trial

This study evaluated the safety and efficacy of clopidogrel versus aspirin monotherapy among patients who had completed the required duration DAPT post-PCI. This trial included patients with NSTEMI: 19.4%, STEMI: 17.2%, CCS: 25.6%, and USA: 36%. Also included patients with high ischemic risk, three-vessel disease: 18%, left main PCI: 5%, and chronic total occlusion PCI: 9%. The duration of follow-up was 24 months. The primary endpoint of all-cause mortality, MI, stroke, and readmission due to ACS major bleeding, for clopidogrel versus aspirin, was 5.7% versus 7.7% (hazard ratio 0.73; 95% confidence interval 0.59–0.90; $p = 0.003$).[12]

CONCLUSION

In patients who underwent PCI with current-generation DES implantation, 1–3 months of DAPT followed by monotherapy with a P2Y12 inhibitor reduce major bleeding at long-term follow-up without increasing ST. Secondary analyses of all these trials showed no differences in all-cause death, MI, and stroke between short and standard use of DAPT.[11] However, each trial had a certain limitation that has been described.

Despite the results of various trials and meta-analyses, some caution is required when considering the generalizability of the results to the STEMI setting. The heterogeneity in major bleeding found across trials represents a further evaluation for an individual patient baseline characteristic analysis of available evidence to define key clinical, angiographic, and procedural

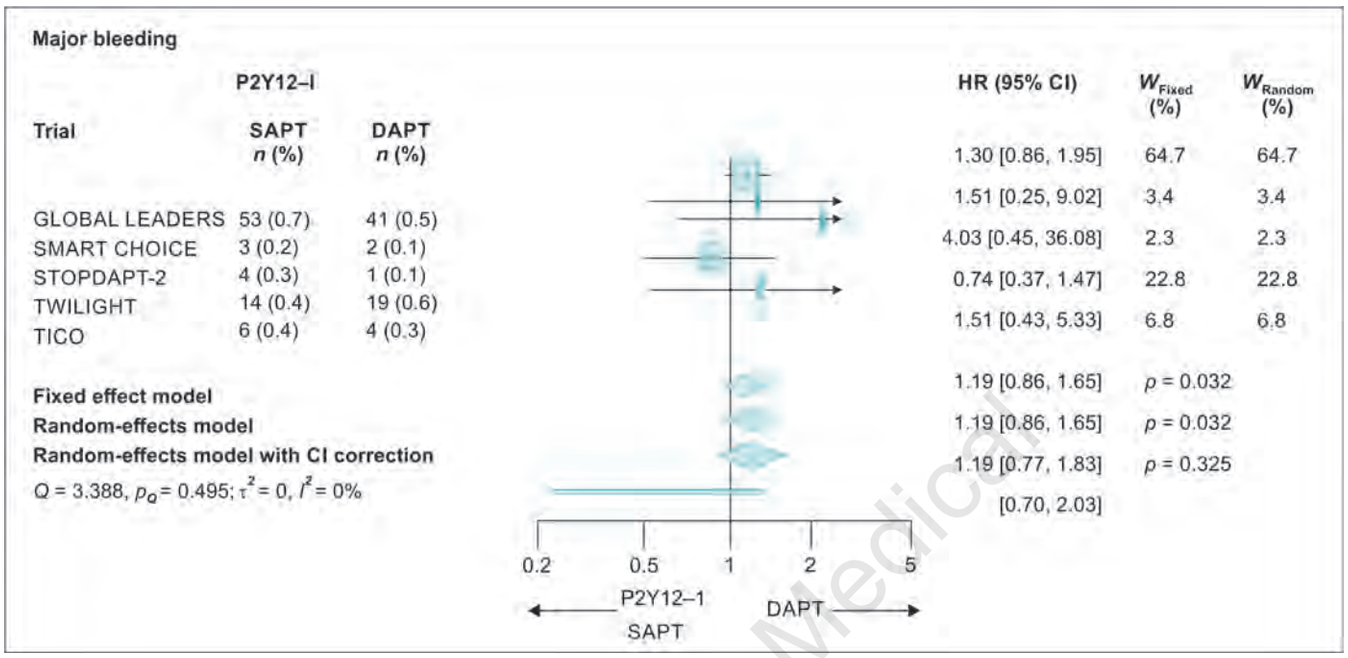

FIG. 1: Major bleeding. Events were adjudicated as per the Bleeding Academic Research Consortium (BARC) type 3 or 5 definitions.[11]
(CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; P2Y12-I SAPT: P2Y12 inhibitor single antiplatelet therapy; W_{Fixed}: relative weight according to fixed-effect model; W_{Random}: relative weight according to random-effect model)

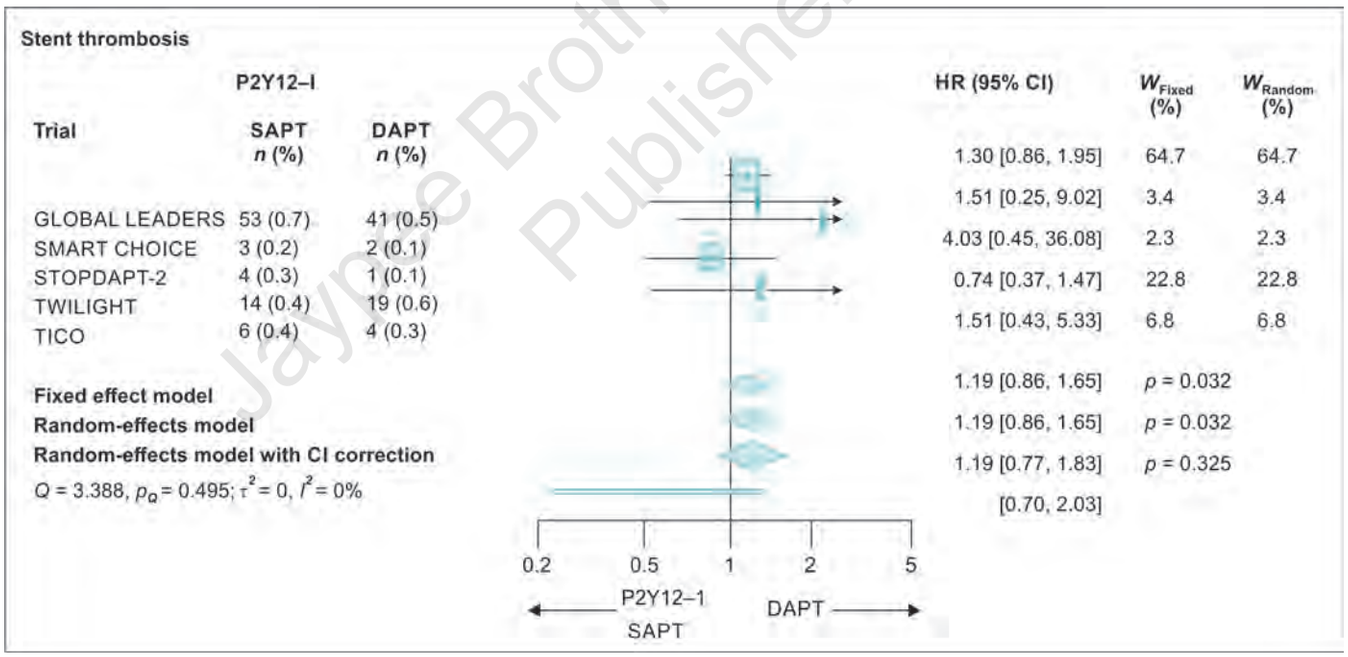

FIG. 2: Stent thrombosis.[11]
(CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; P2Y12-I SAPT: P2Y12 inhibitor single antiplatelet therapy; W_{Fixed}: relative weight according to fixed-effect model; W_{Random}: relative weight according to random-effect model)

characteristics and to adopt these results in daily practice. Based on all these trials, recent 2021 American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) guideline for coronary artery revascularization recommended that in selected patients undergoing PCI, shorter-duration DAPT (1–3 months) is reasonable, with subsequent transition to P2Y12 inhibitor monotherapy to reduce the risk of bleeding events (level of evidence 2a).[13] The results of HOST-EXAM trial also showed that clopidogrel monotherapy is superior

to aspirin monotherapy as chronic maintenance therapy among patients who had successfully completed the required duration of DAPT therapy post-DES PCI. But this study has limited generalizability because it included only South Korean patients. The is always a concern regarding the high interindividual variability of clopidogrel platelet inhibition and its use in the setting of a single antiplatelet therapy (SAPT).[12] Larger RCTs that include patients of different ethnicities with longer follow-up with clinical endpoint are needed to confirm these findings.

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CHAPTER 54

Approach to Antiplatelet Resistance

PK Asokan, Anjana AJ

ABSTRACT

Aspirin and clopidogrel resistance are emerging clinical entities with potentially severe consequences, such as recurrent myocardial infarction (MI), stroke, or death. The mechanism of resistance remains incompletely defined, but there are specific clinical, cellular, and genetic factors that influence therapeutic failure. Laboratory tests, which can identify resistance and correlate this with clinical outcome, are being studied to identify patients at risk of future thrombotic events. Numerous studies have shown that certain patients benefit from either shortened or extended treatment duration. Furthermore, trials evaluating novel antithrombotic strategies, such as P2Y12 inhibitor monotherapy, low-dose factor Xa inhibitors on top of antiplatelet therapy, and platelet function- or genotype-guided (de-)escalation of treatment, have shown promising results. The respective role of genotyping versus phenotyping assessment to guide P2Y12 inhibition has been a subject of debate.

INTRODUCTION

Among patients with percutaneous coronary intervention (PCI) on clopidogrel, the ABCD-GENE (age, body mass index, chronic kidney disease, diabetes, and genotyping) score was helpful in identifying those at higher risk. The ABCD-GENE score may potentially enhance the precision of tailored selection of P2Y12 inhibitors, which needs to be confirmed in prospective investigations.

Platelet activation and aggregation are central to the development of thrombotic complications during acute coronary syndromes (ACSs) and following PCIs. Adenosine diphosphate (ADP) and thromboxane A2 (TXA2) are major secondary agonists released by platelets following activation.[1] These secondary agonists play a key role in the amplification of platelet activation and aggregation and stable thrombus generation at the site of plaque rupture.

Simultaneous inhibition of the P2Y12 receptor by thienopyridines and TXA2 generation by aspirin is an effective antiplatelet treatment strategy to inhibit platelet function. Landmark clinical trials have demonstrated the central role of dual antiplatelet therapy in the treatment of ACS and in the prevention of complications during and after PCI.[2-4] In recent years, despite the well-documented clinical efficacy of clopidogrel and aspirin treatment, the phenomenon of antiplatelet resistance or nonresponsiveness has been repeatedly reported by various investigators and has been correlated in small studies with the occurrence of ischemic events.[5-8]

DEFINITION OF ANTIPLATELET RESISTANCE

Platelets are the key players in pathological thrombus formation, which lead to myocardial infarction (MI), ischemic stroke, and peripheral vascular disease. Despite its effectiveness and the proper intake of drugs, to some extent, aspirin or clopidogrel fails to produce pharmacological action, i.e., when it fails to inhibit platelet aggregation due to a reduction in platelet sensitivity and thus leads to recurrent adverse vascular events, and this phenomenon led in coining the term "resistance," which is now clinically referred to as "high on-treatment platelet reactivity (HTPR)": the treatment failure of antiplatelet therapy. The different approaches used in defining antiplatelet resistance are (1) laboratory resistance—an increase in the levels of TXA2 metabolites due to the inadequate inhibition of TXA2 and platelet aggregation despite antiplatelet therapy and (2) clinical resistance—when there is antiplatelet treatment failure, i.e., a failure to prevent antithrombotic event.

The term "resistance" as applied to antiplatelet medication implies an endogenous mechanism in certain individuals,

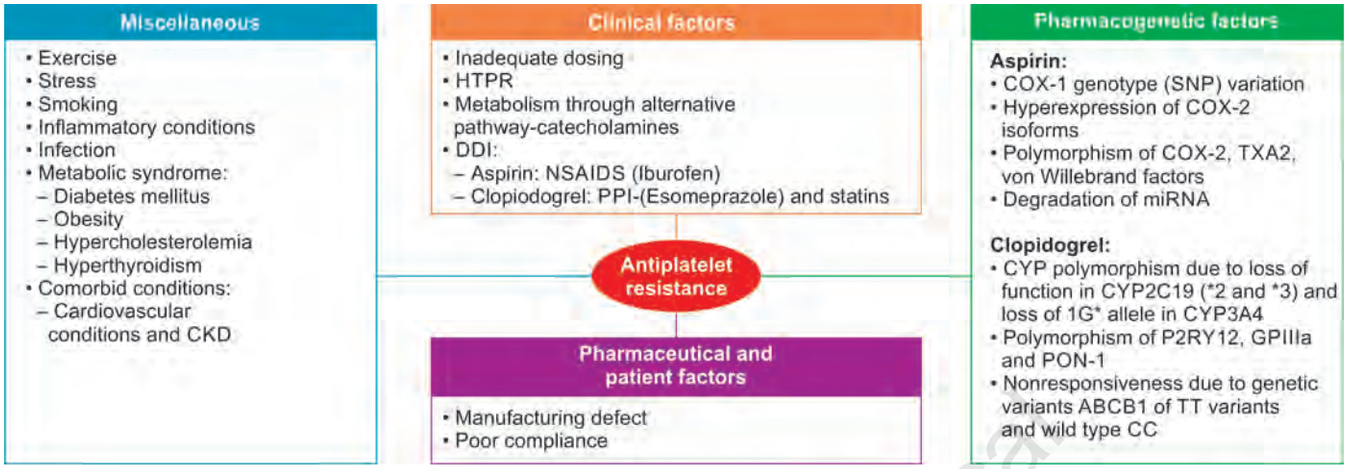

FIG. 1: Causes of antiplatelet resistance.

(CKD: chronic kidney disease; COX: cyclooxygenase; CYP: cytochrome P450; DDI: drug–drug interaction; HTPR: high on-treatment platelet reactivity; miRNA: microribonucleic acid; NSAIDS: nonsteroidal anti-inflammatory drugs; P2RY12: purinergic receptor P2Y12; PPI: proton-pump inhibitor; PON-1: paraoxonase 1; SNP: single nucleotide polymorphism; TXA2: thromboxane A2)

Source: Alhazzani A, Venkatachalapathy P, Padhilahouse S, Sellappan M, Munisamy M, Sekaran M, et al. Biomarkers for antiplatelet therapies in acute ischemic stroke: A clinical review. Front Neurol. 2021;12: 667234.

which prevents the drug from exerting its full antithrombotic effects. The proposed mechanisms underlying antiplatelet resistance to aspirin and clopidogrel are summarized in **Figure 1**.[9]

ASPIRIN RESISTANCE

Aspirin is the cornerstone of antithrombotic therapy. The antiplatelet effect of aspirin is primarily due to the irreversible acetylation of a serine residue (Ser530) in cyclooxygenase (COX)-1 in platelets that prevents the binding of arachidonic acid to the catalytic site and blocks the production of the TXA2—one of the most powerful promoters of platelet aggregation.[10,11] Potential contributors to decreased aspirin efficacy include genetic variability of COX-1, COX-2, or TXA2; medication nonadherence, enteric-coated formulation, drug interactions, absorption limitations, stress, and infection. Platelet evaluation is not routinely performed unless treatment failure warrants laboratory testing to evaluate aspirin effects. Various laboratory tests can be considered for evaluation of aspirin response, without a clear consensus about the right choice of test or normal values for findings.[12] The overall prevalence of laboratory-defined aspirin resistance in cardiovascular disease (CVD) patients is 24.7% [95% confidence interval (CI) 21.4–28.4].[13]

The term "aspirin resistance" has been used to describe a number of different phenomena, including the inability of aspirin to (1) protect individuals from thrombotic complications, (2) cause a prolongation of the bleeding time (BT), (3) inhibit TXA2 biosynthesis, or (4) produce a predicted effect on one or more in vitro tests of platelet function.[14-16] It is estimated that inhibition by aspirin must be >95% in terms of platelet TXA2-forming capacity to be clinically efficient. Multiple factors contribute to lowered aspirin efficacy, with genetic determinants attributed to 30% of cases. Patients with C765G (rs20417) polymorphism of COX-2 were proven to have lowered risk of adverse cardiovascular events in aspirin users [odds ratio (OR) 0.78; 95% CI 0.70–0.87].[17,18]

CLOPIDOGREL RESISTANCE

Similarly, the term "clopidogrel resistance" has been used to denote the nonresponsiveness of ADP-induced platelet aggregation following standard clopidogrel therapy.[16] Clopidogrel is an inactive prodrug that requires oxidation by the hepatic cytochrome P450 3A4 (CYP3A4) to generate an active metabolite. The active metabolite of clopidogrel inhibits platelet activation through an irreversible blockage of the platelet ADP P2Y12 receptor. The P2Y12 receptor inhibits adenylyl cyclase and in turn decreases platelet cyclic adenosine monophosphate (cAMP) levels and cAMP-mediated phosphorylation of the vasodilator-stimulated phosphoprotein (VASP), critical for inhibition of glycoprotein (GP) IIb/IIIa receptor activation. Clopidogrel resistance as discussed, genetic polymorphisms in the cytochrome P450 2C19 (CYP2C19) enzyme, was found in 60% of people identified as Asian and 25% of people identified as white. The CYP2C19 polymorphisms are the most common and well-studied polymorphisms associated with clopidogrel response.[19]

Numerous loss-of-function (LOF) variants in CYP2C19 affect antiplatelet response to clopidogrel. Single nucleotide polymorphism (SNP) rs4244285 of CYP2C19*2,[20] and SNP rs12248560*[17] contribute to altered clopidogrel response.[17] The population frequency of an LOF allele is approximately 60% in East Asian countries and approximately 30% in the rest of the world.[21]

Significant prevalence of HTPR on clopidogrel treatment led to the introduction of more potent P2Y12 inhibitors: Prasugrel (a third-generation thienopyridine), ticagrelor, and cangrelor (cyclopentyltriazolopyrimidines).

There are a number of options for evaluating antiplatelet response; the P2Y12 receptor inhibition assay is commonly used.

If clopidogrel resistance is discovered, an alternate antiplatelet therapy such as ticagrelor or prasugrel can be pursued.

Ticagrelor is also a P2Y12 receptor antagonist, but unlike clopidogrel, it does not require metabolic activation through the hepatic enzyme CYP2C19 and is particularly useful for the population of CYP2C19-negative individuals who are nonresponders to clopidogrel.

Platelet activation and aggregation are processes mediated by various receptor signaling pathways. A single treatment strategy directed against a specific receptor cannot overcome all thrombotic complications, and treatment failure following a single antiplatelet agent is not synonymous with drug resistance. The best definition of resistance or nonresponsiveness to an antiplatelet agent is the failure of the antiplatelet agent to inhibit the target of its action. The identification of resistance would therefore use a laboratory technique that detects the residual activity of the target. In the case of clopidogrel resistance, there would be noteworthy evidence of residual post-treatment P2Y12 activity and in the case of aspirin there would be residual posttreatment COX-1 activity. Individual differences in the rate of platelet activation and reactivity markedly influence normal hemostasis and the pathological outcome of thrombosis.

As extrinsic mechanisms are the most identified reason for aspirin/clopidogrel resistance, the first step when evaluating a potentially aspirin/clopidogrel-resistant patient is to examine dosage, compliance, and possible drug interactions. The second step is to use platelet function tests (PFTs) to evaluate the inhibition of platelets because of antiplatelet therapy and several laboratory methods that have been proposed.

Laboratory Evaluation of Clopidogrel Responsiveness

According to both American and European groups of experts, there are three recommended PFT: The VerifyNow assay, the Multiplate analyzer, and the VASP assay for clinical guidance.[22,23] Interestingly, emerging concepts such as platelet redox assessment [intracellular concentration of reactive oxygen species, activity of antioxidant enzymes, reduced/oxidized glutathione ratio, level of lipid peroxidation, copper/zinc (Cu/Zn) ratio, and molecular oxygen consumption] might be potentially useful to establish the platelet-related etiological factors in different disorders and to evaluate the antiplatelet therapies.[24]

Many different methods to assess platelet function exist, beginning with the historic golden standard—light transmission aggregometry (LTA), which measures the difference between light transmission through platelet-rich plasma and that through platelet-poor plasma, assessment of platelet aggregation on fibrinogen coated microparticles (VerifyNow assay) or metal electrodes (Multiplate analyzer), measurement of the VASP protein phosphorylation (VASP assay), assessment of platelet aggregation in vitro in conditions similar to physiological blood flow [platelet function analyzer (PFA)-100, PFA-200, Innovance P2Y12, IMPACT-R], assessment of the clot strength (thromboelastography), and measurement of the thrombocytes number before and after the addition of an agonist (Plateletworks).[25-27] The routine use of PFT to detect HTPR and undertake action is not recommended by the European Society of Cardiology (ESC) guidelines. Nevertheless, HTPR should be considered if de-escalation is undertaken from potent P2Y12 inhibitors to clopidogrel.[28]

The nonstandardized use of these PFTs and the absence of a formal definition explain most of the disparity reported in the literature with regard to the prevalence of aspirin/clopidogrel resistance. Considering the wide variability of preanalytical and analytical aspects of various PFTs, comparing assay results to those of a gold standard such as LTA, seems to be irrelevant. Instead, all assays should be evaluated to figure out cutoff values that best predict clinical outcomes.

HIGH ON-TREATMENT PLATELET REACTIVITY

Studies have shown that up to 40% of patients exhibit HTPR under clopidogrel treatment. There are several potential causes of this phenomenon, including clinical variables such as ACS at admission, diabetes mellitus, renal failure, drug–drug interactions, nonadherence to therapy, and genetic polymorphism of genes coding cytochrome P450 enzymes (crucial in clopidogrel bioactivation) or glycoprotein P (responsible for clopidogrel absorption in intestines).[24,29-36]

Recently, an association between the circulating proprotein convertase subtilisin/kexin type 9 (PCSK9) levels, HTPR, and ischemic events in ACS patients undergoing PCI were described. There is a clear evidence showing that HTPR on clopidogrel is a significant risk factor for atherothrombotic events, including MI, stent thrombosis, cardiovascular death, and cerebrovascular events. There are some therapeutic options to overcome HTPR on clopidogrel. HTPR may also affect patients treated with newer, more potent antithrombotic agents such as prasugrel or ticagrelor, mainly within the first hours post loading dose in ACS patients undergoing PCI, when sufficient antiplatelet blockade is particularly desired.

The prevalence of HTPR in patients treated with ticagrelor was significantly lower as compared with those receiving prasugrel in a meta-analysis by Lemesle et al.[37] It was previously documented that age, gender, food, preloading with clopidogrel, or genetic polymorphisms do not affect ticagrelor metabolism or its antiplatelet effect. Patients treated with prasugrel and ticagrelor can display HTPR mainly in the acute phase of treatment, which can be in part related to opioid use.

LOW ON-TREATMENT PLATELET REACTIVITY

Due to the widespread use of potent P2Y12 inhibitors, the low on-treatment platelet reactivity (LTPR) phenotype is frequent. LTPR is a well-documented risk factor for bleeding complications. Platelet function–guided dose adjustment of potent P2Y12 inhibitors may be a potential solution in patients who are presenting with a bleeding event.[28]

THERAPEUTIC WINDOW STRATEGY

Based on the growing body of evidence showing an association between HTPR and ischemic events, and LTPR with bleeding events, the therapeutic window hypothesis was developed. It suggests that patients with platelet reactivity values within the middle range achieve the best net clinical benefit. The therapeutic window strategy to guide antiplatelet therapy might be an attractive strategy to improve patients' net clinical benefit in terms of precision medicine. According to the European group of experts, the cutoff values for HTPR are as follows: the VerifyNow assay >208 platelet reactivity unit (PRU), the Multiplate analyzer >46 units (U), and the VASP assay >50% platelet reactivity index (PRI). The cutoff values for LTPR are as follows: the VerifyNow assay.[38]

STUDIES INVESTIGATING DE-ESCALATION OF ANTIPLATELET TREATMENT

The randomized trial TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes) assessed guided de-escalation of antiplatelet treatment in patients with MI treated with PCI in 2,610 patients. Despite early de-escalation, there was no increase in the primary endpoint of ischemic events in the de-escalation group [32 patients (3%)] versus the control group [42 patients (3%); p noninferiority = 0.0115], with similar frequency of Bleeding Academic Research Consortium (BARC) 2 or higher bleeding events in the de-escalation group versus control group [64 (5%) vs. 79 (6%); hazard ratio (HR) 0.82; 95% CI 0.59–1.13; $p = 0.23$].[39]

In the TOPIC (Timing of Platelet Inhibition after Acute Coronary Syndrome) randomized study, 645 patients, 1 month after ACS, were randomly assigned to either continuation of dual antiplatelet therapy composed of aspirin and potent antiplatelet agent or de-escalation to aspirin and clopidogrel. All patients underwent platelet reactivity assessment with the use of the VASP assay at the time of randomization. The primary endpoint combining cardiovascular death, urgent revascularization, stroke, and bleeding as defined as BARC ≥2 occurred in 85 (26.3%) patients in the unchanged drug group versus 40 (13.4%) patients in the de-escalation group [HR 95% CI 0.48 (0.34–0.68; $p < 0.01$)], with significant reduction in the occurrence of BARC ≥ 2 bleeding [48 (14.9%) vs. 13 (4%); HR 95% CI 0.30 (0.18–0.50); $p < 0.01$].[41]

In the recently published ELECTRA (platelet inhibition with standard versus lower maintenance dose of ticagrelor early after myocardial infarction), the antiplatelet efficacy of two ticagrelor maintenance dose (MD) regimens (reduced dose of 60 mg twice daily vs. standard dose of 90 mg twice daily) in stable patients at 30 days after acute MI were compared.[40] These results suggest that lowering ticagrelor MD 1 month after acute MI (AMI) confers an adequate antiplatelet effect that is comparable to the standard dose.

The SCOPE (Switching from Clopidogrel to New Oral Antiplatelet Agents During Percutaneous Coronary Intervention) registry investigated the incidence of P2Y12 inhibitor switching in 1,363 patients undergoing PCI. The P2Y12 inhibitor switch occurred in 10.5% and was not platelet function based. De-escalation of antiplatelet treatment from more potent drugs to clopidogrel was an independent predictor of net adverse clinical event (NACE) defined as a combination of an adverse cardiovascular event and any bleeding event.[42]

CURRENT PLACE OF PLATELET FUNCTION TESTING IN EVERYDAY CLINICAL PRACTICE

The ischemic risk in ACS patients undergoing PCI is relatively high in clopidogrel-treated patients due to its heterogenous and unpredictable antiplatelet effect.[38] With the common use of more potent antiplatelet agents, increased ischemic risk occurs mainly within the first months after ACS, whereas bleeding events are proportional to the duration and intensity of antiplatelet treatment. The choice of P2Y12 inhibitors offers a chance for individualization of the therapy based on the patient.[43,44] In the era of personalized medicine, according to the latest guidelines on myocardial revascularization, PFT-guided P2Y12 inhibitor de-escalation (e.g., switch from a newer more potent drug to clopidogrel after an acute phase) may be considered in ACS patients, particularly those unsuitable for 12-month potent antithrombotic therapy due to the increased bleeding risk (class of recommendation IIb, level of evidence B).[28] In ACS patients undergoing cardiac surgery, PFT is recommended to guide antiplatelet treatment interruption (class of recommendation IIb, level of evidence B) because the preoperative use of P2Y12 inhibitors plus aspirin is associated with an increased risk of bleeding and mortality.[28]

PREDICTION RULE FOR NONRESPONSE TO CLOPIDOGREL: AGE, BODY MASS INDEX, CHRONIC KIDNEY DISEASE, DIABETES, AND GENOTYPING SCORE

Response to clopidogrel differs widely among patients, notably because of CYP2C19 genetic polymorphisms. Genotype information led to stronger platelet inhibition treatment in the vast majority of LOF allele carriers and to similar clinical outcomes to those in patients carrying the wild-type genotype or gain-of-function allele [Genotyping Infarct Patients to Adjust and Normalize Thienopyridine Treatment (GIANT)].[45]

A risk score ABCD-GENE was developed incorporating five independent predictors of high platelet reactivity (HPR): four clinical [age >75 years, body mass index >30 kg/m^2, chronic kidney disease (glomerular filtration rate <60 mL/min) and diabetes mellitus] and one genetic (CYP2C19 LOF alleles). The C-statistics for the score as an integer variable were 0.71 (95% CI 0.68–0.75) and 0.64 (95% CI 0.60–0.67) in the pharmacodynamic derivation and validation cohorts, respectively. A cutoff score ≥10 was associated with the best sensitivity and specificity to find HPR status.[46] In TAILOR-PCI (Tailored Antiplatelet Initiation to Lesson Outcomes due to Deceased Clopidogrel Response after Percutaneous Coronary Intervention), genotype-guided selection of P2Y12 inhibitors after PCI did not significantly reduce the risk of ischemic events at 12 months. The aim of this study was to investigate the value of the ABCD-GENE score for tailoring P2Y12 inhibitor selection after PCI. Among 3,883 patients discharged on clopidogrel in

the genotype-guided and conventional therapy groups, 15.8 and 84.2% had high (≥10 points) or low (<10 points) ABCD-GENE scores, respectively. At 12 months, both the primary (5.2% vs. 2.6%, $p < 0.001$) and the secondary outcomes (7.7% vs. 4.6%, $p = 0.001$) were significantly increased in patients with high ABCD-GENE score.[47] The ABCD-GENE score has similar limitations to the PRECISE-DAPT or DAPT score; it is important to highlight its utility. The utility of this score is to argue against de-escalation in the presence of a high score. ABCD-GENE score is the utility of a risk score integrating CYP2C19 LOF genotypes with clinical risk factors influencing clopidogrel response that would allow the identification with more precision of subjects at risk for HPR and adverse clinical outcomes.

CONCLUSION

High on-treatment platelet reactivity is a significant and modifiable risk factor for cardiac ischemic events, and it is often present in clopidogrel-treated patients. HTPR can be detected by a variety of platelet reactivity testing. The routine use of PFT to detect HTPR and undertake action is not recommended by the ESC guidelines. Nevertheless, HTPR should be considered if de-escalation is undertaken from potent P2Y12 inhibitors to clopidogrel.

According to the recent guidelines, PFT use is narrowed to certain clinical scenarios, such as P2Y12 inhibitor de-escalation and guidance of antiplatelet treatment interruption in ACS patients undergoing cardiac surgery. The main goal of the precision-based therapy concept is to supply the right drug in the right dose to fit the needs of an individual patient from the very beginning. The physician's choice would then be based on clinical, genetic, cellular, and environmental variables. The gathered clinical information (e.g., based on the PREDICT score), results of PFT and genetic status (CYP2C19 carrier) could be used to personalize antiplatelet therapy in patients with high-thrombotic or bleeding risk.

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CHAPTER 55

Coronary Atherosclerosis and Endothelial Dysfunction

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ABSTRACT

Progress in the management of conventional coronary risk factors has diminished the burden of atherosclerotic cardiovascular disease (ASCVD), but it still remains the leading cause of mortality worldwide. The reason seems to be underlying factors that are yet unknown or not treated to the effective extent. Endothelial dysfunction has been seen to play a leading role in the development and progression of atherosclerosis and long and extensive research has continued from long back in understanding and managing the endothelial health. Thus, in this chapter, we have tried to look into the timeline of the development of the present understanding of endothelial dysfunction, to outline the pathophysiology, clinical implications, assessment, and management of endothelial dysfunction and resultant progression of atherosclerosis. We have also tried to focus on the recent updates and future directions of coronary atherosclerosis and endothelial dysfunction, namely gene therapy and role of microribonucleic acid (miRNA) among others. Further extensive research is needed to fully understand and treat this entity and thus prevent and effectively manage atherosclerosis and resultant reduction of cardiovascular adverse events.

INTRODUCTION

Endothelial function maintains the vascular homeostasis and its derangement leads to atherosclerotic cardiovascular disease (ASCVD).[1] Initially, endothelial dysfunction of epicardial coronary vessels was associated with local atherosclerotic lesion development and progression.[2,3] Subsequently, it has been noticed that even coronary microvascular endothelial dysfunction (CMED) raises the risk of myocardial infarction, revascularization, and even cardiac mortality.[4-8] Prevalence of CMED is not negligible in patients with nonobstructive coronary artery disease (CAD).[9] Godo et al. have demonstrated that independent of conventional coronary risk factors, CMED is associated with vulnerable plaque characteristics in nonobstructive CAD.[10] In this review, we try to share the recent updates on coronary atherosclerosis and endothelial dysfunction.

TIMELINE

Coronary atherosclerosis has been demonstrated even in Egyptian mummies.[11] Years of research have shown that arterial changes challenge the mechanical approaches such as coronary artery bypass grafting (CABG) and percutaneous interventions (PCI), which alleviate the myocardial ischemia due to CAD.[12] Thus, understanding the vascular biology is imperative to limit the atherosclerotic process. In the mid-nineteenth century, Rudolph Virchow postulated the inflammatory basis of atherosclerosis.[13] The importance of smooth muscle cells (SMC), accumulation of "cholesterin" and cell death finds importance in his examination of atherosclerotic arteries. Karl van Rokitansky proposed the thrombotic accumulation in the arterial wall as the cause of atherosclerosis.[14] Nikolay Anitschkow observed that feeding a cholesterol-rich diet to rabbits can lead to atherosclerosis-like lesions.[15] Adolf Windaus isolated cholesterol from human atherosclerotic lesions.[16] Michael Brown and Joseph Goldstein demonstrated the pathophysiologic basis of low-density lipoprotein (LDL)-receptor pathway in familial hyperlipidemia.[17] Thus came the discovery of statins from Akira Endo that markedly reduced the atherosclerotic and lipid burden in human body.[18] The in vitro culturing of arterial wall cells, SMC, and endothelium gave us more insights.[14] Russell Ross conceptualized the SMC proliferation and extracellular matrix (ECM) generation as key factors. The role of endothelial-leukocyte adhesion molecules (E-LAMs) was highlighted by Michael Gimbrone. Thus, the inflammatory theory of Virchow has grown stronger with time

and research.[13] This inflammatory mechanism has led to the study of proinflammatory cytokine interleukin-1β, which has a substantial role in human atherosclerosis. On the other hand, thrombus formation as a healing process to disrupted atheromatous lesions leads to progression of disease as well. Thus, today's understanding of atherosclerosis has a major space for endothelial dysfunction and inflammation besides the thrombotic milieu. The important events of this timeline have been summed up in **Flowchart 1**.[14]

1850: Rudolph Virchow-inflammation and cell proliferation in atherosclerotic plaques
↓
1860: Carl von Rokitansky – role of resorbed thrombus in atherogenesis
↓
1910: Adolf Windaus – cholesterol in atheroma
↓
1913: Nikolay Anitschkow – cholesterol feeding in rabbits producing atheroma
↓
1973: Michael Brown and Joseph Goldstein – low-density lipoprotein receptor pathway
↓
1974: Smooth muscle cell proliferation
↓
1976: Akira Endo et al. – statins
↓
1986: Role of adaptive and innate immunity and vascular cells in atherosclerosis
↓
1987: Michael Gimbrone et al. – cytokine inducible endothelial-leukocyte adhesion molecule
↓
2003: PCSK9 regulation of low-density lipoprotein metabolism
↓
2014: Clonal hematopoiesis recognized as cardiovascular risk factor
↓
2015: PCSK9 inhibtor approved
↓
2016: GLP-1 receptor agonist can reduce atherosclerotic events
↓
2017: CANTOS trial
↓
2019: Single cell immune landscape of atherosclerotic plaques
↓
CRISPR gene editing of PCSK9

FLOWCHART 1: Timeline of discoveries in atherosclerosis.
(CANTOS: Canakinumab Anti-inflammatory Thrombosis Outcome Study; GLP-1: glucagon-like peptide-1; PCSK9: proprotein convertase subtilisin/kexin type 9)

PATHOPHYSIOLOGY

Endothelium is not simply an inert barrier between the blood and vascular wall. It is a single layer of cells responding to physical and chemical stimuli by a variety of mechanisms.

Vascular Tone

Endothelium produces multiple autocrine and paracrine vasoactive factors that have roles in regulating the vascular tone, thrombogenicity, SMC proliferation, inflammation, and cell adhesion.[19,20] The endothelium plays a direct role in meeting oxygen demand–supply and thereby maintaining organ perfusion.[21] Vascular tone is maintained by a balance between the vasoconstrictors and dilators **(Fig. 1)** and disruption of this balance leads to endothelial dysfunction.

Endothelium-derived Vasodilators

Nitric Oxide

Furchgott and Zawadski identified the first endothelium-derived vasodilator, which was found to be nitric oxide (NO). Endothelium-derived NO synthase (eNOS) generates NO from L-arginine. NO diffuses to adjacent SMC to activate guanylate cyclase, leading to cyclic guanosine monophosphate (cGMP)-mediated dilation of vessels.[22] NO also inhibits inflammation and thrombosis by reducing the biological activity of a wide range of proteins by S-nitrosylation of cysteine residues.[23] Laminar shear stress is the major activator of eNOS.[24,25] Bradykinin, adenosine, vascular endothelial growth factor (VEGF), serotonin, and acetylcholine (Ach) can also stimulate eNOS.[26]

Prostacyclin

Arachidonic acid is broken down by cyclooxygenase to produce prostacyclin, which activates the adenosine triphosphate (ATP)-sensitive potassium channels, inwardly rectifying potassium channels, large conductance calcium-activated potassium

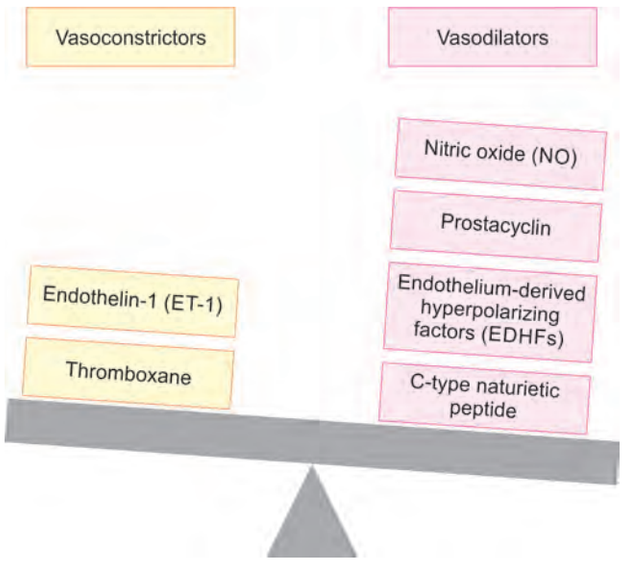


FIG. 1: Factors influencing vascular tone.

channels, and/or voltage-activated potassium channels to induce vasodilation.[27,28]

Endothelium-derived Hyperpolarizing Factors

Endothelium-derived hyperpolarizing factor (EDHF)-mediated vasodilation may be the result of potassium channel opening in the plasmalemma and expression of myoendothelial gap junctions.[29-31]

C-type Natriuretic Peptide

C-type natriuretic peptide (CNP) acts as a vasodilator in both veins and arteries and is produced predominantly by vascular endothelial cells. It affects leukocyte and platelet reactivity apart from having an antiproliferative effect on cultured SMCs.[32-35]

Endothelium-derived Vasoconstrictors

Endothelin-1

Endothelin-1 (ET-1) is a potent vasoconstrictor and plays a role in renal salt regulation. It is released by endothelium and maintains the vessel tone, hence, the fall in blood pressure (BP) on administration of systemic endothelin antagonists.[36]

Thromboxane A2

Thromboxane A2 (TxA2) is formed from arachidonic acid by action of cyclooxygenase and released from activated platelets as a potent vasoconstrictor.[37,38]

Endothelial Dysfunction

The production of reactive oxygen species (ROS) and mitochondrial superoxide dismutase (SOD) from mitochondria during oxidative phosphorylation is balanced physiologically. Cardiovascular (CV) risk factors such as obesity, hyperlipidemia, diabetes, smoking, hypertension, and aging lead to a change in endothelial functioning, and expression of cytokines, chemokines, and adhesion molecules, likely due to a switch in signaling that further leads to inflammatory process and interaction with platelets and leukocytes.[39-41]

Mechanisms of Endothelial Dysfunction

Apolipoprotein B (ApoB) enters the subendothelium and plays a pivotal role in activating the inflammation. Nicotinamide adenine dinucleotide phosphate (NADP) oxidases are increased in the vessel wall in the presence of CV risk factors stated above, leading to ROS production. Combination of ROS and NO leads to peroxynitrate generation, which is the initial step of chronic endothelial dysregulation.[42-46] Thus, a vicious cycle is set up with peroxynitrate oxidizing tetrahydrobiopterin (BH4) cofactor of eNOS, leading to uncoupling of eNOS. In this uncoupled or monomeric form, eNOS produces superoxide which combines with NO along with other ROS to produce more peroxynitrate. Peroxynitrate itself mediates LDL oxidation and has a direct effect on zinc binding which further enhances eNOS uncoupling. All these factors lead to proatherogenic milieu.[45,47,48] ROS upregulates the expression of intercellular adhesion molecule-1 (iCAM-1), vascular adhesion molecule-1 (VAM-1), and macrophage chemoattractant peptide-1 (mCAP-1).[45] Association of reduced eNOS activity and increased C-reactive protein (CRP) has been demonstrated.[49,50] Increased NADP oxidase and xanthine oxidase (XO) activity is noted in the arteries of patients with CAD.[44,51]

Endothelial Shear Stress and Coronary Atherosclerosis

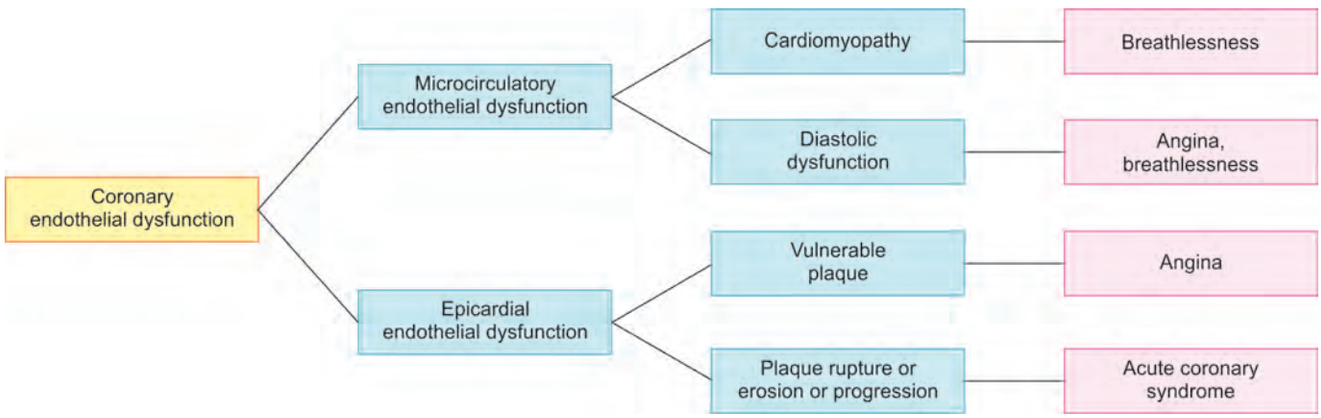
The complex anatomy and physiology of the coronary arteries determines the pattern of tangential force exerted by the blood column upon the endothelium which is known as endothelial shear stress (ESS).[52,53] Laminar flow protects the endothelium whereas oscillatory, nonlaminar flow having a low ESS pattern is proatherogenic.[54] Low ESS results in increased collagenase and elastase activity, resulting in fibrous cap thinning and remodeling of vascular wall, respectively, which leads to plaque enlargement and resultant luminal obstruction.[55,56] This is mediated by a reduction in NO bioavailability.[57]

CLINICAL IMPLICATIONS OF ENDOTHELIAL DYSFUNCTION

Clinical features have been outlined in **Flowchart 2**.[58]

Assessment of Endothelial Function

Assessment of NO-mediated vasodilation is the most widely used clinical endpoint in the tests assessing endothelial function. Invasive and noninvasive methods have been proposed.[58]



FLOWCHART 2: Clinical implications of endothelial dysfunction.

Invasive Methods

The reference standard for evaluating coronary endothelial function has been intra-arterial administration of Ach with measurement of vascular diameter change and blood flow change. The vasodilator leads to NO release resulting in measurable vasodilation and increased blood flow in normal coronaries. In endothelial dysfunction, Ach leads to direct muscarinic receptor activation on vascular SMC leading to vasoconstriction and lack of accentuation of blood flow.[58,59] This was first demonstrated by Ludmer et al. and Schächinger et al., who demonstrated the long-term prognostic value of coronary endothelial dysfunction on ASCVD.[60,61] Other ways are pacing-induced tachycardia, adenosine infusion, or exercise. The invasive methods have been outlined in **Table 1**.[36]

Noninvasive Methods

Two major noninvasive methods for assessment of endothelial dysfunction are forearm flow-mediated vasodilatation (FMD), which correlates with the invasive method and reactive hyperemia-peripheral arterial tonometry (RH-PAT).[62,63] FMD represents conduit artery endothelial function, while RH-PAT indicates microvasculature endothelial function. RH-PAT is easier and operator independent.[58] The noninvasive methods are outlined in **Table 1**.

Biomarkers of Endothelial Dysfunction

Plasma levels of NO breakdown products, such as asymmetric dimethyl arginine (ADMA), CRP, CD40, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), plasminogen activator inhibitor-1 (PAI-1), P-selectin, and fibrinogen, can be used as indirect measures but are costly, effected by multiple factors, such as diet and inflammation; moreover, they are limited by interassay variability.[36] Few cellular components such as endothelial progenitor cells and circulating endothelial particles have been researched as markers of endothelial dysfunction.[36]

Association of Endothelial Dysfunction and Cardiovascular Outcomes

Traditional risk factors for ASCVD are associated with endothelial dysfunction.[64-66] Four large studies by Anderson et al., Yeboah et al., and Rubinshtein et al. showed that FMD and RH-PAT were significantly associated or predictor of CV events.[67-70]

Percutaneous Intervention and Endothelial Dysfunction

Balloon angioplasty leads to coronary endothelial dysfunction and it is worse after PCI with stent implantation than plain old balloon angioplasty (POBA) or directional atherectomy alone.[71,72] Compared to bare-metal stents (BMS), zotarolimus-eluting stents (ZES) and biolimus-eluting stents (BES) do not show coronary vasoconstriction in response to Ach, exercise, or pacing while reactive vasoconstriction is noted with sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) in chronic phase (after 6 months).[73]

Treatment Approach

Moderate-intensity aerobic activity, weight loss, smoking cessation, use of angiotensin-converting enzyme (ACE) inhibitors, statins, and β-blockers have been recommended by the clinical guidelines supported by clinical evidence.[74]

TABLE 1: Methods for assessment of endothelial dysfunction.

Method	Stimulus	Procedure
Invasive	Intracoronary acetylcholine	Quantitative coronary angiography
	Exercise	Quantitative coronary angiography
	Pacing-induced tachycardia	Quantitative coronary angiography
	Intracoronary adenosine	Coronary flow reserve (CFR) by Doppler flow wire
	Intracoronary adenosine, substance P	Coronary blood flow by pressure wire–derived thermal dilution
	Intrabrachial infusion of acetylcholine and nitroprusside	Forearm blood flow by gauge strain plethysmography
Noninvasive	Isometric hand grip	Cardiac magnetic resonance imaging (MRI)—cross-sectional area of coronaries, coronary flow velocity
	Cold pressor	Positron emission tomography (PET)—myocardial blood flow and myocardial flow reserve
	Flow-mediated vasodilation (FMD)	Proximally placed occlusion cuff—after 5 minutes of forearm occlusion-rapid deflation—brachial artery diameter change
	Reactive hyperemia-peripheral arterial tonometry (RH-PAT)	Proximally placed occlusion cuff—after 5 minutes of forearm occlusion-rapid deflation—augmentation of the fingertip pulse amplitude
	Low flow-mediated vasoconstriction	Distally placed occlusion cuff—brachial artery diameter change
	Acetylcholine by microdialysis or noninvasively as iontophoresis, postocclusive hyperemia or local thermal hyperemia	Laser Doppler-based methods—skin microvascular blood flow
	Brachial artery occlusion	Photoplethysmography—variations in blood volume in the finger

Physical Activity

A meta-analysis in subjects with increased CV risk and another in type 2 diabetes mellitus subjects reported improved endothelial function with physical activity.[75,76] Another study showed improved RH-PAT with exercise training in obese patients and demonstrated correlation between improvement of insulin resistance and improved endothelial function.[77]

Weight Loss

Both medical and surgical weight loss (gastric bypass surgery) have been suggested to reverse endothelial dysfunction.[78-80]

Smoking Cessation

Celermajer et al. reported the dose-related reversible endothelial dysfunction with cigarette smoking way back in 1993, which was also reported later in subjects with passive smoking.[81,82] A study on 1,504 smokers showed the independent association of smoking with endothelial dysfunction at baseline and improvement of the function after 1 year among those who quit smoking.[83]

Angiotensin-converting Enzyme Inhibitors

Peripheral endothelial function improvement with ACE inhibitors has been reported in a meta-analysis of randomized controlled trials (RCTs) which also reported its superiority to calcium channel blockers and β-blockers in this respect; the effect is due to reduction of angiotensin II and increasing bradykinin levels.[84-86]

Statins

Anti-inflammatory and antioxidant properties of statins play a role in improving endothelial dysfunction apart from their lipid-lowering property.[87] A meta-analysis of 46 RCTs has shown the benefit of statins on coronary and peripheral arterial endothelial dysfunction.[88]

β-blockers

Nebivolol and carvedilol improve endothelial function by β-receptor activation and antioxidant properties, respectively.[89,90] An RCT demonstrated the superiority of carvedilol to metoprolol in improving endothelial function in hypertensive and diabetic patients.[91] First- and second-generation β-blockers have no significant role in endothelial dysfunction.[58]

Continuous Positive Airway Pressure Therapy

Endothelial dysfunction worsens with the severity of obstructive sleep apnea syndrome (OSAS).[92] Treatment of OSAS, including continuous positive airway pressure (C-PAP) therapy, has been reported to be beneficial in endothelial dysfunction and to improve CV outcomes.[93-96]

RECENT ADVANCES

Multifaceted and advanced research in basic science and clinical front is underway to understand and manage endothelial dysfunction and atherosclerosis better.

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

Evolocumab has been shown to improve coronary artery cross-sectional area and coronary blood flow and thus overall coronary artery health in people living with human immunodeficiency virus (HIV) and those with dyslipidemia. These results could be extrapolated to a wider population based on further studies.[97]

Glucagon-like Peptide-1 Analogs

Liraglutide has proven to be cardio- and vasoprotective at the cellular level. Glucagon-like peptide-1 receptor (GLP-1R) activation reduces vessel inflammation by acting on the endothelial GLP-1R and thereby reduces CV events and complications.[98]

Sodium-glucose Cotransporter-2 Inhibitors

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have already demonstrated significant improvement in heart failure outcomes. Recent research has linked inhibition of SGLT-2 with improved macro- and microvascular endothelial functions by regulation of endothelial physiology.[99]

Canakinumab

Canakinumab targets the IL-1β innate immunity pathway and can significantly reduce CV events. The role of IL-1β in atherosclerosis has gathered importance with the publication of CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) trial.[100]

Role of Ribonucleic Acid in Endothelial Dysfunction

Microribonucleic acids (miRNAs) and long noncoding RNAs (lncRNAs) are bioactive cargos that maintain cell-to-cell communication and are delivered by extracellular vesicles (EVs). These RNAs are associated with initiation and development of atherosclerosis. Various miRNAs and lncRNAs have been implicated as biomarkers and treatment targets for ASCVD, but more data are needed for converting research to practice.[101]

Gene Therapy

Regression of atherosclerosis was noted in rabbits with in vivo gene transfer of eNOS.[102] Adenovirus-mediated eNOS delivery in stents reduced neointimal proliferation and enhanced endothelial regeneration.[103] But more research is needed before gene-directed treatment can be considered beneficial for ASCVD and endothelial dysfunction.

FUTURE DIRECTIONS

To ensure reproducible outcomes, standardized protocols and guidelines are needed for atherosclerosis and endothelial dysfunction. The role of combined noninvasive endothelial function assessment and biomarker use needs further study. The so-called microvascular angina and correction of endothelial dysfunction as its potential therapy need further investigation.

CONCLUSION

Traditional risk factors along with untraditional or unknown factors have significant predictive value for future CV events and endothelial dysfunction forms an integral component of the ongoing vascular disease. It has a role in all phases of atherosclerosis and therein lies the importance of endothelial function–guided therapies. It is a continuously evolving field of research and we look forward to its usefulness in guiding therapy and changing outcomes in ASCVD.

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CHAPTER 56

Myocardial Bridge

Shibba Takkar Chhabra, Sushil Kumar, Riya Aggarwal

ABSTRACT

Myocardial bridging, i.e., tunneling of an epicardial coronary artery beneath a muscle bridge causing systolic compression of tunneled part, usually involves the mid left anterior descending (LAD). Traditionally believed to asymptomatic, now recent studies are suggesting increasing prevalence and symptoms attributed to bridging. The usual pathophysiological mechanisms are inclusive of fluid mechanics and variant wall sheer stress leading to increased atherosclerotic burden in pre- and postbridged segments. Besides coronary angiogram, diastolic fractional flow reserve (FFR) and single-photon emission computed tomography (SPECT) play an important role not only in diagnosis but also in detecting functional significance of bridging.

The medical therapy comprises intensive antiplatelet and β-blockers regimen. Percutaneous coronary intervention (PCI) with bare metal stents (BMS) and drug-eluting stent (DES) in symptomatic patients are fraught with complications such as stent fracture, stent thrombosis, and stent restenosis. Coronary artery bypass grafting (CABG) offers better results in deeper and longer segmented myocardial bridge vis-à-vis myotomy.

INTRODUCTION

Myocardial bridging refers to tunneling of an epicardial coronary artery under muscular bridge.[1] It causes systolic compression of tunneled part of coronary artery and is asymptomatic in large proportion of the cases. The middle segment of the left ascending artery is usually the most common to get affected by bridging.[2] However, any coronary artery can be involved.

Autopsies and coronary computed tomography angiography (CCTA) studies have revealed higher prevalence of myocardial bridging when compared with coronary angiography (CAG). Based on these studies prevalence of myocardial bridging ranges between 0.5 and 16%.[3]

Myocardial bridges have also been classified into superficial and deep depending on (1) range of depth 0.3–28 mm, (2) superficial fibers which lie over left anterior descending (LAD) and deep fibers which enclose LAD, and (3) fibers >5 mm in depth respond poorly to surgical myotomy **(Fig. 1)**.[4]

PATHOPHYSIOLOGY

The pathophysiological basis of development of symptoms in patient with myocardial bridge is attributed to increased potential for developing atherosclerosis. Several studies have suggested that the intramyocardial course of coronaries have a beneficial effect on the genesis of atherosclerosis at the location of myocardial bridge. However, concentric intimal thickening of the artery underneath the bridge and increased tendency for development of atherosclerotic plaques proximal to bridge along with augmented wall shear stress is believed to contribute in the development of atherosclerosis. Biomechanical forces can explain these changes. Fluid mechanics is thought to have a major role in atherosclerotic plaque formation because altered near-wall blood flow patterns play an important role in the spatial dissemination of atherosclerosis. Low and oscillatory wall shear stress (LWSS) leads to increased expression of vascular cell adhesion molecule-1 and release of reactive oxygen species which in turn causes a proatherogenic environment. Various studies have shown prebridge portion where WSS is low and has altered endothelial cells geometry whereas bridge segment where WSS is physiologic or high endothelial cells are normal.

Effect of Bridging on the Coronary Blood Flow

Myocardial bridging is present during the systole but it has also been shown that the compression of the bridged segment extending into diastole resulting in poor coronary artery

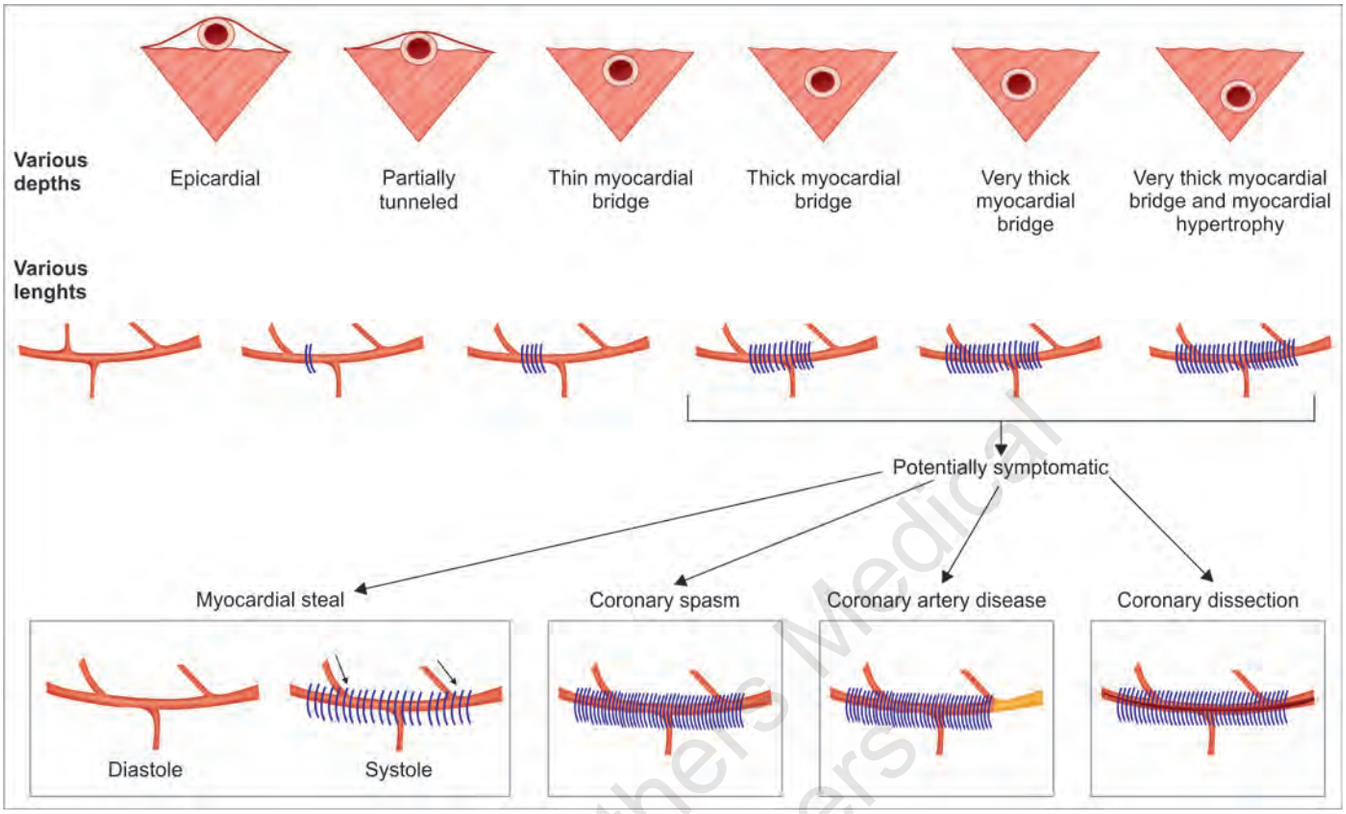

FIG. 1: Myocardial bridge in left anterior descending artery illustrating anatomic and pathophysiological properties.

perfusion. The more critical thesystolic narrowing is, the more are the chances that there will be compression prolonging into diastole. Therefore, ischemia can likely be provoked by factors such as increased heart rate and strenuous exercise which lead to increased systolic compression and reduced diastolic coronary artery filling time and blood flow.[5]

HISTOLOGY

Histology falls into two subcategories:

1. *Superficial variant*: It involves LAD in the groove between the ventricles, crossed by a muscle bundle at a right or an acute angle.
2. *Deep variant*: It involves LAD during its course toward the right ventricle and seeps in-between the intraventricular septum with an overlying longitudinal muscle bundle arising from the RV apex and crossing the tunneled segment horizontally, obliquely, or helically before ending in the intraventricular septum **(Fig. 2)**.

CLINICAL PRESENTATION

Myocardial bridges were initially considered as benign but several recent studies have suggested that people with myocardial bridges can present with symptoms such as chest pain on exertion and shortness of breath mimicking acute coronary syndrome. Some people can also present with cardiac arrhythmias.[6,7] Development of diastolic dysfunction,coronary vasospasm, and ventricular hypertrophy can also cause symptoms in previously asymptomatic patients.

DIAGNOSIS

Several different diagnostic modalities are being used to investigate myocardial bridges.

- *Coronary CT angiography*: CCTA may be utilized to give information regarding myocardial bridge anatomy and structure but additional modalities are needed for assessment of the functional relevance of CCTA findings.
- *Coronary angiography*: Coronary angiography is the most widely used diagnostic for providing structural and functional information of myocardial bridges. Classical findings like systolic compression of the epicardial artery can be seen on CAG.

Intracoronary nitroglycerin can be used to amplify this narrowing of bridged segments as it vasodilates the noninvolved segments.

Other newer techniques involve intravascular ultrasound (IVUS), intracoronary Doppler and intracoronary pressure devices.

Signs on CAG:

- "Milking effect" seen on CAG systolic narrowing of myocardialbridges is termed as the "milking effect".
- *Intravascular ultrasound*: IVUS can be used to detect bridging when angiography results are unclear. On IVUS

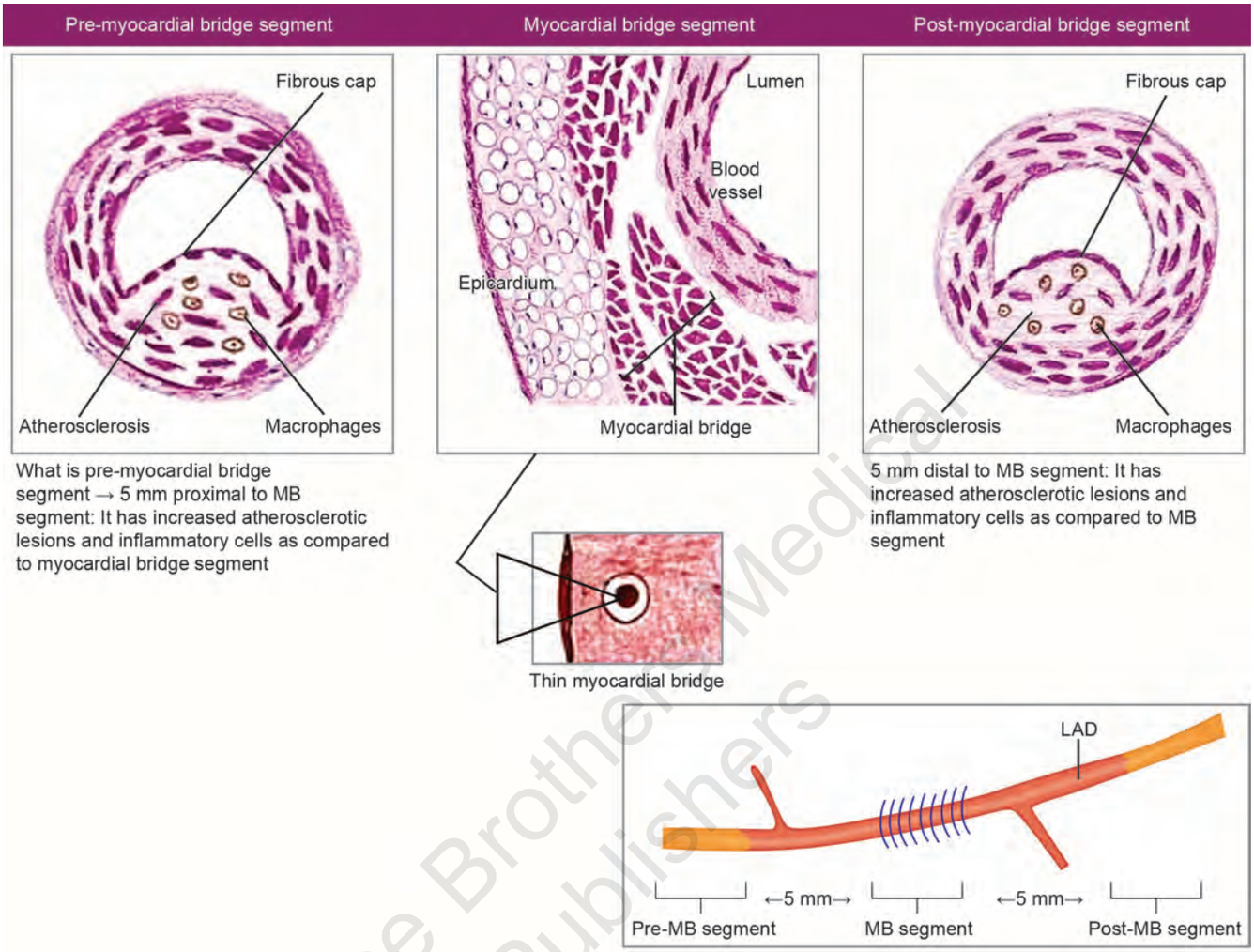

FIG. 2: Histologic appearance of pre-MB, MB, and post-MB coronary segment.
(LAD: left anterior descending; MB: myocardial bridge)

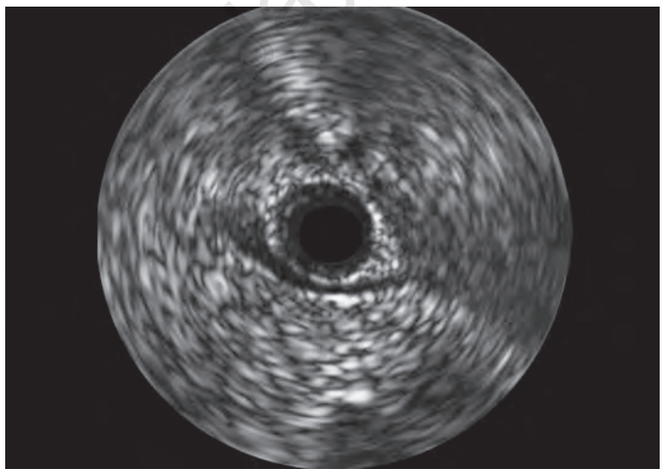

FIG. 3: Intravascular ultrasound "half-moon" sign (Echolucent area noted between the bridged coronary segment and the epicardial tissue).

there is systolic compression of the tunneled segment of the artery that persists into the diastole.

Half-moon sign: It is defined as the "echolucent area" which is noted between thebridged segment and the epicardial tissue **(Figs. 3 and 4)**.

- *Fractional flow reserve (FFR)*: To assess the pathophysiology of bridging, dobutamine provocation and diastolic FFR may be utilized. Diastolic FFR is preferred and since dobutamine provocation is better than use of adenosine for provocation, this proves the role of inotropic state in vessel compression.

Diastolic FFR, during inotropic stimulation with high-dose dobutamine, provides more definitive functional significance of myocardial bridging causing stress-induced myocardial ischemia than the conventional FFR **(Fig. 5)**.

Therefore, dobutamine provocation-guided diastolic FFR serves as a better index in detecting functional limitation due to myocardial bridging and can guide in decidingtherapeutic interventions.

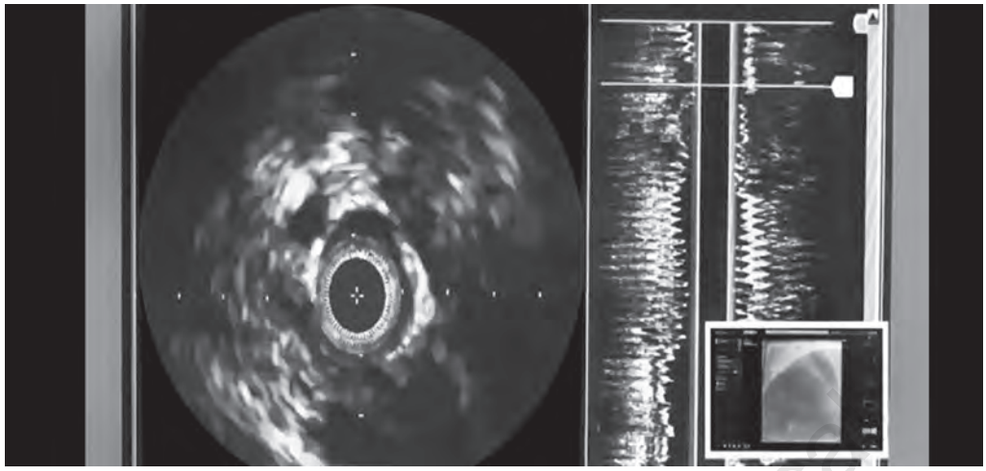

FIG. 4: Intravascular ultrasound (IVUS) picture showing echolucent area between myocardial bridge segment and epicardium.

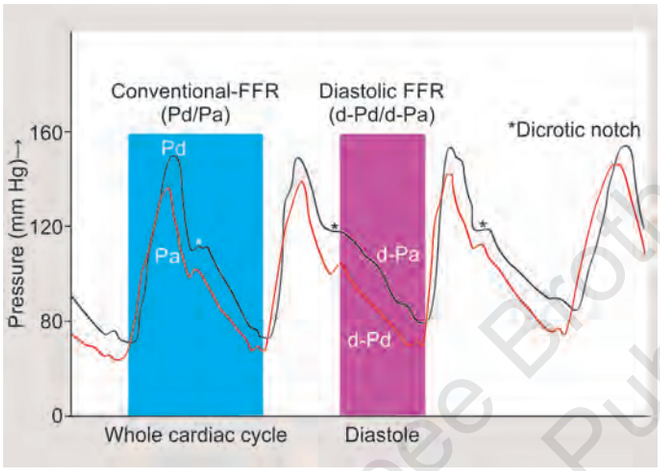

FIG. 5: Conventional and diastolic FFR measurements. The onset of diastole defined from the nadir of dicrotic notch on the aortic pressure signal (Pa), while the end of diastole was defined as the point of the lowest pressure just before the Pa upstroke.

[d-Pa indicates aortic blood pressure waveform during diastole; d-Pd: distal intracoronary pressure waveform during diastole; FFR: fractional flow reserve; Pa (black line): aortic blood pressure waveform during the whole cardiac cycle; and Pd (red line): distal intracoronary pressure waveform during the whole cardiac cycle]

Calculation of diastolic FFR:

Diastolic FFR = (Mean diastolic-Pd/mean diastolic-Pa)

Where, Pd: distal intracoronary pressure; Pa: aortic blood pressure

To be calculated after each dose of IV adenosine and dobutamine infusion. Diastolic-ΔP across the myocardial bridge was calculated as the maximal difference between diastolic-Pa and diastolic-Pd, while systolic-ΔP was calculated as the maximal difference between systolic-Pa and systolic-Pd.

INVESTIGATIONS FOR MYOCARDIAL BRIDGING

See **Table 1**.

Specific Considerations for Athletes

Cardiac symptoms in athletes should raise a concern for diagnosis of myocardial bridge. Autopsy and CCTA studies have suggested an increase in the prevalence of myocardial bridge. Development of hypertension and left ventricular hypertrophy may cause the compression of the bridged artery segment and precipitate coronary compression and reduce the coronary blood flood explaining why they become symptomatic later in life.[8,9]

Those who showcase the symptoms can be started on beta-blockers with regular stresstesting to check for the efficacy of treatment.

TREATMENT

Classification

The Schwarz classification may help in decision making about the management of patients having myocardial bridge as it has been associated with prognosis after opting various treatment modalities **(Table 2)**. Type A which has only clinicalsymptoms but no signs of ischemia do not need treatment usually, type B has signs of ischemia on noninvasive stress testing and requires medical management (β-blockers and calcium-channel blockers), and type C has signs of ischemia with altered intracoronary hemodynamics on invasive testing and may require revascularization if no response to medical therapy.

Medical Therapy

As patients with myocardial bridging are at increased risk of developing atherosclerosis, therefore, intensive-risk factor

TABLE 1: Investigations for myocardial bridging.

Modality	Finding	Benefit	Drawback
Coronary angiography	Milking effect	Availability, hallmark for diagnosis	Invasive, no quantitative assessment
IVUS	Half moon	Identify the remodeling and magnitude of compressibility	Invasive, infrequently used and quantitative assessment not required
Intracoronary Doppler and pressure measure	Finger-tip and hemodynamic limitation (FFR < 0.75–0.8)	Gives physiological assessment and endothelial function	More time-consuming, invasive modality, drug-related adverse effects, and FFR cutoff not established
SPECT	Identifies reversibility of myocardial perfusion defect (following stress induction) in absence of obstructive CAD)	Gives physiological assessment	Not easily available and exposure to radiation

(CAD: coronary artery disease; FFR: fractional flow reserve; IVUS: intravascular ultrasound; SPECT: single photon emission computed tomography)

TABLE 2: Schwarz classification for myocardial bridge and management.

Type	Findings	Symptomatic	Management
A	Supplemental on CAG	–	None
B	Stress testing	+	Medical
C	Invasive testing	±	Medical and/or revascularization

(CAG: coronary angiography)

modification and antiplatelet therapy are advocated in patients with myocardial bridging because they are at increased risk for developing atherosclerosis. Pharmacologic treatment with β-blockers is the usual first-line treatment. β-blockers decrease the peak heart rate, contractility, and compression of artery and increase the diastolic filling times, hence relieving the symptoms and ischemia. Other agents that can be used are calcium-channel blockers as they relieve the vasospasm. Nitrates are contraindicated because they dilate the adjacent nonbridged vessels and hence worsen the compression of the bridged vessel.

Percutaneous Coronary Intervention

Stent implantations in symptomatic patients with myocardial bridge can decrease intracoronary "systolic pressure" and vessel narrowing, normalize flow resulting in eradication of symptoms;[10] but because of apprehension regarding perforation during stent deployment,[11,12] "stent fracture",[13] in-stent "restenosis",[13-17] and "stent thrombosis".[18] Their use has not been considered widely.

Studies about percutaneous coronary intervention (PCI) in myocardial bridge have concluded two important things:

1. Symptomatic patients undergoing PCI have high incidence of early in-stent restenosis (ISR) which can be attributed to decreased lumen area of vessels secondary to myocardial bridge.
2. Drug-eluting stents (DES) have reduced rate of "target vessel revascularization" (TVR) comparison with "bare metal stent" (BMS) **(Table 3)**.

Rate of restenosis was higher in myocardial bridge patients undergoing PCI with bare metal stent for symptomatic isolated myocardial bridge patient. In a prospective study (n = 11), TVR was required in patients with early ISR.[14] Despite DES resulting in lower TVR rates compared to BMS, restenosis is more commonly noted with PCI in myocardial bridge patients versus PCI in obstructive CAD. Study (n = 70) analyzing PCI with DES in both myocardial bridge and LAD lesions and divided study population into two groups depending where the stent ended, i.e., before the bridge or within the bridged segment. It was found that TVR was more in patients with stent extending into the bridged segment compared to other group (29% vs. 3%).[17] Importantly, the cross-sectional area of stents extending into bridged segment was quite less when compared with those ending proximally (4.8 mm^2 vs. 5.8 mm^2). Recently, a study reported that 3 out of 15 patients with PCI with DES in bridge patients required revascularization at 6 months.[12]

Percutaneous coronary intervention with DES in symptomatic patients with myocardial bridge aims not only to treat plaque burden proximal to bridge but also negative remodeling and dynamic obstruction within the bridge. Bare metal stents give adequate scaffolding which achieves sufficient diastolic and systolic blood flow but continuous stress can result in-stent thrombosis, fracture, or restenosis.

In absence of randomized clinical trials (RCTs) comparing medical therapy alone with medical therapy and revascularization, medical therapy still continues to be better than PCI. Ischemia-directed therapy can be advocated for patients who are not responding to optimal pharmacological therapy and are poor candidates for surgery.

Surgical therapy ***(Table 4)***: Surgical options can be considered in patients who do not respondto medical therapy. Currently, there are two major surgical options available for myocardial bridging, coronary artery bypass grafting (CABG) and myotomy.

Coronary artery bypass grafting is preferred if the myocardial bridge is deep (>5 mm) and long (>25 mm) to avoid graft rejection, otherwise myotomy is the preferred approach.

In myotomy, muscle fibers which lie over the bridged segment are resected. This helpsto improve the blood flow in the vessel.[19]

TABLE 3: Percutaneous coronary intervention (PCI) studies in myocardial bridging.

Study	Number	Stent type	Follow-up period	Inference
Klues et al.,1997	MB-3	BM	7 weeks	No ISR or MACE
Haager et al., 2000	MB-11	BM	2 years	45% ISR
Kursaklioglu et al., 2004	MB-12 Non-MB-39	BM	6 months	ISR 67% vs. 28% in MB vs. Non-MB
Kunamneni et al., 2009	MB-12	BM-4 DE-8	1 year	ISR 75% BM vs DE
Tsujita et al., 2009	MB-70 (Only 34% stents covered MB)	BM-4 DE-66	1 year	MB group—33% MACE Non-MB group—11% MACE
Ernst et al., 2013	MB-15	DE	5 years	1 perforation during PCI 19% ISR

(BM: bare metal; DE: drug eluting; ISR: in-stent restenosis; MACE: major adverse cardiac event; MB: myocardial bridge)

TABLE 4: Studies about surgical therapy in myocardial bridge.

Study	Study type	Technique	Follow-up period	Immediate results	Late results
Rezayat et al., 2006	Retrospective	Myotomy	Mean 34.2 months	1 had angina, CAG showed LAD narrowing, underwent CABG with LIMA graft	2 had angina treated medically and had No MACE
Wan and Wu, 2005	Retrospective	4-PCI with DES, 8-CABG and 7-myotomy	Mean 23.5 months	No complications	No MACE in surgical group, 50% PCI patients had ISR
Wu and Xu, 2007	Retrospective	16-CABG 15-myotomy	Mean 31 months	1 patient had RV perforation	21 out of 31 underwent angiogram but no flow limiting
Huang et al., 2007	Retrospective	8-CABG, 3-myotomy	Mean 35.3 months	1 patient had RV perforation	2 had chest pain treated medically, no MACE
Sun et al., 2012	Retrospective	CABG 13 patients with LIMA graft	24–55 months	No complications	7 patients had chest pain underwent CCTA at 1 year but no stenoses and no MACE
Bockeria et al., 2013	Retrospective	CABG 19-SVG graft 20-LIMA graft	LIMA: 6–23 months and SVG: 2–25 months	2 patients required inotropes and other 2 patients had to undergo repeat sternotomy for bleeding	6 patients had chest pain, CAG showed LIMA occlusion in 12 and SVG in 3. No mortality

(CABG: coronary artery bypass graft; DES: drug-eluting stent; ISR: in-stent restenosis; LAD: left anterior descending; MACE: major adverse cardiac events; SVG: saphenous venous graft)

Because of lack of clear RCTs comparing myotomy and CABG, it is unclear which one is superior. Myotomy aims to rectify the pathology, so it could be offered for patients' refractory to medical treatment. On the contrary, CABG is preferred when the myocardial bridge is extensive (i.e., >20 mm) or deep (>5 mm) because of the increased risk with myotomy in such patients. CABG is also considered in patients with failed myotomy, i.e., where there is still diastolic compression after myotomy.

Importantly, due to lack of clear guidelines and RCTs analyzing medical therapy with surgical therapy there is no consensus about treatment options in patients with myocardial bridge. Based on the limited data it may be derived that surgical interventions whether myotomy or CABG are safe and efficacious in myocardial bridge patients with symptoms despite being on optimized medical therapy.

CONCLUSION

Myocardial bridge usually involves "left anterior descending artery" and can be either superficial or deep. The usual pathophysiological mechanisms are inclusive of fluid mechanics and variant wall sheer stress leading to increased atherosclerotic burden in the pre- and postmyocardial bridge segments. Besides coronary angiogram, identifying the milking effects, intravascular ultrasound, diastolic FFR with provocative agents like dobutamine and SPECT play an important role in diagnosis and functional significance of myocardial bridging.

Medical therapy inclusive of aggressive antiplatelet therapy and β-blockers is the usual line of management. While the percutaneous coronary intervention with drug-eluting stents has better results than bare metal stents. Both bare metal stents and drug-eluting stents are fraught with complications

as stent fracture, stent restenosis, and stent thrombosis, given extreme wall sheer stress in the myocardial bridge area. While coronary artery bypass surgery would offer better results in deeper and longer segmented myocardial bridges vis-à-vis myotomy. The data on comparison of percutaneous coronary intervention versus surgical intervention is limited.

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SECTION 5

ACUTE CORONARY SYNDROME

CHAPTER 57: **Approach to Large Thrombus Burden in ST-elevation Myocardial Infarction**
Vijay Bang, Ashish Deshpande, Rajkumar Ghumare

CHAPTER 58: **High-dose Statin in Acute Coronary Syndrome Percutaneous Coronary Intervention**
Subhasish Dey, Debabrata Roy

CHAPTER 59: **Myocardial Reperfusion Injury after Acute Myocardial Infarction Interventions: Bedside Evaluation**
Jagdish C Mohan, Madhu Shukla

CHAPTER 60: **Women and Spontaneous Coronary Artery Dissection: Is it Different?**
Lekha Adik Pathak, Ronak V Ruparelia

CHAPTER 61: **STEMI in Women: Is it Different?**
Jyotsna Maddury

CHAPTER 62: **An Approach to STEMI: Late Presenters**
Lijo Varghese, Balakumaran Jeyakumaran, Thomas Alexander

CHAPTER 63: **Culprit Vessel or Multivessel PCI during PAMI: Which One to Adopt?**
Dev B Pahlajani

CHAPTER 64: **Plaque Rupture versus Erosion: Common Consensus in ST-elevation Myocardial Infarction**
Dhiman Kahali, Ritwik Ghosal, Asit Das

CHAPTER 65: **Colchicine and Cardiology: What is New?**
Sudhir Chandra Sinha, T Suresh Babu, Siva Kumar Damireddy, G Venkateshwar Reddy

CHAPTER 66: **Mechanical Complications of Acute Myocardial Infarction: Diagnosis and Management**
P Rajendra Kumar Jain, Mohammed Sadiq Azam

CHAPTER 67: **Free Wall Rupture, Can We Mend the Broken Heart?**
Ashesh Halder, DP Sinha

CHAPTER 68: **ECG Localization of Culprit Artery in Acute Myocardial Infarction**
Dipak Sarma, MS Chaliha, Shekharjyoti Gogoi

CHAPTER 69: **Management of Atrial Fibrillation after Acute Coronary Syndrome Intervention**
Asok Kumar Kar, Ayan Kar

CHAPTER 70: **Coronary Ectasia and Aneurysm, Diagnosis and Management**
Dharmesh Solanki, Jaydeep Desai, Dharmil Patel, Jay Vithlani

CHAPTER 71: **Approach to Non-ST-elevation Myocardial Infarction**
Satish M Roplekar, Kedar S Roplekar, Kanchan S Roplekar

CHAPTER 72: **Acute Myocardial Infarction: Primary Angioplasty in Myocardial Infarction versus Lytics**
Y Vijayachandra Reddy, Antony Wilson, Shalini M

CHAPTER 73: **Left Ventricular Thrombus Following Acute Myocardial Infarction**
Saumitra Ray, Supratip Kundu

CHAPTER 74: **Postmyocardial Infarction Ventricular Septal Rupture: Challenges in Diagnosis and Management**
Smit Shrivastava

CHAPTER 75: **Left Ventricular Remodeling after Myocardial Infarction: The Current Approach and Novel Interventions**
Sandeep Bansal, Aseem Basha M

CHAPTER 57

Approach to Large Thrombus Burden in ST-elevation Myocardial Infarction

Vijay Bang, Ashish Deshpande, Rajkumar Ghumare

ABSTRACT

Large intracoronary thrombus has been reported in a significant number of patients presenting with ST-elevation myocardial infarction (STEMI). Primary percutaneous coronary intervention (PPCI) is currently the standard of care in patients with STEMI. Despite the availability of drugs such as dual antiplatelets, glycoprotein (GP) IIb/IIIa inhibitors, and effective anticoagulation regimens, large intracoronary thrombus remains one of the biggest challenges during PPCI. A large intracoronary thrombus may lead to complications such as distal embolization, no-/slow-reflow, or embolization into a nonculprit vessel which is associated with adverse cardiovascular outcomes. There is no ideal management strategy that can safely and effectively manage this subset of patients. We hereby discuss the currently available methods/strategies to deal with the large thrombus burden encountered during PPCI in the current manuscript.

INTRODUCTION

Large thrombus burden (LTB) is a common finding in the setting of percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS), especially during primary PCI (PPCI) in ST-elevation myocardial infarction (STEMI) patients. Angiographic evidence of thrombus is seen in 91.6% of patients who present with STEMI. Massive intracoronary thrombus has been reported in 16.4% of patients with ACS. Moreover, intracoronary thrombus is a strong predictor of PCI-related major adverse coronary events such as no-reflow, acute and late stent thrombosis, and increased rate of in-hospital complications as well as delayed mortality.[1-3] The management of LTB needs proper assessment, risk stratification, and planning of an appropriate treatment strategy to minimize further complications.

PATHOPHYSIOLOGY OF INTRACORONARY THROMBUS

In most cases, either disruption or erosion of an underlying vulnerable atherosclerotic plaque acts as a nidus for thrombus formation, followed by the resultant subsequent exposure of thrombogenic subendothelial matrix and plaque to circulating platelets.[4] The ruptured plaque initiates the coagulation cascade in either of the two following different but eventually synergistic pathways. In the first pathway, denuded endothelium exposes underlying collagen leading to direct binding of platelet glycoprotein (GP) VI to it. Simultaneously, platelet GP Ib-IX-V interacts with collagen-bound von Willebrand factor (vWf). This leads to platelet activation, adherence, and accumulation to the vessel wall leading to the formation of a "white" thrombus. On the contrary, the second pathway leads to the formation of "red" thrombus where tissue factor initiates a proteolytic cascade, which leads to the generation of thrombin which in turn converts fibrinogen to fibrin and also triggers activation and accumulation of platelets through the release of various agonists including adenosine, thromboxane A2, and serotonin. These agents activate other platelets, thereby further amplifying the thrombogenic process. Coronary thrombus consists of platelets, erythrocytes, inflammatory cells, and fibrin. The thrombin-generating process leads to a denser, more fibrin-rich thrombus, which becomes progressively more difficult to disrupt (both pharmacologically and mechanically) with time **(Fig. 1)**.[5,6]

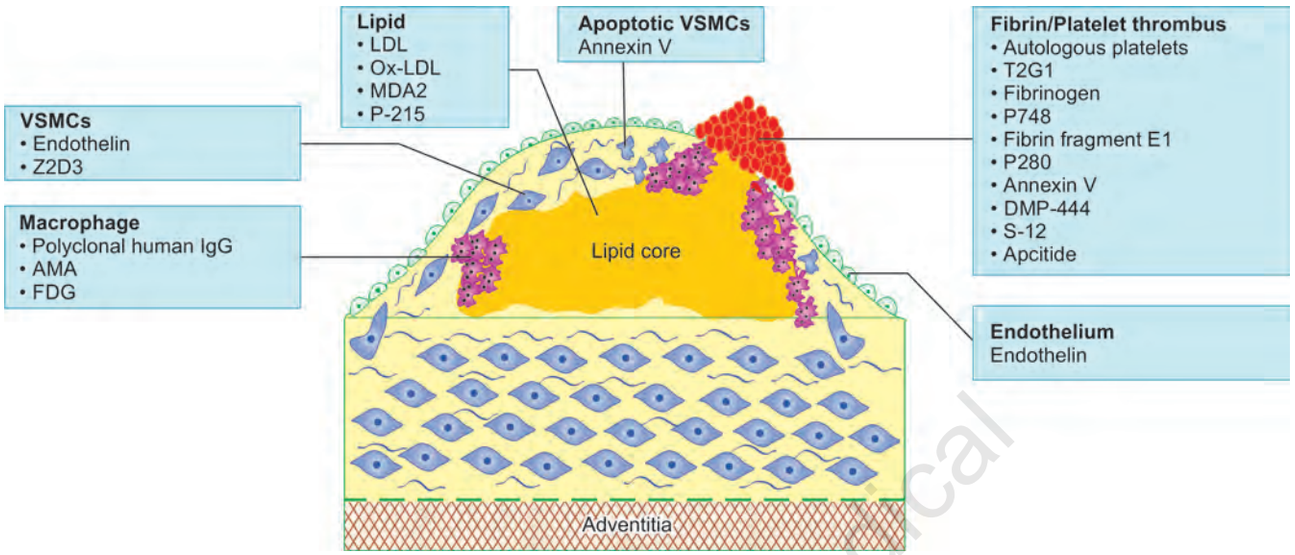


FIG. 1: Pathophysiology of intracoronary thrombus.
(AMA: anti-mitochondrial antibody; FDG: 18F-fluorodeoxyglucose; IgG: immunoglobulin G; LDL: low-density lipoprotein; Ox-LDL: oxidized low-density lipoprotein; VSMC: vascular smooth muscle cells)

GRADING OF THROMBUS BURDEN

Various tools are used to grade the severity of intracoronary thrombus. The commonly used thrombolysis in myocardial infarction (TIMI) scale is a simple numerical grading system ranging from 0 to 5.[6,7] Visual angiographic scales such as TIMI tend to underestimate the actual thrombus burden as compared to intravascular imaging techniques such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT). TIMI thrombus grade 0–3 are defined as small thrombus burden (STB), while TIMI thrombus grade 4–5 is defined as LTB **(Table 1)**.

Yip et al.[8] proposed six angiographic features that are suggestive of "LTB":

1. A cut-off pattern of occlusion.
2. Accumulated thrombus proximal to the occlusion.
3. A reference lumen diameter of the infarct-related artery (IRA) of >4.0 mm.
4. An incomplete obstruction with an angiographic thrombus with the greatest linear dimension more than three times the reference lumen diameter.
5. The presence of a floating thrombus proximal to the lesion.
6. A persistent dye stasis distal to the occlusion.

TABLE 1: Grading of thrombus.

Grade	Characteristics
0	No angiographic evidence of thrombus
1	Angiographic features suggestive of thrombus (decreased contrast density, haziness of contrast, irregular lesion contour, a smooth convex meniscus at the site of a total occlusion, suggestive but not firmly diagnostic of thrombus)
2	Definite thrombus present in multiple angiographic projections (marked irregular lesion contour with a significant filling defect—the greatest dimension of thrombus is <1/2 vessel diameter)
3	Definite thrombus appears in multiple angiographic views (greatest dimension from >1/2 to <2 vessel diameters)
4	Definite large size thrombus present (greatest dimension >2 vessel diameters)
5	Definite complete thrombotic occlusion of a vessel (a convex margin that stains with contrast, persisting for several cardiac cycles)

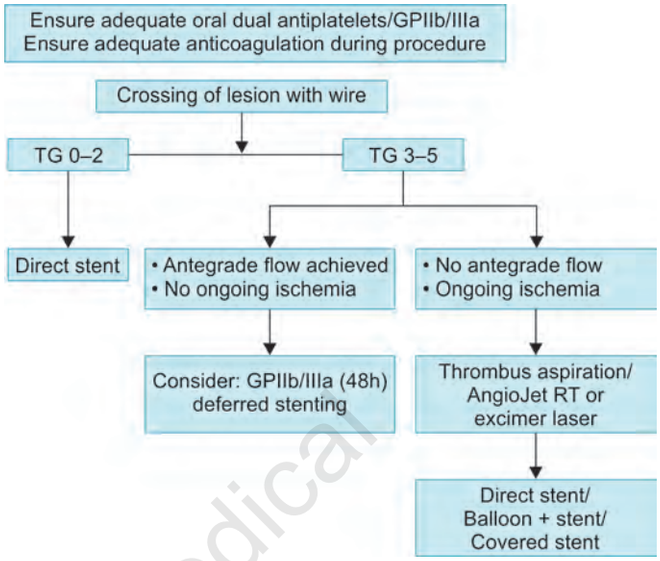
PROGNOSTIC IMPORTANCE OF INTRACORONARY THROMBUS

Intracoronary thrombus during PPCI for STEMI is an established adverse prognostic factor. It has been associated with a significant increase in in-hospital and long-term major adverse cardiac events (MACE).[9,10] An LTB and a high plaque burden are independent predictors of distal embolization,[7,11] and correlated with worse final TIMI flow/myocardial blush grades, as well as 2-year mortality and MACE rates.[7] The approximate rate of distal embolization is about 6–18% during PPCI, as per the data derived from multiple STEMI studies.[1,2,12,13] Moreover, patients who develop distal embolization showed reduced procedural success rates with increased slow-/no-reflow rates, lower left ventricular ejection fraction (LVEF), greater rise in cardiac enzymes, with overall higher in-hospital and late mortality.[2,10] The size of the coronary thrombus and its composition are the major predictors of distal embolization, as well as slow TIMI flow grade before PCI, long target lesion, and large vessel diameter.[1,2,14] Epicardial, as well as myocardial perfusion, can be impaired by either spontaneous or PCI-induced occlusion of an epicardial vessel or distal embolization of plaque and thrombus.

MANAGEMENT

Primary percutaneous coronary intervention is the standard of care for patients presenting with STEMI, especially in a PCI-enabled center;[15,16] proven to be more effective than intravenous thrombolytic therapy for achieving patent IRA, smaller infarct size, lesser incidence of recurrent myocardial infarction (MI), and death. For patients presenting in a center not equipped with a facility for PCI and if the expected delay in shifting to a PCI-enabled facility is >60 minutes, thrombolysis is reasonably a good alternative.[17] During PPCI, management of large intracoronary thrombus remains a big challenge. Various pharmacological and mechanical interventions have been proposed to tackle the thrombus burden during PCI **(Flowchart 1)**.

Figures 2A and B shows the OCT and IVUS images of a coronary thrombus.



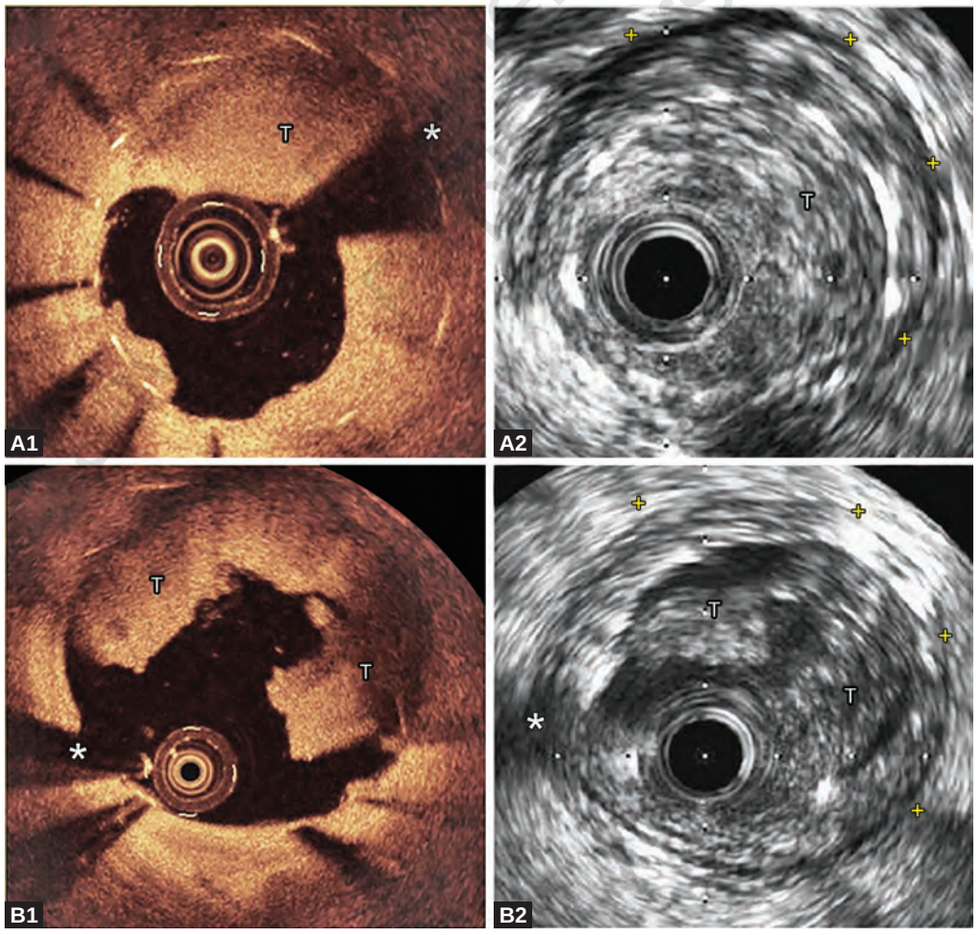
FLOWCHART 1: Proposed algorithm for management of large thrombus burden (LTB) during primary percutaneous coronary intervention (PPCI).[60]

(GP: glycoprotein; RT: rheolytic thrombectomy; TG: triglyceride)

PHARMACOLOGICAL INTERVENTIONS

Antiplatelet Drugs

Due to the self-propagating nature of thrombogenesis, early and effective pharmacological interventions to inhibit this process



FIGS. 2A AND B: Coronary thrombus [optical coherence tomography (OCT) and intravascular ultrasound (IVUS)]

are of utmost importance. At the point of first medical contact and STEMI diagnosis, patients should be administered a loading dose of aspirin (e.g., 300–350 mg) and a P2Y12 antagonist (e.g., clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg).[17-19] With increasing awareness among the family physicians and the overall population in general, community STEMI diagnosis may occur, and even earlier administration of these antiplatelet drugs is possible.[20] Usually, these drugs are administered in the emergency department, and patients are immediately transferred to the cardiac catheterization laboratory for PPCI. This may lead to suboptimal platelet inhibition during the PPCI procedure.[21] This is an important consideration, particularly after stenting in a patient who is naive to antiplatelet therapy and in cases where the thrombus burden is higher. In such a scenario, rapid onset intravenous P2Y12 antagonists such as cangrelor or GPIIb/IIIa inhibitors may prove useful as a bridge until the maximal antiplatelet effect of oral agents has been achieved.[22] Intravenous cangrelor may also be advantageous in STEMI patients that are intubated or unable to take oral antiplatelet agents.

GPIIb/IIIa Inhibitors

Glycoprotein inhibitors (GPIs) (abciximab, tirofiban, and eptifibatide) compete with vWF and fibrinogen for GPIIb/IIIa receptor binding and inhibit the final pathway of platelet aggregation. These agents achieve rapid and almost complete inhibition of platelet aggregation and are, therefore, more potent antiplatelet agents than P2Y12 inhibitors.[23] GPIs have been found to be effective in dissolving the angiographically documented thrombus and in restoring the TIMI flow.[24] Based on available data, recent guidelines[17] do not recommend routine use of upstream GPIs in STEMI patients undergoing PPCI and should be considered as a bailout therapy (Class IIa, C) only if there is evidence of an LTB, slow- or no-reflow or a thrombotic complication, or could be administered upstream only in high-risk patients undergoing transfer for PPCI (Class IIb, B). Some small studies have shown the benefits of intracoronary bolus administration of abciximab,[25] but these results have not been confirmed in large-scale clinical trials. A meta-analysis by Shimada et al.[26] demonstrated a favorable effect of an intracoronary bolus of GPI during PCI on TIMI flow as well as on target vessel revascularization and short-term mortality with no increase in overall bleeding risk. Presently, in the absence of concrete evidence, the role of an intracoronary bolus of GPIs still needs to be established by large, randomized trials.

Anticoagulation

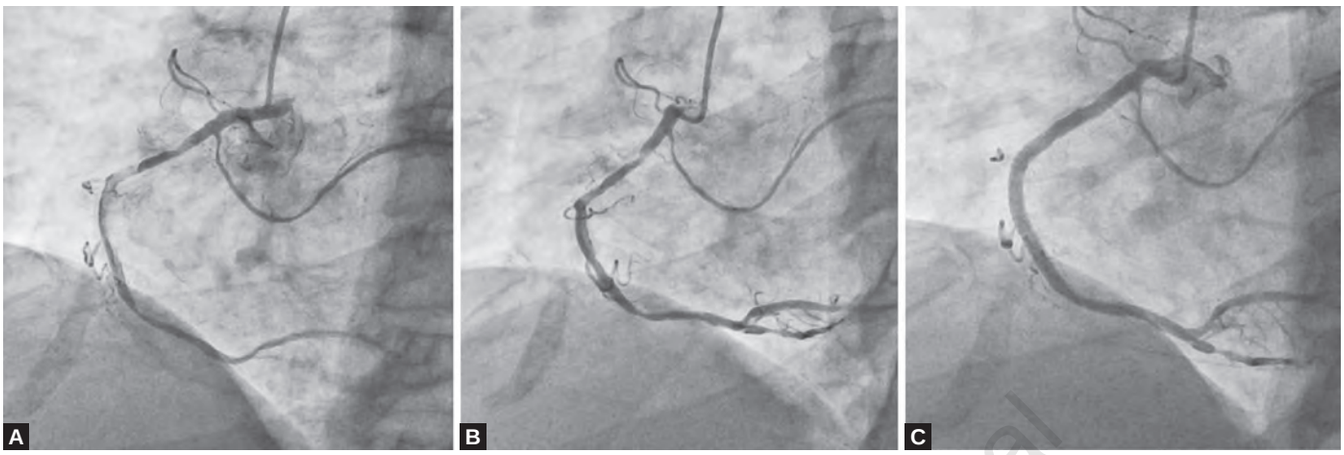
Periprocedural anticoagulation is generally achieved using unfractionated heparin at a dose of 100 U/kg and further dosage guided by activated coagulation time (ACT) titrated to maintain an ACT above 300 seconds. In some centers, low-molecular-weight heparin (e.g., enoxaparin), factor Xa inhibitor (e.g., fondaparinux), or a reversible direct thrombin inhibitor (bivalirudin)[27,28] are utilized for achieving anticoagulation. Each agent has individual merits, and therefore, the choice is largely determined by the individual operator and institutional practice. The incidence of vascular access complications such as bleeding has significantly come down as a result of a progressive shift from transfemoral to transradial intervention for primary percutaneous transluminal coronary angioplasty (PTCA).[29,30] Consequently, the superiority of agents such as bivalirudin that reduce bleeding to improve clinical outcomes is less relevant nowadays.[31] As a result, ACT-guided unfractionated heparin remains the most commonly used agent for procedural anticoagulation. There is a variability between different catheterization laboratories regarding the routine ACT assessment during PCI. ACT monitoring is especially recommended in cases with a high thrombus burden to ensure that patients have achieved therapeutic response to anticoagulation and may need additional heparin as required.

Ancillary Pharmacotherapy

Various other pharmacological therapies have been tried to manage distal embolization as a result of intracoronary thrombus. These agents include nicorandil, calcium channel blockers, GPIIb/IIIa inhibitors, vasodilators, adenosine, nitroglycerin, and nitroprusside. Calcium channel blockers may inhibit platelet aggregation and have a direct effect on calcium flux through the sarcolemmal membrane that could protect injured myocytes.[32,33] Adenosine affects intracellular calcium and inhibits neutrophil accumulation and superoxide generation.[34,35] Nicorandil, an adenosine triphosphate (ATP)-dependent potassium channel opener, can prevent reperfusion injury and protect cardiac myocytes.[36-38] GPIIB/IIIA inhibitors have also been used in cases of no-reflow and inhibit platelet aggregation.[39,40] Each of these agents has had variable success, and none has been proven to be superior to another. Additionally, it is unclear whether to administer these agents before or after the deployment of the stent. The clinical benefit of each of these agents on the epicardial flow and myocardial salvage continues to be limited.

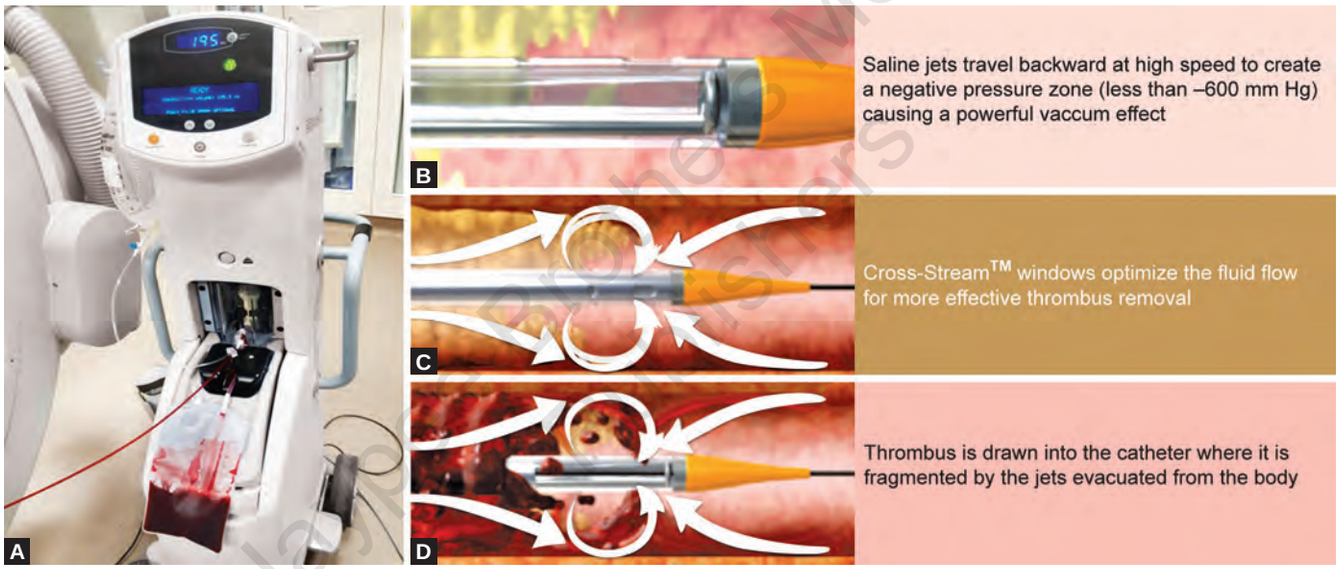
Intracoronary Thrombolysis

Intracoronary thrombolytic alone or as an adjuvant to aspiration thrombectomy could also be considered in selective cases. Multiple small studies have shown the benefits of intracoronary lysis. The dose used has been in the range of 1/3–1/2 of the systemic dose of the thrombolytic agent. Most of the studies have used tenecteplase. The various methods used for delivering the drug are as follows: (1) Using a microcatheter, (2) using a thrombus aspiration catheter, and (3) using a coronary balloon after manually splitting the membrane and creating multiple holes using a 24-gauge needle. The DISSOLUTION (Delivery of Thrombolytics before Thrombectomy in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention) trial[41] compared intracoronary thrombolytic delivered via microcatheter and aspiration thrombectomy with aspiration thrombectomy alone. Patients treated with upfront thrombolytic had a high rate of TIMI 3 flow and a higher proportion of patients with myocardial blush grade of 2/3. Patients also had a greater volume of aspirate compared to aspiration thrombectomy alone. In a meta-analysis of 12 randomized controlled trials, compared with aspiration thrombectomy, intracoronary-administered thrombolytics significantly improved myocardial perfusion and MACE in STEMI patients **(Figs. 3A to C)**.[42]



IWMI with LTB with TIMI 1 flow **Post-IC tenecteplase** **Post-deferred stenting**

FIGS. 3A TO C: Illustration of intracoronary (IC) thrombolysis.
(IWMI: inferior wall myocardial infarction; LTB: large thrombus burden; TIMI: thrombolysis in myocardial infarction)



FIGS. 4A TO D: Rheolytic thrombectomy device.

Thrombectomy

Although PPCI is the established reperfusion strategy for STEMI patients, it may sometimes have limited benefits. The reasons for this may be delays in time from symptom onset to reperfusion, reperfusion injury, and distal embolization leading to no-reflow. Since thrombus is the crux of the problem, it gave impetus to the development of thrombus removal with the concept that prevention of distal embolization might improve outcomes of PPCI. Thrombectomy catheters though bulky, have the advantage of better thrombus aspiration. Multiple systems exist that have different mechanisms of action, which include rheolytic and manual thrombectomy.

- *Rheolytic*: This system uses high-velocity jets of saline, which creates negative pressure through a Venturi effect. The AngioJet is an example of a rheolytic system.[43] Trials of this device have demonstrated increased mortality with no difference in infarct size or the resolution of ST segments.[44,45] Hence, the system has lost its popularity among interventional cardiologists **(Figs. 4A to D)**.
- *Manual or aspiration*: This thrombectomy is simple and easy to use. It has been studied in multiple large randomized controlled trials and emerged as the preferred method of thrombus removal. Early smaller randomized trials demonstrated the feasibility and potential benefit of thrombus aspiration on myocardial perfusion indices and ST-segment resolution. These studies observed smaller infarct size in patients undergoing thrombectomy before stenting compared with controls undergoing stenting without prior thrombectomy.[46,47] This initial positive evidence led to an increased usage of manual thrombectomy during PPCI. The postulated benefits were reduced distal embolization, prevention of reperfusion injury, improved myocardial perfusion with lesser need

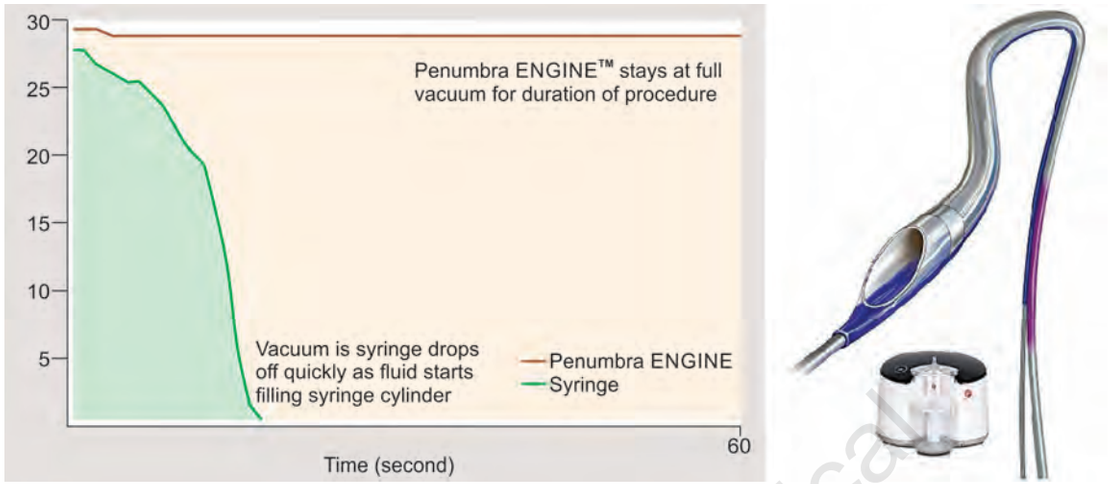


FIG. 5: CAT RX mechanical aspiration system powered by Penumbra ENGINE in comparison to manual syringe-based aspiration.

for predilatation, and improved myocardial blush. However, the large randomized TOTAL [Trial of Routine Aspiration Thrombectomy with Percutaneous Coronary Intervention (PCI) Versus PCI Alone in Patients with ST-Segment Elevation Myocardial Infarction (STEMI)] trial did not show any benefit of routine thrombectomy. On the contrary, there was a signal for harm with an increased risk of stroke in the thrombectomy arm of the study.[46-48] The reason for the increased incidence of strokes is probably secondary to aspiration back of thrombus and subsequent embolization to the brain. Even the real-world registries of manual thrombectomy have not consistently demonstrated benefits over standard PCI.[49] Current European Society of Cardiology guidelines do not recommend routine use of thrombus aspiration. However, patients who have very large thrombus may benefit, but this has not been robustly proven with randomized controlled evidence.[17] A recent meta-analysis[50] of the three randomized trials showed a trend toward less cardiovascular death with aspiration thrombectomy compared to PCI. Of concern, there was also an increased risk of stroke or transient ischemic attack despite a benefit in mortality. The pathophysiology is likely multifactorial and more complex, warranting further studies. Additionally, thrombectomy may be helpful in cases where thrombus develops during PCI and after post-stent deployment. Aspiration thrombectomy may aid restoration of flow and help guide subsequent PCI.

- *Mechanical thrombectomy*: Mechanical power aspiration with the Indigo® System CAT™ RX (Penumbra, Inc, Alameda, CA, USA) was introduced in 2018, and it continues to gain popularity as a solution for the high thrombus burden in the coronaries. The Indigo CAT RX Aspiration Catheters and Indigo Separator™ 4 (Penumbra, Inc, Alameda, CA, USA) are indicated for the removal of fresh soft emboli and thrombi from vessels in the coronary and also the peripheral vasculature **(Fig. 5)**.

It was first introduced in neurology when Penumbra revolutionized thrombus removal for acute ischemic stroke patients. Since its launch, the CAT RX has become an essential part of the treatment if thrombus is present in the coronaries.

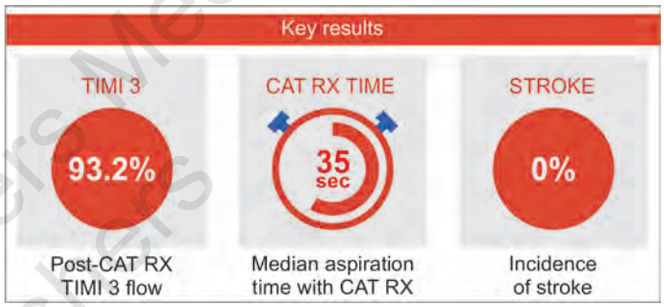


FIG. 6: Results from data presented at American College of Cardiology (ACC) 2019.
(TIMI: thrombolysis in myocardial infarction)

Indigo System CAT RX has been designed to address the limitations of traditional treatment options with manual aspiration. Manual aspiration suffers from diminished aspiration force as fluid fills in the syringe, which can potentially result in systemic embolization during catheter removal, as shown in the TOTAL trial published in 2015.[47] The goal of the Indigo System CAT RX mechanical aspiration system powered by the Penumbra ENGINE™ is to provide a sustained aspiration for the duration of the procedure with enhanced deliverability to navigate tortuous anatomy and track to the distal coronary vasculature.

The advantages of CAT RX with Penumbra ENGINE include the potential to remove the thrombus intact and reduce the potential of systemic embolization while at the same time increasing the visualization of the underlying stenosis and distal vessel. There is also a reduction in GPIIb/IIIa inhibitor usage (which may be associated with higher rates of bleeding) in a few cases. These benefits may suggest a reduction in the cost of care and improved patient outcomes.

The initial data presented at the American College of Cardiology (ACC) 2019 showed promising results for mechanical power aspiration for thrombus removal during PCI using CAT RX **(Fig. 6)**. This retrospective case series included 59 patients from four institutions around the United States. Pre-procedure TIMI 0 flow was seen in 76.3% of patients; TIMI

3 flow immediately post-CAT RX was demonstrated in 93.2% of patients. The median aspiration time with CAT RX was 35 seconds, with no incidence of stroke within 30 days of the procedure.[51]

Stenting Strategy

The various challenges faced at the time of PPCI due to the LTB are sizing of the stent, stent apposition, and final TIMI flow, which in turn leads to an increased risk of stent thrombosis. Although not recommended routinely by the current guidelines, aspiration thrombectomy may prove useful in the presence of LTB to properly visualize the vessel as well as to guide the appropriate stent size.[17] Drug-eluting stents are recommended for PPCI. Various strategies evaluated for stenting in cases of PPCI are as follows:

- *Direct stenting*: Direct implantation of the stent without predilatation has been found to reduce distal embolization, the incidence of slow-flow/no-reflow, procedural time, contrast load, and radiation exposure. The analysis from the large-scale HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial[52] suggests that direct stenting in eligible lesions in patients with STEMI may result in improved TIMI flow, ST-segment resolution, and survival, thereby confirming and extending the results of previous multiple smaller studies.
- *MGuard stent*: MGuard is a mesh-covered stent that is designed to prevent distal embolization of thrombus. It has been tested in small trials but has not been proven beneficial for routine use.[53,54]
- *Deferred stenting*: PPCI and stenting restore flow in the IRA and reduce reocclusion. Implanting a stent in a highly thrombotic milieu at the time of initial presentation with STEMI can be associated with the risk of distal embolization, slow flow, and increased periprocedural events. Furthermore, at the time of stent implantation, many times the antiplatelet drugs are yet to achieve their desired therapeutic effect. In such scenarios, the strategy of "deferred stenting" may prove to be beneficial. It is not recommended routinely for all STEMI patients.[55] However, in selected cases, with high thrombus burden that are hemodynamically stable, deferred stenting may offer a therapeutic option. The flow may need to be restored with a wire or predilatation with a balloon. If an LTB is observed, deferred stenting with an interim period of adjunctive antiplatelet/antithrombotic therapy may be useful to reduce the thrombus burden and minimize complications (such as no-reflow) at the time of stenting **(Fig. 7)**.[56,57]

Embolic Protection Device

Distal protection prevents the embolization of athero-thrombotic debris during PCI. The DEDICATION (Drug Elution and Distal Protection in ST-Elevation Myocardial Infarction) trial[58] randomly assigned 626 patients with STEMI to have PCI with or without distal protection. There was no difference in ST resolution, troponin/creatine kinase-MB (CK-MB) levels, and left ventricular wall motion index. Moreover, there was a higher tendency toward recurrent MI and target lesion

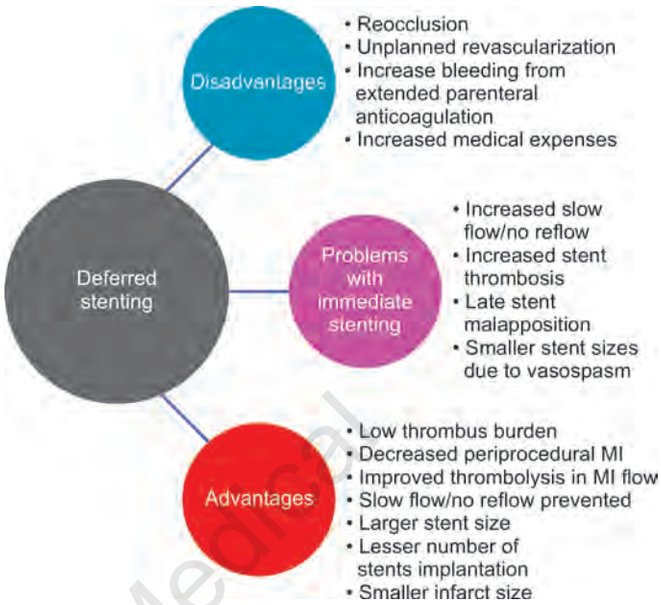


FIG. 7: Potential advantages and pitfalls of a deferred stenting strategy compared to immediate stenting in large thrombus burden (LTB).
(MI: myocardial infarction)

revascularization in patients with distal protection. Currently, routine use of distal protection has not been recommended for patients with STEMI undergoing PCI. PCI of saphenous vein graft (SVG) carries a significant risk of no-reflow, periprocedural MI, and adverse clinical events as the degenerated SVG lesions contain friable lipid-rich plaques. The SAFER (Saphenous vein graft Angioplasty Free of Emboli Randomized) trial[59] demonstrated that the use of distal protection devices decreased the risk of PCI in SVG. The 2011 PCI guidelines recommend the distal (embolic) protection devices as Class I for SVG PCI.

The extent of intracardiac thrombosis (ICT) observed during PPCI correlates strongly with both procedural success and clinical outcome. Due to the complex nature of intracoronary thrombogenesis, a multifaceted and systematic approach is required to achieve successful thrombus dissolution. This includes the arrest of the coagulation cascade (usually achieved using pharmacotherapy), flow restoration (usually through mechanical techniques), and occasionally the use of thrombus extraction tools.

CONCLUSION

Large thrombus burden in STEMI can further complicate a PPCI due to distal embolization, no-/slow-reflow or embolization into a nonculprit vessel. Each patient requires an individualized approach depending upon operator experience and expertise. Thrombus aspiration and intracoronary-targeted thrombolysis are effective and safe strategies for managing the high coronary thrombus burden in STEMI patients. Compared with aspiration, intracoronary-targeted thrombolysis is more beneficial in improving myocardial microcirculatory perfusion.

A strategy of deferred stent implantation may be useful in selected patients with high intracoronary thrombus burden

in the IRA. Interim medical treatment using adjunctive antiplatelet/antithrombotic therapy may not only help reduce the thrombus load, thereby minimizing procedural complications, but can also avoid unnecessary stenting in patients with nonocclusive stenosis. Large-scale randomized trials need to be performed on this group of patients to further document the safety and efficacy of this technique.

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CHAPTER 58

High-dose Statin in Acute Coronary Syndrome Percutaneous Coronary Intervention

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ABSTRACT

Treatment with statin reduces the risk of cardiovascular events in patients with acute coronary syndrome (ACS) through cholesterol lowering as well as pleiotropic effects. It also reduces periprocedural myocardial infarction (MI) and incidence of contrast nephropathy after percutaneous coronary intervention (PCI) for ACS, thereby improving the long-term outcome. An early loading with a high-dose statin, especially atorvastatin, prevents myocardial damage in patients with ACS undergoing early PCI. The benefit is extended even to patients already on chronic statin therapy. This evidence favors an "upstream administration" of high-dose statins in all patients of ACS undergoing PCI.

INTRODUCTION

Statins and antiplatelets form the backbone in treatment of acute coronary syndrome (ACS). Early initiation of intensive lipid lowering has several benefits which are well established. Along with cholesterol reduction, statin also has added pleotropic effects such as suppression of plaque vulnerability, reduction of necrotic core in high-risk plaques, reduction of lipid accumulation in plaque, anti-inflammatory actions, and improvement of endothelial function. However, certain controversies exist regarding high-intensity statin use in ACS, especially regarding—dosage, timing of initiation, duration of treatment, and adverse effects. All these issues will be addressed in this article.

HOW EARLY SHOULD WE START STATIN?

In the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study a clear benefit of high intensity statin in ACS was demonstrated.[1] This was a randomized control, double-blind study conducted on 3,086 adults with unstable angina and non-Q-wave myocardial infarction (MI) across 122 centers in Europe, North America, South Africa, and Australasia. ACS patients were randomized to receive 80 mg atorvastatin or placebo within 24–96 hours of hospitalization, which showed a reduced incidence of cardiovascular events (14.8 vs. 17.4%, relative risk: 0.84, $p = 0.048$) including death, MI cardiac arrest with resuscitation, and recurrent ischemic symptom within 16 weeks in patients with ACS. However, patients undergoing or planned for percutaneous coronary intervention (PCI) were excluded from the study.

The PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) trial documented that intensive statin therapy versus standard therapy improved clinical outcomes over 2 years in ACS patients.[2] Up to 4,162 ACS patients with total cholesterol level ≤240 mg/dL were randomized to intensive statin therapy (atorvastatin, 80 mg) or standard therapy (pravastatin, 40 mg) within 10 days of ACS. Up to 69.1% patient in pravastatin group and 68.7% in atorvastatin group underwent PCI for index event before randomization. Compared to pravastatin group, atorvastatin group showed a 16% reduction in major adverse cardiac events (MACEs) over 2 years which was proportional to level of low-density lipoprotein (LDL) reduction. There was a significant 14% reduction in the need for revascularization ($p = 0.04$), and 29% reduction in the risk of recurrent unstable angina ($p = 0.02$) in the high-intensity statin group. The benefits started appeared as early as 15 days and continued throughout the follow-up period of 2.5 years. Thus, it is recommended to start high-intensity statin therapy as early as possible during hospitalization and continue for long term.[3]

The ARMYDA-ACS (Atorvastatin for Reduction of Myocardial Damage During Angioplasty-Acute Coronary Syndromes) a randomized, placebo-controlled trial, was the first to evaluate effects of loading with high-dose atorvastatin on 30-day clinical outcome in statin-naïve ACS patients undergoing early

PCI (<48 hours).[4] In this trial, 171 patients were randomized to two groups—placebo or pretreatment with atorvastatin (loading dose of 80 mg at a mean of 12 hours before coronary angiography, and a further 40-mg approximately 2 hours before PCI). The primary composite endpoint of 30-day MACE is significantly lower in the atorvastatin group as compared to the placebo group (5 vs. 17%; $p = 0.01$), mainly driven by a lower incidence of periprocedural MI in the atorvastatin arm (5 vs 15%; $p = 0.04$). Also the secondary endpoints of postprocedural elevation of creatine kinase-myocardial band (CK-MB) and troponin-I were significantly lower in the group receiving atorvastatin (CK-MB: 7 vs. 27%; $p = 0.001$; troponin I: 41 vs. 58%; $p = 0.039$). Cardioprotection by loading dose of atorvastatin was associated with decrease in C-reactive protein (CRP) levels after PCI. Multivariate analysis revealed an 88% risk reduction of 30 days MACE (OR 0.12; 95% CI 0.05–0.50; $p = 0.004$) and a 70% risk reduction of periprocedural MI in the atorvastatin group. This benefit is significantly greater than that observed in MIRACL (16% risk reduction of the composite primary endpoint), and PROVE IT trials (28% risk reduction in overall population and 22% in the PCI group).

A meta-analysis of 20 randomized controlled trials, comprising 8,750 patients, showed that statins when given to naïve patients before PCI decreased the rate of MI at 30 days [OR 0.38, 95% CI 0.24–0.59; $p < 0.0001$], whereas when statins were given post-PCI, the effect was not significant (OR 0.85, 95% CI 0.64–1.13; $p = 0.28$).[5]

Pretreatment with statin before coronary intervention has also shown to reduce the risk of contrast-induced acute kidney injury.[6]

LOADING DOSE: YES OR NO?

In the SECURE-PCI (Statins Evaluation in Coronary procedUres and REvascularization Percutaneous Coronary Intervention) trial, 4,191 patients with ACS (with or without ST-segment elevation) were randomized to receive two doses of atorvastatin—80 mg prior and 24 hours after PCI or placebo.[7] All patients in the study received 40 mg of atorvastatin for 30 days starting 24 hours after the second dose of study medication. Although there was no significant difference in the 30-day rate of MACE HR 0.88; 95% CI 0.69–1.11; $p = 0.27$], in prespecified subgroup analysis, patients who underwent PCI (67% of all patients) and who were randomized to receive early treatment with atorvastatin, had a significant reduction in 30-day MACE (HR 0.72; 95% CI 0.54–0.96; p interaction = 0.02). Further, there was a significant reduction in 30-day MACE (HR 0.66; 95% CI 0.48–0.98; P-interaction with the no-PCI group = 0.04) in ST-elevation myocardial infarction (STEMI) patients who underwent PCI and received loading treatment, whereas in patients with non-STEMI there was no significant effect in the PCI group. Although the primary outcome of the SECURE-PCI trial was negative which may be due to a short follow-up of 30 days, but the results in the PCI subgroup may suggest that in ACS patients undergoing PCI, early loading statin treatment is more important than in those who are managed medically or by coronary artery bypass graft surgery. This beneficial effect in STEMI group undergoing primary PCI may be due to pleiotropic effects of statin such as decreased distal embolization, improved endothelial healing post-PCI, and improved microcirculation and reduction in no reflow.[8,9]

In another randomized control trial STATIN STEMI (Efficacy of High-Dose AtorvaSTATIN Loading Before Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction), 171 patients with STEMI were randomized to receive 80 mg atorvastatin ($n = 86$) or 10 mg atorvastatin ($n = 85$) before PCI and post-PCI both groups were treated with atorvastatin 10 mg.[10] Although there was no significant reduction of 30-day MACE in high-dose atorvastatin group compared to low-dose atorvastatin, there was significantly improved immediate coronary flow after primary PCI as evidenced by lower corrected TIMI frame count (26.9 ± 12.3 vs. 34.1 ± 19.0, $p = 0.01$), higher myocardial blush grade and higher ST-segment resolution in 80-mg atorvastatin arm.

Thus, by improving microvascular myocardial perfusion in STEMI patients undergoing PCI high-dose atorvastatin may produce an optimal result in primary PCI.

Another small study done on 52 patients compared the short-term effects of high (80 mg) versus moderate doses of atorvastatin (20 mg) in patients with STEMI undergoing primary PCI on endothelial function and vascular inflammation. The drugs were initiated within 48 hours of STEMI and showed significant differences in high-sensitivity CRP levels (0.04 ± 0.02 mg/dL vs. 0.36 ± 0.3 mg/dL, $p = 0.001$), IL-6 (1.12 ± 0.93 pg/mL vs. 3.13 ± 2.84 pg/mL; $p = 0.03$), and improvement in RH-PAT (reactive hyperemia–peripheral arterial tonometry) index (1.96 ± 0.16 vs. 1.72 ± 0.19, $p = 0.002$) in the high-dose versus moderate-dose atorvastatin at 1 month of treatment.[11]

The ROSEMARY (Efficacy of early intensive ROsuvastatin therapy in patients with ST-segment elevation Myocardial infarction undergoing primARY percutaneous coronary intervention) study compared loading dose of rosuvastatin 40 mg versus placebo before PCI followed by daily maintenance doses of rosuvastatin 10 mg in both groups for following 7 days. The study did not show significant differences in periprocedural coronary microvascular flow, reduction in infarct volume on cardiac magnetic resonance imaging, or clinical outcomes.[12]

In multicenter, randomized, prospective, double-blind ARMYDA RECAPTURE trial, 383 previously statin-treated patients (>30 days) with stable angina or non-ST-segment elevation ACS (NST-ACS) undergoing PCI were randomized to receive placebo or atorvastatin (loading dose of 80 mg given at a mean of 12 hours before coronary angiography, with a further 40 mg dose approximately 2 hours before the procedure).[13] Patients with NST-ACS requiring emergency PCI were excluded from the study. The baseline mean LDL level was 92 mg/dL in atorvastatin group and 93 mg/dL in placebo group. The 30-day MACE was less in the atorvastatin reload group than in the placebo arm (3.7 vs. 9.4%; $p = 0.037$) mainly driven by a reduction in periprocedural MI (3.7 vs. 8.9%; 2.4-fold reduction). On subgroup analysis, benefit of atorvastatin reload was highly significant in patients treated for an ACS (MACE incidence: 3.3 vs. 14.8% in the placebo group; OR 0.18; 95% CI 0.10–0.83; reduction of relative risk 82%; $p = 0.027$), whereas no difference in event rates was evident in patients with stable angina (4 vs. 4.9%; OR 0.74; 95% CI 0.20–2.90; $p = 0.70$). Thus, in patients already on chronic statin therapy, reloading with high-dose statins reduced the 30-day MACE rates significantly in those suffering from ACS.

In the prospectively planned subanalysis of the ARMYDA trial, the ARMYDA-Cell Adhesion Molecules (ARMYDA-CAMS) study, VCAM-1, ICAM-1, and E-selectin plasma levels were blindly measured in 38 patients each in pretreatment with atorvastatin and placebo groups at randomization prior to PCI (7 days before), immediately before the PCI, and after 8 and 24 hours.[14] In either arm, ICAM-1, E-selectin, and VCAM-1 levels were not different at randomization and before intervention though the atorvastatin group after PCI showed significantly attenuated ICAM-1 and E-selectin levels confirming the protective actions of statins on endothelial function.

The 2017 European Society of Cardiology (ESC) guidelines for the management of acute MI in patients presenting with ST-segment elevation recommend to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it for long term (Class IA).[15]

HOW LONG TO CONTINUE HIGH-DOSE STATIN?

The appropriate duration of statin therapy post-ACS is doubtful. In a literature review, the benefit of high-dose atorvastatin was seen to be sustained for at least 5 years, and it was concluded that high-dose atorvastatin should be continued for at least 5 years post-ACS. Though high-dose atorvastatin demonstrated a reduction in coronary events, it was associated with dose reductions and higher discontinuation rates.[16]

In SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin) trial, effect of high-dose atorvastatin 80 mg on progression of atherosclerosis was compared with high dose of rosuvastatin 40 mg over a period of 2 years. There was significant regression of coronary atherosclerosis in both the groups. The rosuvastatin group achieved a lower level of LDL cholesterol (LDL-C) and higher level of high-density lipoprotein (HDL) cholesterol, but the regression of percent atheroma volume was similar in both the groups. Only 2% in atorvastatin group and 0.7% in rosuvastatin group had raised liver enzymes more than three times of upper limit.[17]

In PROVE IT-TIMI 22 trial, there was 28% risk reduction of death, MI, or rehospitalization for recurrent ACS in intensive statin therapy group (atorvastatin, 80 mg) compared to standard therapy (pravastatin, 40 mg) at 6 months to 2 years post-ACS.[2]

The 2017 ESC guidelines for the management of acute MI in patients presenting with ST-segment elevation recommend an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70–135 mg/dL) (Class IB). A lipid profile should be obtained as early as possible after admission for STEMI and can be non-fasting, and should be re-evaluated 4–6 weeks after the ACS to determine whether the target levels have been reached. Safety issues should be addressed and lipid lowering therapy is then adjusted accordingly.

According to 2019 ESC guideline for the management of dyslipidemias, high-intensity statin should be started in all statin naïve ACS patient without contraindication with a target to achieve 50% reduction of LDL from baseline and LDL-C <55 mg/dL.[18]

ADVERSE EFFECTS

High-intensity statins are associated with statin associated muscle symptoms, rhabdomyolysis, elevated liver enzymes, proteinuria, and new onset diabetes mellitus. The incidence of these adverse effects is negligible compared to the beneficial effects. In a meta-analysis of several studies, only 4.99% of patients administered high-intensity statin therapy developed myopathy or myalgia as compared to 2.98% of those administered standard statin therapy. Rhabdomyolysis was extremely rare. About 1.84% in the high-intensity statin group had elevated serum aminotransferase and/or liver aminotransferase amounts (3 × upper limit of normal) versus 0.84% in the standard statin group.[19]

CONCLUSION

The current findings suggest that early initiation of high-intensity statin after an ACS (during hospitalization and before PCI) might reduce MACE in ACS in comparison with standard statin therapy, but the effect might not be same in all patients. Loading should be done even in patients on chronic statin therapy and even if baseline LDL level is around 90 mg/dL. Atorvastatin is the most tested statin in RCTs. The LDL goal should be achieved as early as possible and periodic monitoring should be done to look for response to therapy and any potential adverse event. However, serious adverse events associated with high-intensity statin administration were rare.

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CHAPTER 59

Myocardial Reperfusion Injury after Acute Myocardial Infarction Interventions: Bedside Evaluation

Jagdish C Mohan, Madhu Shukla

ABSTRACT

Clinicians understand ischemic cascade of acute myocardial infarction beginning with cessation of perfusion and ending with myonecrosis in the form of a wavefront traveling from subendocardial to subepicardial layers of the myocardium in a progressive and time-dependent manner. The intermediary steps include shutting-off oxidative metabolism, enhanced anaerobic metabolism, cellular acidosis and swelling, diastolic dysfunction, and systolic dysfunction. However, the final step in this cascade is, often, reperfusion which can be spontaneous or intentional. The well-meaning reperfusion is a highly desired end goal. It is presumed to be an ultimate aim and bull's eye. However, the devil may hide inside this final step of ischemic cascade in the form of reperfusion injury. This complex and characteristic phenomenon may overcome endogenous prosurvival kinase pathways and accelerate cell death induced by signaling pathways such as apoptosis, necrosis, pyroptosis, and ferroptosis. Clinical manifestations of reperfusion injury could be acute heart failure, ventricular arrhythmias, mechanical complications, or sudden death. The process of postreperfusion damage is multifactorial, and its pathogenesis involves imbalance between antisurvival and prosurvival mechanisms. Reactive oxygen species are considered key molecules in reperfusion injury due to their potent oxidizing and reducing effects that directly damage cellular membranes. An undesirable injury produced by reperfusion has been recognized for the last several decades, and its mechanisms are well elucidated. However, its bedside appreciation is rare. Following reperfusion, a residual nonprotected zone may show ischemic infarct with capillary rarefaction, hemorrhagic infarct with burst capillaries, and swollen area at risk with leaking capillaries. These three distinct phenotypes have unique patterns on imaging. This review aims to sensitize the clinicians about reperfusion injury as understood at the bedside and the need for a possible change in subsequent strategy.

INTRODUCTION

In acute myocardial infarction, the area at risk (AAR) is that portion of myocardium that represents the vascular territory of the affected artery and is destined to undergo irreversible damage in absence of any reperfusion. A section of this AAR undergoes necrosis and is called infarct zone (IZ; **Fig. 1**). The difference between the two parameters post reperfusion therapy is called the salvaged myocardium. Salvaged myocardium divided by AAR denotes myocardial salvage index, which is a metric of success of reperfusion therapy. However, no direct evidence exists on the evolution of infarct size normalized to AAR in man. The confounders include prior ischemic conditioning, collateral flow, speed, method of revascularization, etc. The biology of acute coronary syndrome could be more complex in human beings. There could be cycles of occlusion–reperfusion–reocclusion in some patients. Hence, reperfusion injury may be observed even in patients who at the time of presentation have an occluded infarct-related artery.

The ultimate aim of reperfusion therapy in acute myocardial infarction is to salvage the ischemic myocardium and limit myonecrosis. Time to reperfusion is of great importance because the wavefront of irreversible injury proceeds from the subendocardial layer to the subepicardial layer **(Fig. 2)**. Myocardial edema precedes myonecrosis and occurs within minutes of onset of ischemia.[1] Edema is a nonspecific potentially reversible response to any cellular injury. The early edema is due to myocyte swelling because dysfunctional energy-requiring ion channels promote sodium and water influx. This early onset edema may be reversible. However, sometimes, massive edema occurs after reperfusion which is sinister and is associated with acute fall in cardiac performance[2] and additional myonecrosis **(Figs. 3 to 5)**. It can be picked by bedside echocardiography[3]

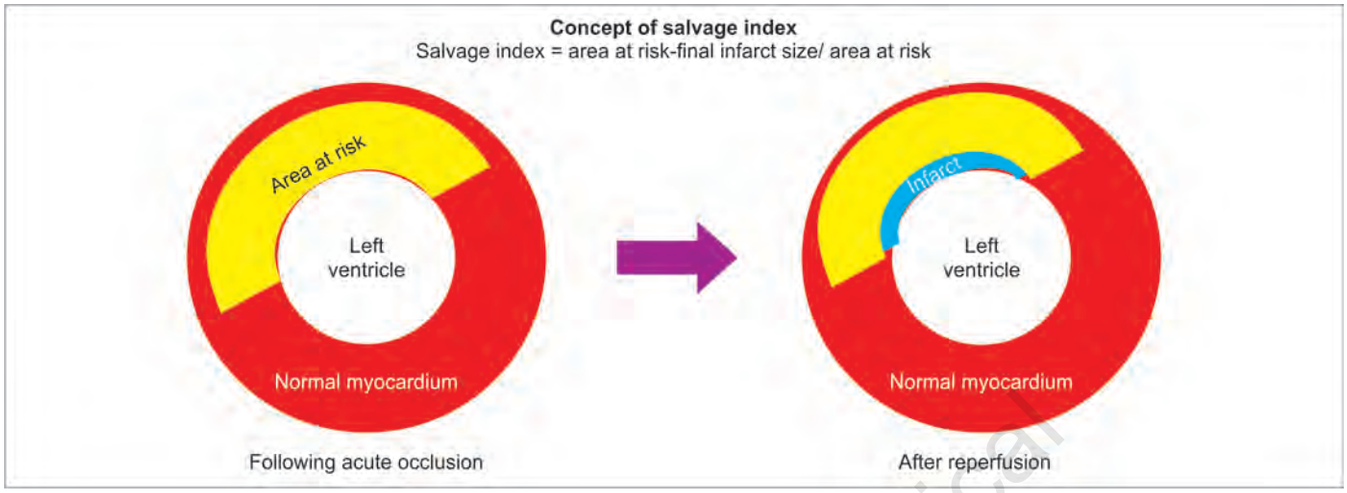


FIG. 1: Schematic diagram showing area at risk (AAR) and infarct zone (IZ).

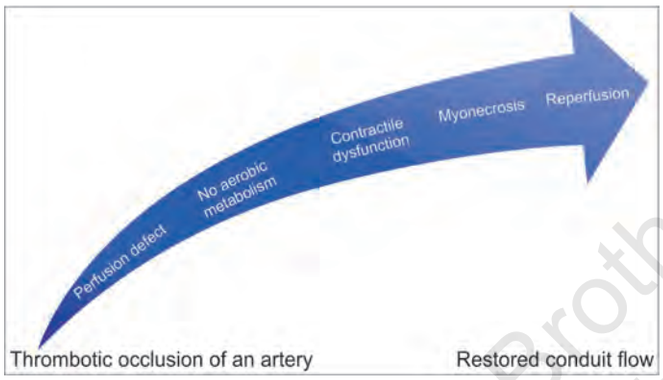


FIG. 2: Schema of ischemic cascade.

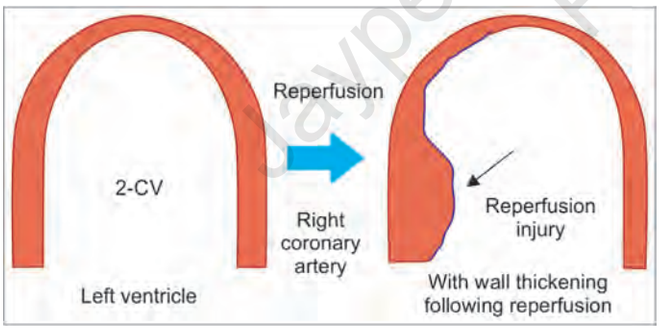
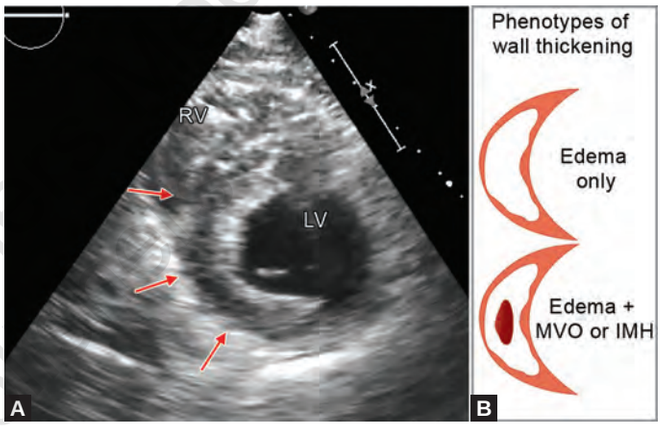


FIG. 3: Reperfusion injury shown as marked segmental wall thickness with akinesis.

and confirmed by T2-weighted cardiac magnetic resonance imaging if necessary. Myocardium at risk can be identified by the segments which have significant myocardial thickness with akinesis on echocardiography.[3-6] Lethal injury of potentially viable endothelial and myocardial cells following edema occurring during the restoration of flow is the underlying mechanism **(Fig. 5)**. The greater is the increase in end-diastolic wall thickness following reperfusion, the greater is the degree of myonecrosis.[4] There is usually a unimodal evolution of myocardial edema, which peaks around day 7–10 but manifests



FIGS. 4A AND B: A 60-year-old male with heart failure 3 days after primary angioplasty of the right coronary artery following acute inferior myocardial infarction. (A) Red arrows show markedly thickened basal septum and inferior and inferolateral basal segments in echocardiographic short-axis view. Core of wall thickness may contain blood [intramural hematoma (IMH)] or may be avascular due to microvascular obstruction [microvascular obstruction (MVO), cartoon in (B)].

(LV: left ventricle; RV: right ventricle)

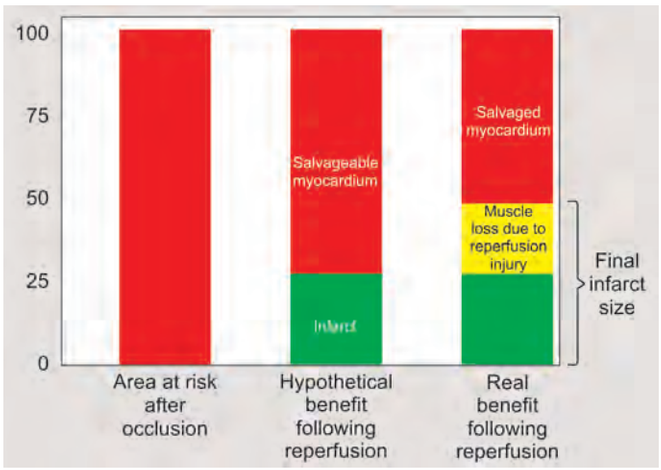


FIG. 5: Impact of reperfusion injury on final infarct size.

within 4–10 hours.[6] Others have described a bimodal pattern of myocardial edema which peaks at day 2–3, subsides for a few days, and reappears at 1 week. The significance of these patterns is poorly understood.

PATHOGENESIS OF MYOCARDIAL EDEMA

Myocardial ischemia promotes cellular (cardiomyocytes and endotheliocytes) swelling by accumulation of osmotically active anaerobic metabolites and sodium due to impaired transmembrane ion channel function.[1] Weakened cell membrane may allow leakage of fluid and concomitant increase in extracellular volume, which is prevented to some extent by reduced extracellular osmotic pressure due to capillary rarefaction.[2] With onset of reperfusion, extracellular osmotic and hydrostatic pressures increase. Increase in hydrostatic pressure induced by rapid reperfusion increases capillary leakage, while the increase in osmotic pressure sucks fluid out of cardiomyocytes causing lethal injury **(Figs. 6 and 7)**. Increase in hydrostatic pressure within the interstitial compartment due to rapid reperfusion can exacerbate the extent of necrosis by capillary compression as well.[7] Bursting

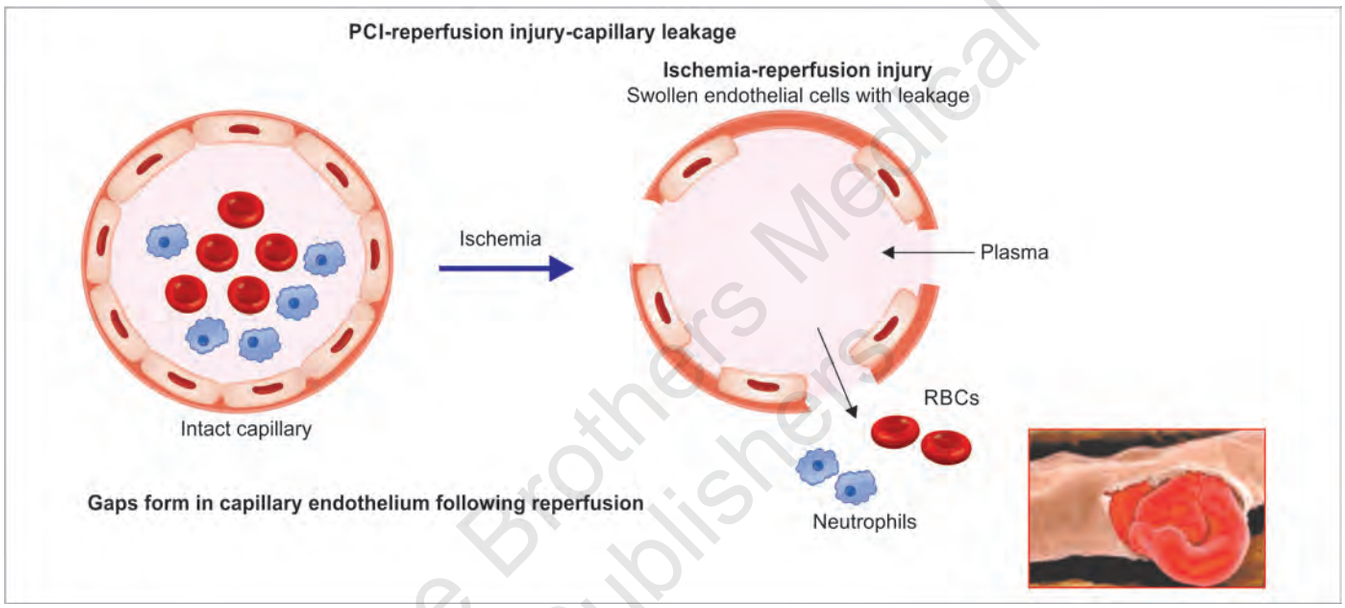
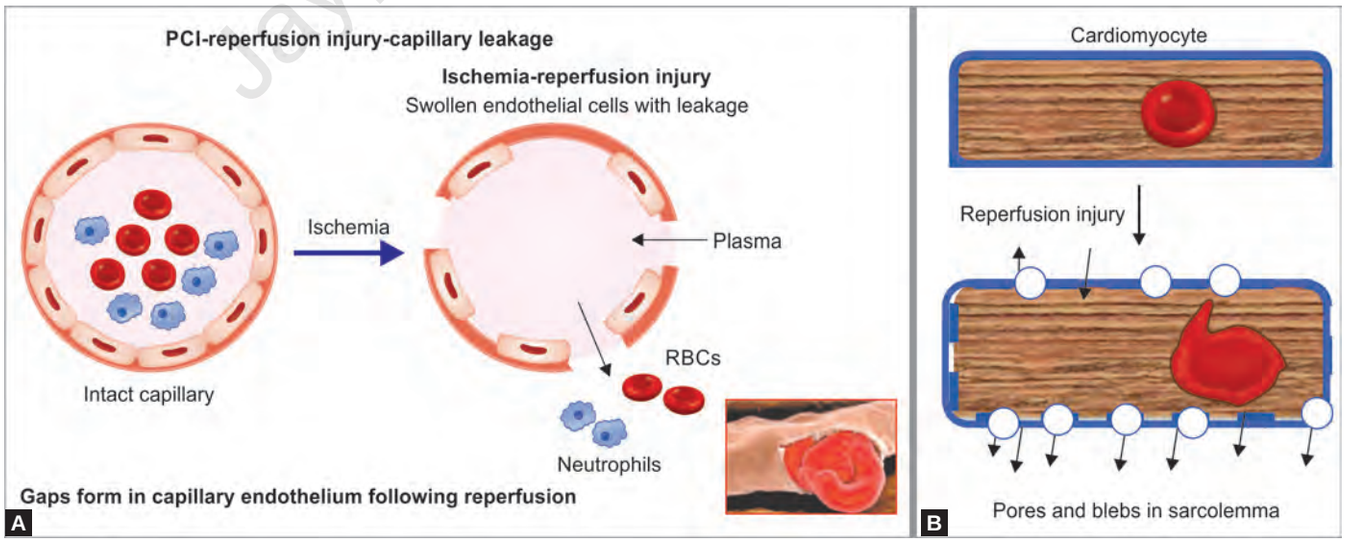


FIG. 6: Theoretical mechanism of capillary leakage following reperfusion.
(PCI: percutaneous coronary intervention; RBCs: red blood cells)



FIGS. 7A AND B: Schema showing reperfusion-induced myocardial edema. (A) Extracellular ; (B) Intracellular. Part of an increase of extracellular edema is due to sarcolemmal rupture.
(PCI: percutaneous coronary intervention; RBCs: red blood cells)

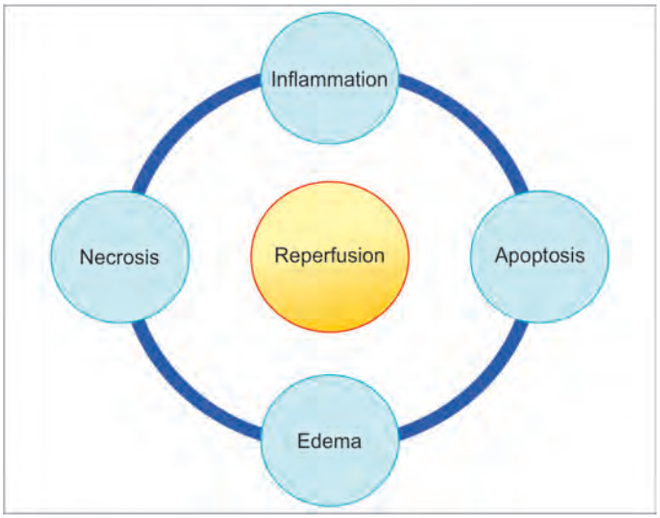


FIG. 8: Putative mechanisms of postreperfusion myocardial injury.

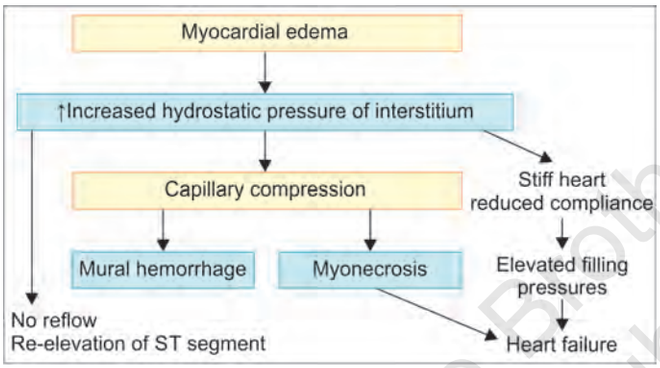


FIG. 9: Cascade of reperfusion-induced myocardial edema.

of capillaries also leads to intramyocardial hemorrhage and contributes to an increase in segmental wall thickness. Standard care in acute myocardial infarction with speedy reperfusion and antithrombotic therapy to keep macro- and microvasculature open may promote intramural hemorrhage. With increasing ischemia duration, the swelling of ischemic tissue on reperfusion (edema + inflammation + hemorrhage) impedes microvascular flow and contributes to necrosis **(Fig. 8)**.

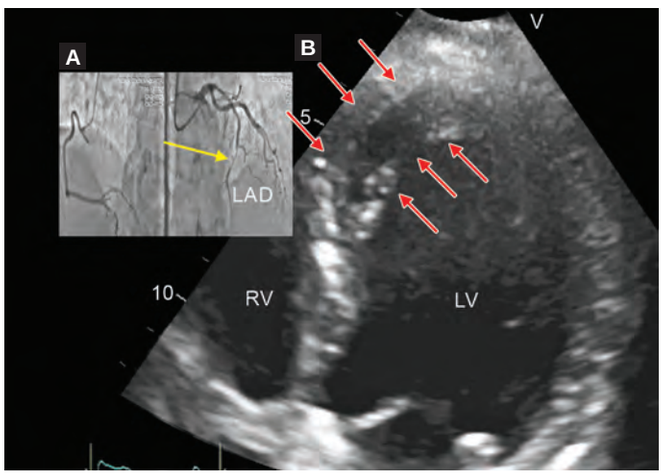
After reperfusion, myocytes become edematous and swollen from osmotic overload.[8] Endothelial cell changes are similar but lag behind myocardial cell injury.[9,10] Endothelial cells become voluminous with large intraluminal endothelial protrusions into the vascular lumen and disrupted basement membrane. Along with swollen surrounding myocytes and extravasated fluid, these may compress relatively healthy or partially damaged myocytes and capillaries **(Fig. 9)**.[8-10]

Myocardial edema, to a variable extent, is frequently observed in ischemia-reperfusion injury. In some patients, it plays a significant role in myocardial dysfunction and cell death.[10] Edema is both intra- and extracellular. Discrimination between intra- and extracellular myocardial edema is presently difficult at the bench and impossible at the bedside. Control of transmicrovascular fluid exchange in the heart is of critical importance in the prevention of myocardial edema formation. A large surface area of myocardial exchange vessels coupled with lymphatics of relatively low performance create a system that promotes edema formation. However, a very active lymphatic system can, theoretically, mitigate edema. Edema not only kills cells but also promotes fresh collagen synthesis.[11]

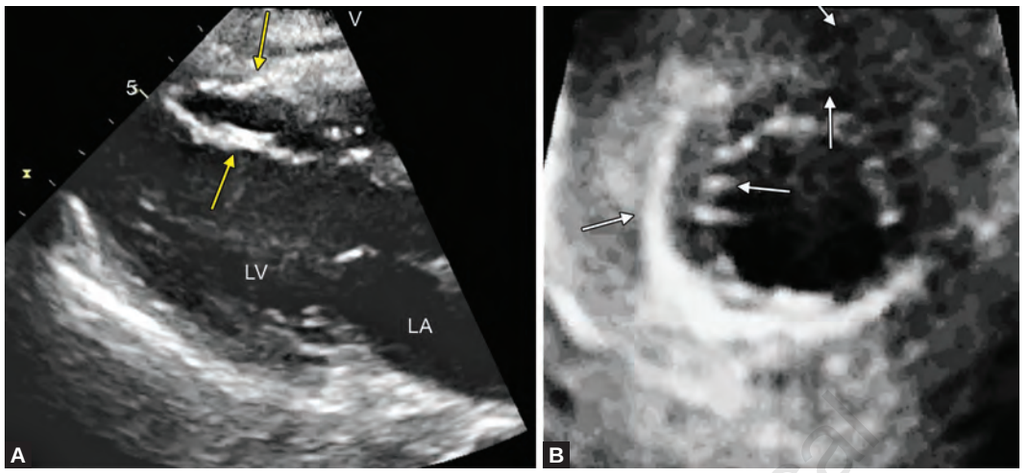
DETECTION OF MYOCARDIAL EDEMA

At present, there is no gold standard to detect myocardial edema in vivo. The abnormally thickened segments affected during ischemia-reperfusion injury and identified by echocardiography, magnetic resonance imaging, and contrast-enhanced computerized tomography serve as surrogate. Myocardial swelling can occur not only because of increased water content but also due to inflammation and hemorrhage. Sooner or later, expansion of extravascular space is at the expense of myocyte volume; hence cellular necrosis does occur with ensuing edema.[11,12] Magnetic resonance imaging is the only technique that can characterize tissue content (water, blood, or dead cells) but is not available at the bedside, besides other caveats. Echocardiography is the only technique available at bedside and provides useful information if performed serially with careful attention to the regional wall thickness and its echogenicity. Sensitivity of echocardiography is likely to be low, but its positive predictive value is high. There are no head-to-head comparisons between the two techniques in a serial systematic manner.

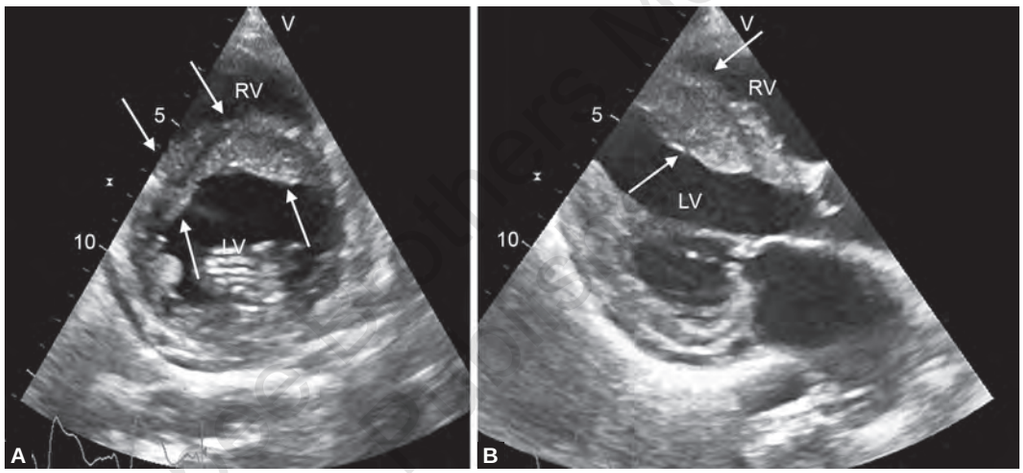
Edematous areas in the heart appear bright in T2-weighted magnetic resonance images because the T2 relaxation time becomes longer along with the native T1 time. However, these areas largely appear echolucent on echocardiography unless there are acoustic speckling by remnants of tissue tags, clotted blood, and inflammatory exudates **(Figs. 10 to 12)**. A bi-layered or tri-layered appearance of the affected segment is very typical of ischemia-reperfusion injury **(Figs. 12A and B)**. Lakes of echolucency may correlate with blood pools.



FIGS. 10A AND B: Spontaneous reperfusion in a 57-year-old male with ongoing acute chest pain and anterior myocardial infarction.
Note: The patent left anterior artery (yellow arrow) in the inset and echolucent thickening of the mid- and apical septum in the four-chamber view (red arrows).
(LAD: left anterior descending; LV: left ventricle; RV: right ventricle)



FIGS. 11A AND B: A 51-year-old female immediately after percutaneous coronary intervention (PCI) of left anterior descending artery.
Note: Echolucent thickened anterior ventricular septum (yellow and white arrows) in parasternal long- and short-axis views.
(LA: left atrium; LV: left ventricle)



FIGS. 12A AND B: Layered appearance of the anterior interventricular septum (both panels, white arrows, short- and long-axis views) after percutaneous coronary intervention (PCI) of the left anterior descending artery following acute myocardial infarction.
(LV: left ventricle; RV: right ventricle)

Some thickening of affected segments following reperfusion is physiological. When does it become pathological is a moot question. Oh et al., in a seminal study,[3] showed that if wall thickness exceeds 115% of that observed on day 1, it usually portends bad prognosis. They proposed that an increase in end-diastolic wall thickness after reperfusion beyond a certain level may be caused by accelerated myocardial and microvascular damage after reperfusion **(Fig. 13)**. Interestingly, 70% of their patients with >115% wall thickness compared to day 1 had re-ST-segment elevation.[3] Up to 20% difference in regional wall thickness compared to remote normal wall thickness is how we define reperfusion injury. Based upon these and other observations, we have hypothesized that increase in myocardial water content following reperfusion and hence an increase in end-diastolic wall thickness may have three different responses **(Figs. 14 and 15)**.

Based upon the above hypothesis, it can be surmised that acute myocardial infarction can have three distinct phenotypes **(Fig. 16)**.

Research is going on in the field of quantitative parametric tissue characterization mapping techniques by magnetic resonance imaging that can correlate with histology better.

CONSEQUENCES OF ABNORMAL MYOCARDIAL THICKENING AND MYOCARDIAL EDEMA

Eighty percent of the myocardium by volume is water and mostly intracellular.[13] A small increase in the amount of myocardial fluid content can cause some significant systolic dysfunction. An increase in myocardial fluid content by

3.5% can reduce cardiac output by 30–50%.[2,13] Myocardial edema reduces ventricular compliance and promotes diastolic dysfunction.[14] The increase in the interstitial fluid can accentuate microvascular resistance by external capillary compression and reduce coronary perfusion. Increased diffusion distance to myofibril causes a decrease of oxygen diffusion and inadequate oxygen supply. Both conditions can lead to myocardial ischemia.[15] Consequences of myocardial edema are, thus, multifactorial. Cardiac arrhythmias and conduction disturbance can also occur, which in turn reduce myocardial performance. Reperfusion-induced arrhythmias and myocardial stunning are the reversible consequences of ischemia-reperfusion injury.

Acute heart failure is the most common manifestation of reperfusion-induced myocardial edema. It can occur either immediately after percutaneous coronary intervention (PCI) or after a few days **(Figs. 17 to 20)**.

An interesting presentation observed by us has been ongoing acute chest pain, marked ST-segment elevation, and patent-affected coronary artery **(Figs. 21A and B)**. Transmural edema secondary to spontaneous reperfusion with tissue expansion is the likely mechanism of chest pain.

Another unusual observation is the presence of marked regional wall thickening in some patients with occluded infarct-related artery **(Figs. 22 and 23)**. This kind of presentation is apparently contradictory to the hypothesis that reperfusion causes myocardial edema and wall thickening. However, it is our presumption that such patients represent the sequential phenomenon of occlusion-reperfusion-myocardial edema-increased microvascular resistance-reocclusion. Such patients may also have several phases of occlusion and reperfusion. Occlusion of an infract-related artery without intervening reperfusion is associated with a small amount of edema, which is largely intracellular and not detectable by echocardiography.

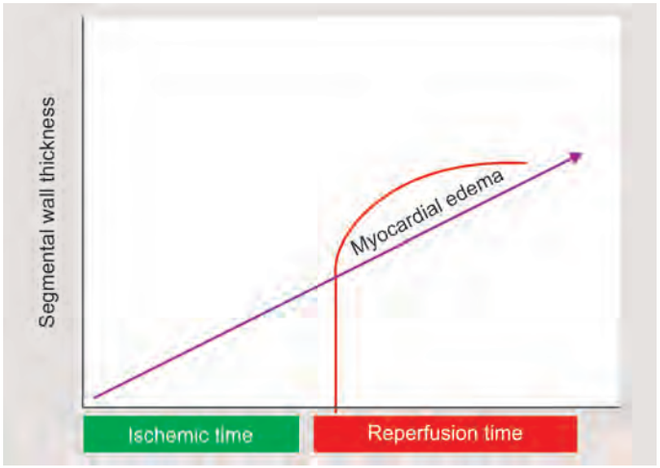


FIG. 13: Physiological response of segmental end-diastolic wall thickness to reperfusion.

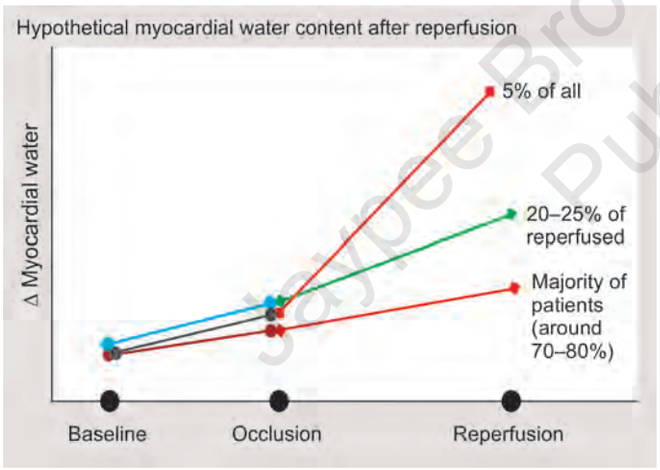


FIG. 14: Change in infarct-related myocardial water content after successful reperfusion.

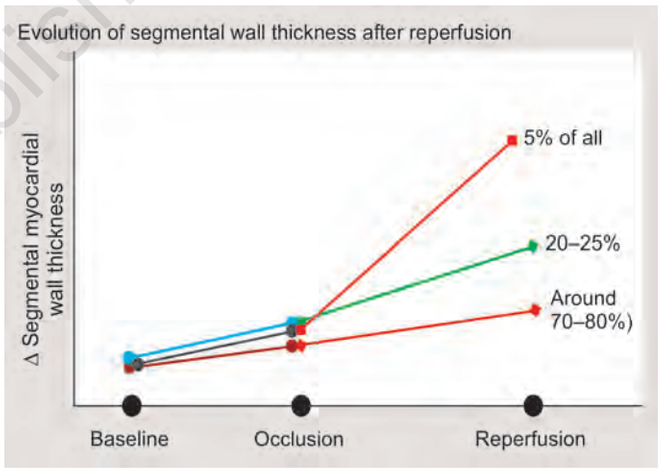


FIG. 15: Change in infarct-related myocardial end-diastolic wall thickness after successful reperfusion.

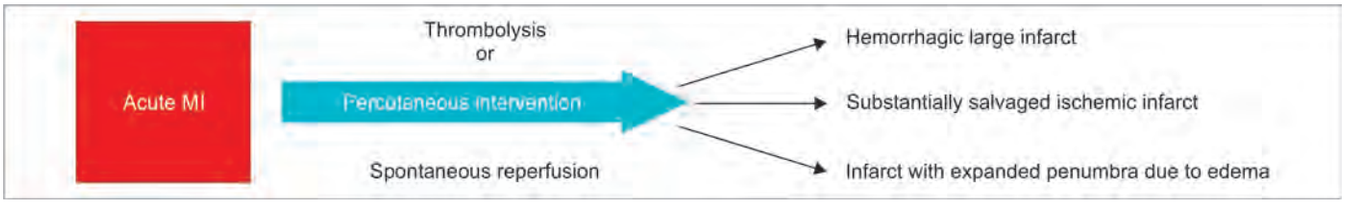
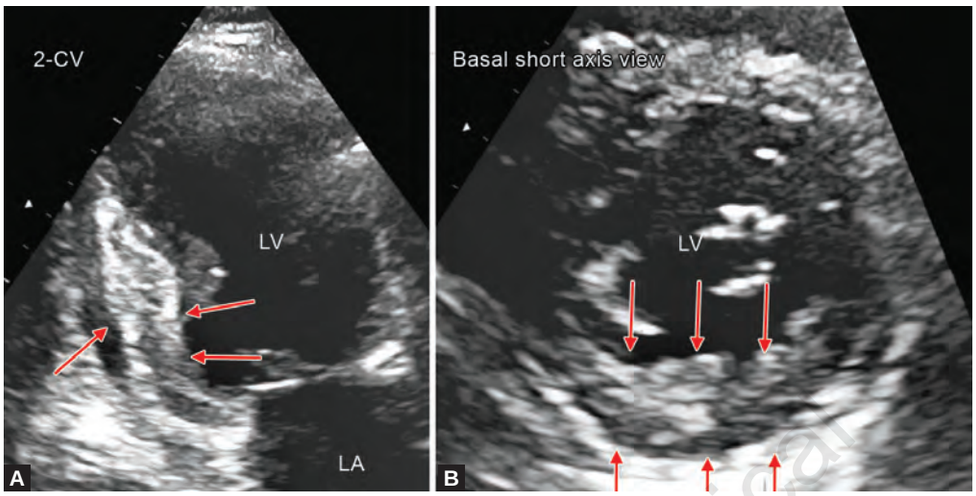
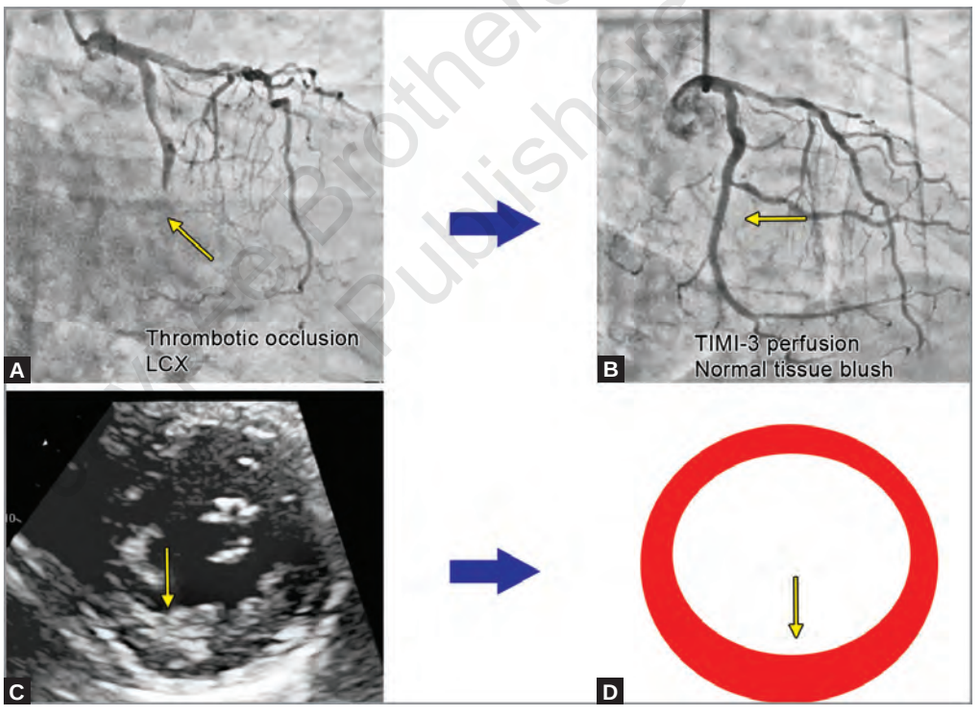


FIG. 16: Phenotypes of acute myocardial infarction (MI) after reperfusion therapy.



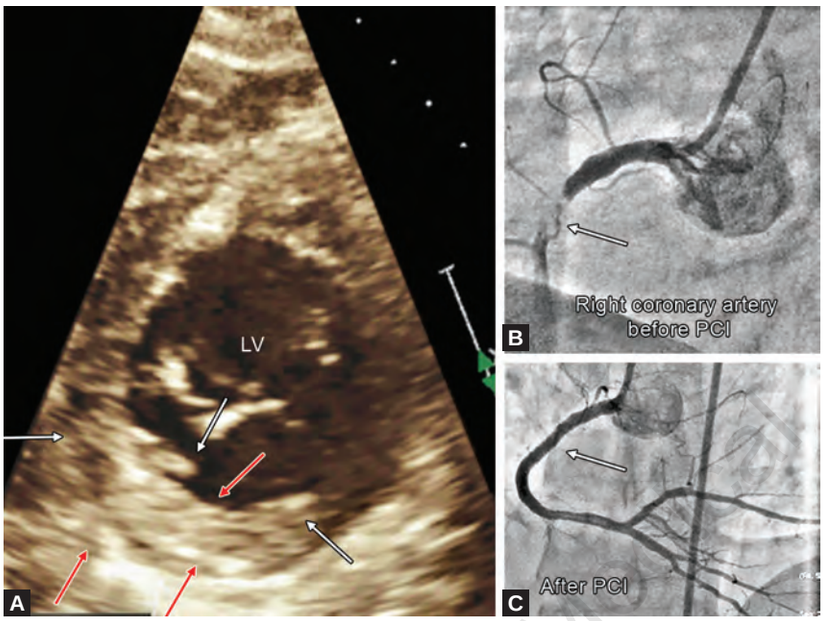
FIGS. 17A AND B: Refractory heart failure in a 53-year-old male immediately after primary angioplasty of left circumflex artery. (A) Two-chamber and (B) basal short-axis view recorded 4 days after percutaneous intervention show markedly thickened basal and mid inferior and basal inferolateral segments (red arrows). Pericardial effusion is noted in (A). End-diastolic wall thickness of the inferolateral segment is twice that of anterior interventricular septum.

(CV: cardiovascular; LA: left atrium; LV: left ventricle)



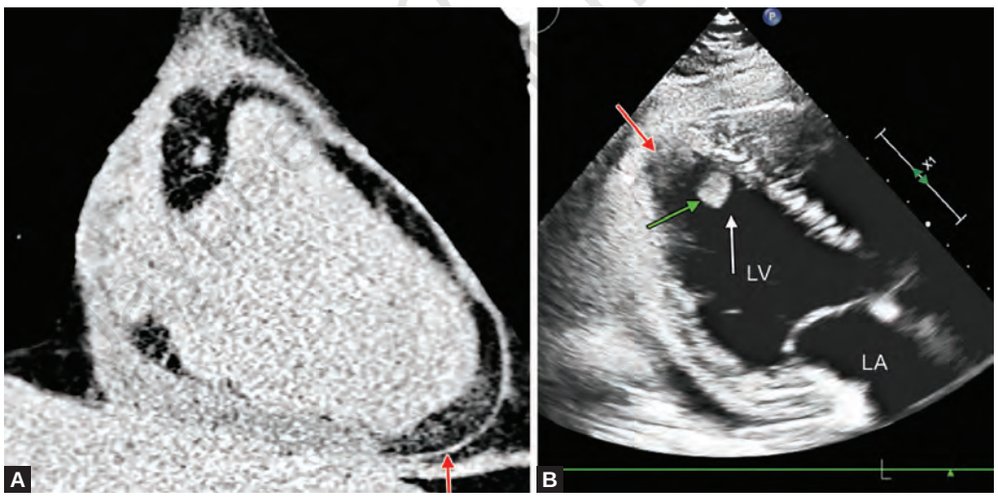
FIGS. 18A TO D: Same patient as in **Figure 17**. (A) Occluded left circumflex artery (LCX); (B) Its successful opening with stent implantation; (C) Abnormal end-diastolic thickening of the basal inferolateral wall; (D) Cartoon shows the schematic change.

(TIMI: thrombolysis in myocardial infarction)



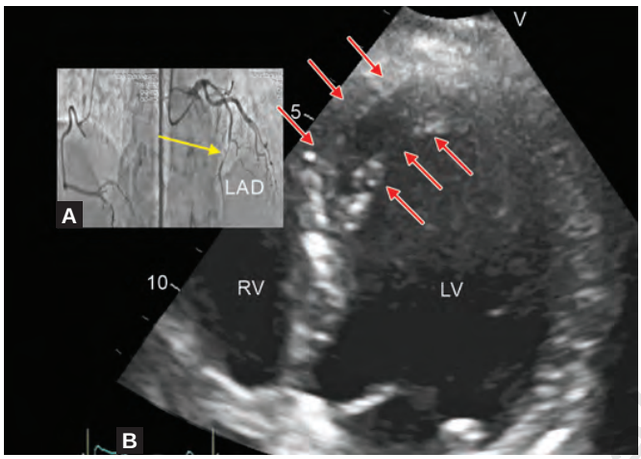
FIGS. 19A TO C: A 72-year-old female with acute inferior myocardial infarction presenting with heart failure 3 days after percutaneous intervention of the right coronary artery (B and C). (A) Highly echogenic increased end-diastolic wall thickness of the basal inferolateral segment (white and red arrows).

(LV: left ventricle; PCI: percutaneous coronary intervention)



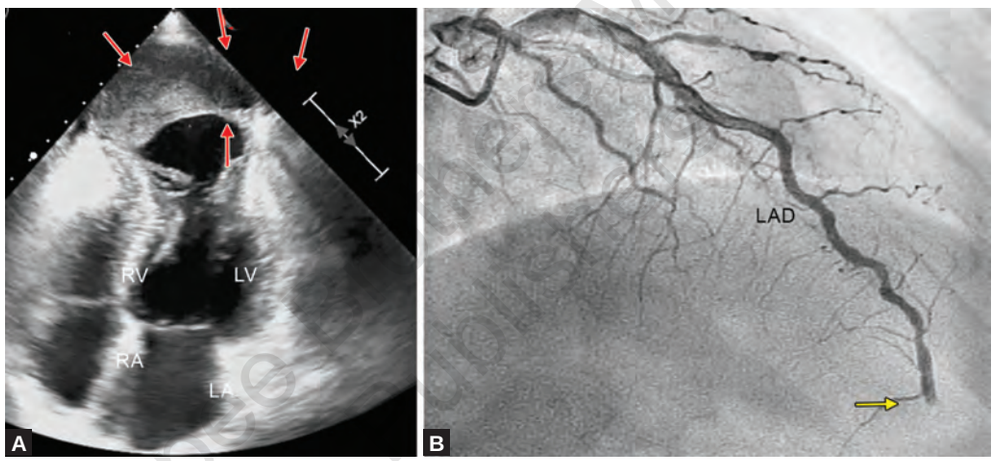
FIGS. 20A AND B: A 42-year-old male presenting with heart failure a week after successful percutaneous coronary intervention (PCI) of the left anterior descending artery with two stents implantation. (A) Coronal view of contrast-enhanced computerized tomographic image. Red arrow points toward apical myocardial thickening with some speckling. (B) Modified long-axis view exhibiting a small intracavitary thrombus (small arrows), apical thickening (red arrow), and pericardial effusion.

(LA: left atrium; LV: left ventricle)



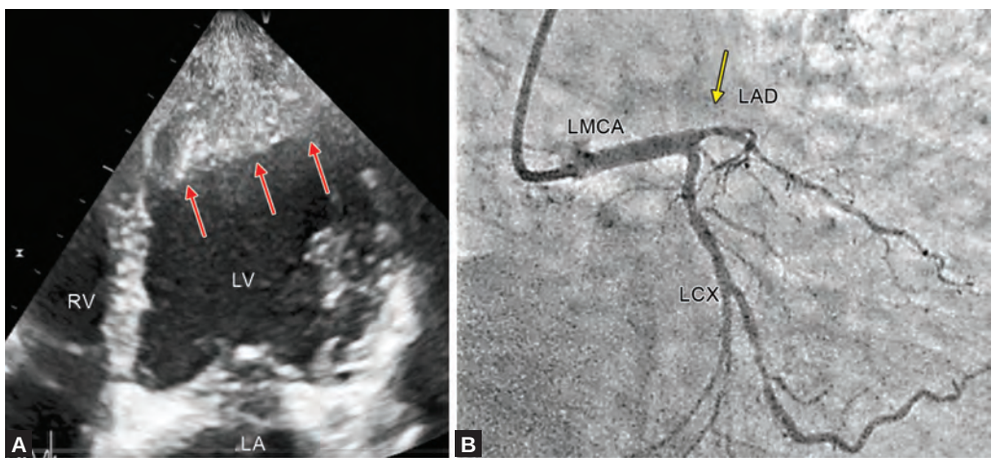
FIGS. 21A AND B: A 67-year-old diabetic male patient with ongoing chest pain with acute anterior myocardial infarction. Coronary angiogram (in inset) reveals 75% stenosis in the middle of the left anterior descending artery with good epicardial flow. Echocardiographic apical four-chamber view shows echolucent thickening of the mid- and apical septum (red arrows).

(LAD: left anterior descending; LV: left ventricle; RV: right ventricle)



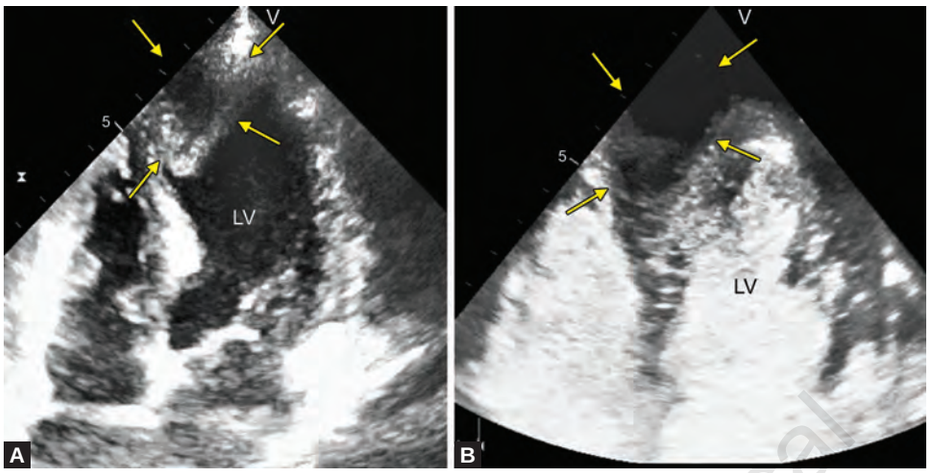
FIGS. 22A AND B: (A) Marked tumor-like apical thickening (red arrows) with two-layered appearance in four-chamber echocardiographic view in a 58-year-old male presenting with stuttering anterior myocardial infarction. (B) Occlusion of distal left anterior descending (LAD) artery (yellow arrow).

(LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle)

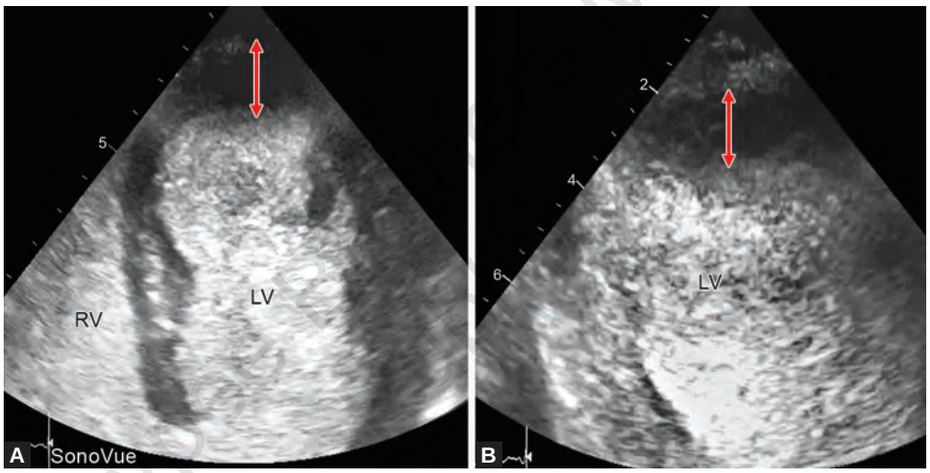


FIGS. 23A AND B: (A) Markedly thickened apical segments (red arrows) in a patient with acute anterior myocardial infarction and delayed presentation. (B) Occluded proximal left anterior descending (LAD) artery (yellow arrow).

(LA: left atrium; LCX: left circumflex artery; LMCA: left main coronary artery; LV: left ventricle; RV: right ventricle)



FIGS. 24A AND B: A 67-year-old physician presenting with diffuse dull aching chest pain 4 days after percutaneous coronary intervention (PCI) of the left anterior descending artery within a window period of 3 hours. (A) Apical thickening with a crevasse; (B) Large area of nonreperfusion with marked wall thickening (yellow arrows).
(LV: left ventricle)



FIGS. 25A AND B: End-diastolic frames after SonoVue injection showing segmental wall thickening with absence of myocardial flow (red double arrows).
(LV: left ventricle; RV: right ventricle)

Occasionally, patients after successful PCI may have significant constant pain more like that seen in acute pericarditis **(Fig. 24)**.

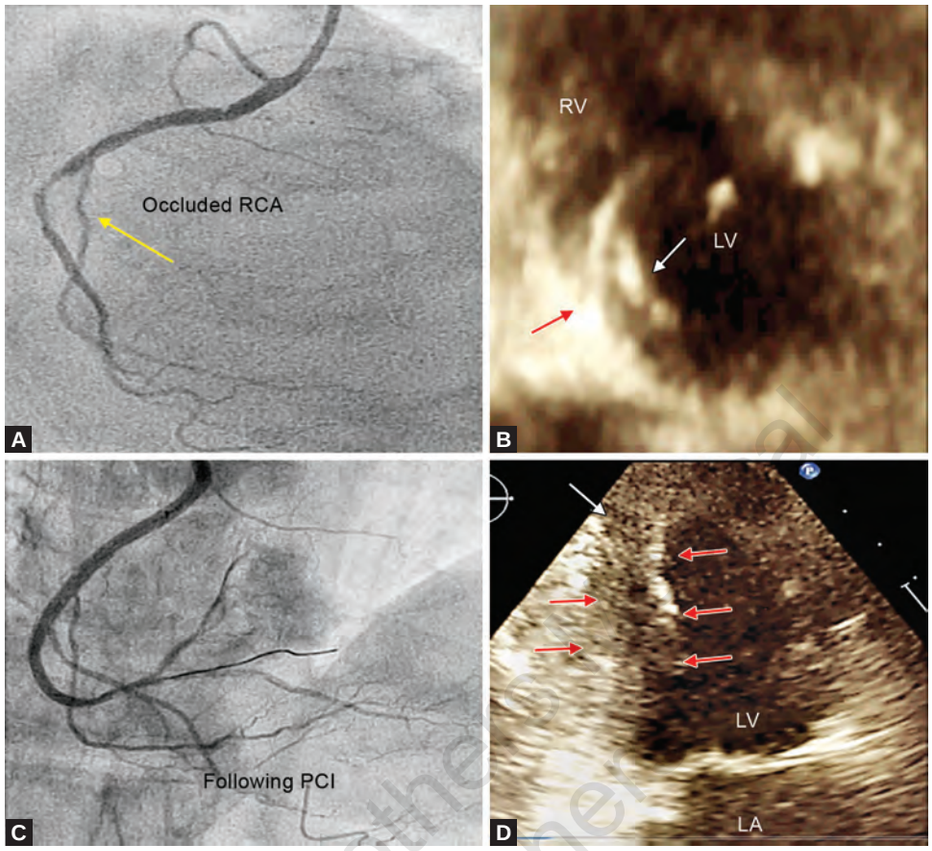
In a given case involving apical segments, reperfusion-induced myocardial edema may not be appreciated without the use of contrast agents **(Figs. 25A and B)**. This is due to near field artifacts.

It is also possible to suspect reperfusion injury after coronary intervention in a catheterization laboratory when a cloud of persistent contrast is visible in a follow-up angiogram **(Figs. 26A to D)**.

Delayed presentation after successful primary angioplasty may be incidental on routine echocardiography. The echocardiographic appearance may need to be differentiated from layered thrombi, and magnetic resonance imaging may be needed **(Figs. 27A and B)**. Lakes of echolucency can also be seen in thrombus undergoing spontaneous thrombolysis.

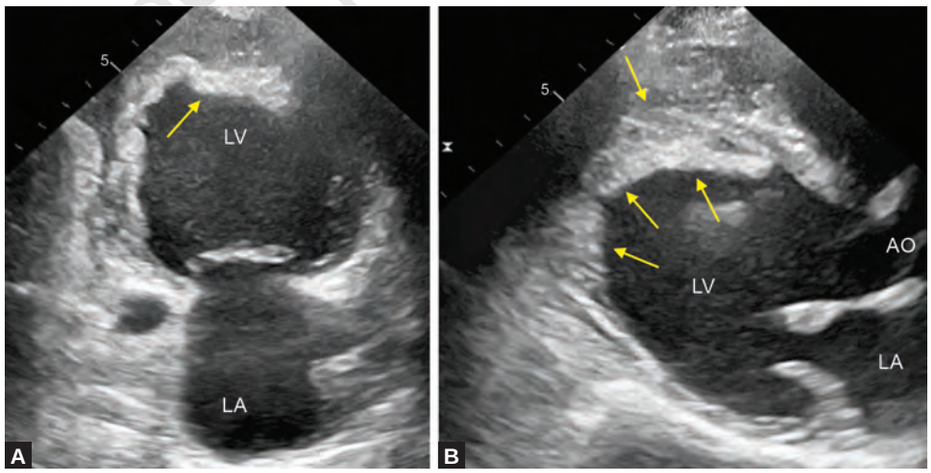
NATURAL HISTORY OF MYOCARDIAL EDEMA

Myonecrosis promotes a multifactorial and dynamic inflammatory response which is intense and participates in the removal of dead cells and repair.[16-18] Myocyte membrane disruption causes a release of intracellular contents and triggers an inflammatory response by activating the innate immune system. Hence myocardial edema and wall thickening tend to increase in the first few days, and then there is a period when normalization of wall thickness starts. There are endogenous mechanisms to control inflammation. Myocardial edema and wall thickening tend to subside in 7–10 days **(Figs. 28A and B)**. The patients who survive ischemia-reperfusion injury may recover partially with a resolution of stunning or be left with a larger infarct area, as such segments usually have transmural infarcts **(Figs. 29 and 30)**. It has been suggested that up to 50% of



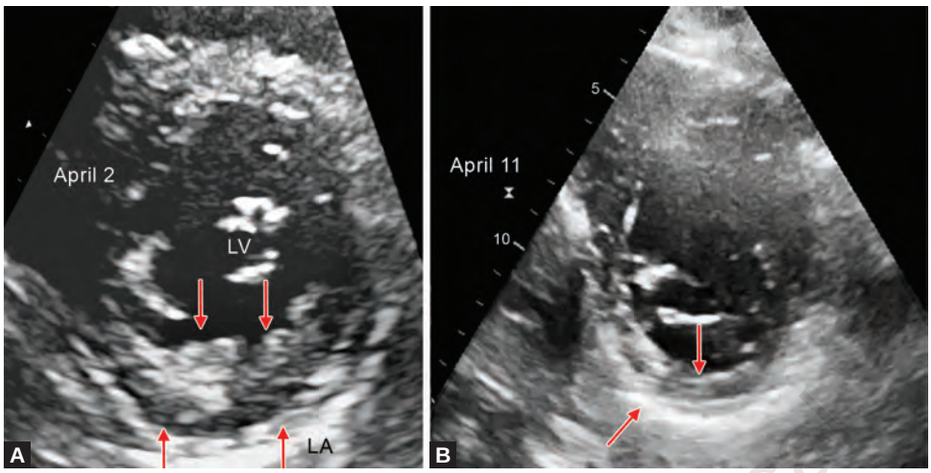
FIGS. 26A TO D: (A and C) Occluded right coronary artery and its patency after percutaneous coronary intervention (PCI). (C) Persistent contrast in the inferior wall, which is matched by abnormal thickening of the entire inferior wall in two-chamber view (D, red arrows) and short axis view (C).

(LA: left atrium; LV: left ventricle; RCA: right coronary artery; RV: right ventricle)



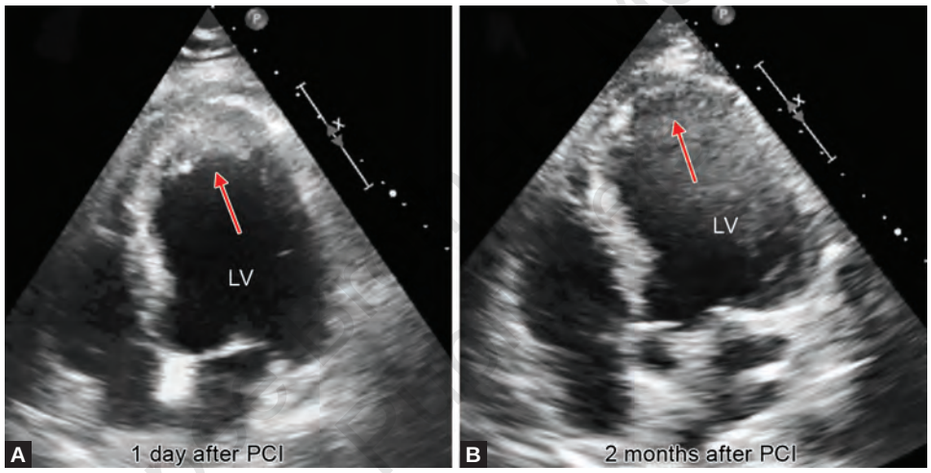
FIGS. 27A AND B: Extensive wall thickening of the mid anterior interventricular septum and the apical segments in both the two-chamber view and parasternal long-axis views (yellow arrows). Such appearance may be confused with thrombi or even endomyocardial fibrosis. Cardiac magnetic resonance imaging is of great diagnostic value in such cases.

(AO: aorta; LA: left atrium; LV: left ventricle)



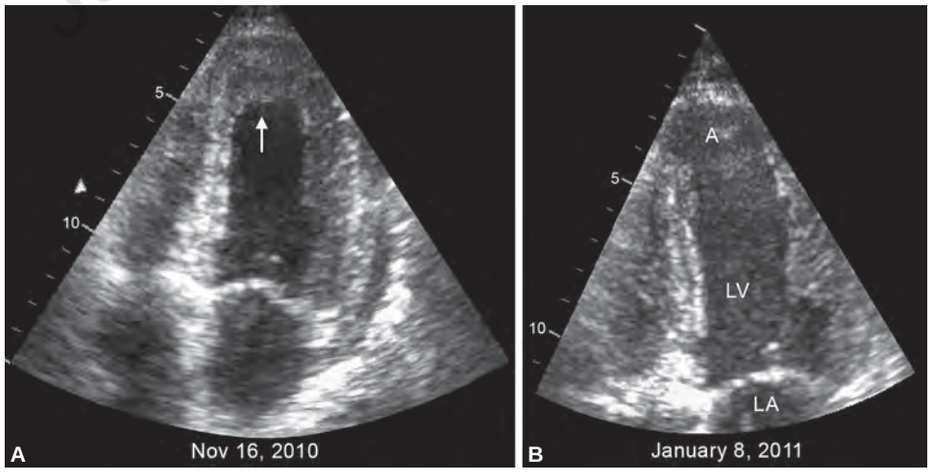
FIGS. 28A AND B: A 39-year-old male who underwent primary coronary angioplasty of codominant left circumflex artery. (A) Basal short axis with marked thickening of the inferolateral wall (red arrows) on April 2. (B) Near normalization of wall thickening after 9 days with residual high echogenicity and significant akinesis.

(LV: left ventricle)



FIGS. 29A AND B: Apical wall thickening following percutaneous coronary intervention (PCI) in four-chamber view (A), which resulted in true aneurysm formation after 2 months (B).

(LV: left ventricle)



FIGS. 30A AND B: A 45-year-old policeman immediately after percutaneous coronary intervention (PCI) of the proximal left anterior descending artery (A, four-chamber view) and after 2 months (B).

Note: The formation of apical aneurysm labeled A.

(LA: left atrium; LV: left ventricle)

the ultimate infarct is due to reperfusion injury.[16] Understanding of myocardial edema and inflammation, inhibitory signals in the infarcted heart, identification of patients with uncontrolled postinfarction inflammation, and defective cardiac repair are the next frontier to be conquered.

PREVENTION AND MANAGEMENT

Reduction of myocardial edema may serve as a novel target to minimize irreversible injury and improve left ventricle remodeling.[1,13] Differences in the mechanisms and clinical relevance of reperfusion-associated myocardial edema have hampered the acceptance of this concept of reperfusion injury in clinical practice. The extracellular edema appears a few minutes after reperfusion and can contribute to changes in the mechanical function of the myocardium with resultant acute heart failure that lasts for several days and sometimes is refractory.[19] It is treated in the usual manner with no specific different therapy. There are no defined guidelines to protect against reperfusion injury following acute myocardial infarction. Despite the improved understanding of the process of reperfusion injury, there are no proven specific therapies to prevent or treat it. Postconditioning, as a concept with repeated balloon inflation–deflation cycles of 60 seconds or more, is a good idea but not very practical or undisputed. Drugs remain to be developed for many potential targets for treating reperfusion injury. Adenosine has been shown to preserve the postischemic coronary flow reserve, coronary blood flow, and the postischemic regional contractility.[20] However, clinical trials with drug failed to show favorable outcome data.[21,22] Other agents which have been tried include intravenous antiplatelet agents, statins, steroids, colchicine, nitric oxide, magnesium, glucose–insulin–potassium infusion, nicorandil, immunomodulatory agents, anticomplementary therapy antioxidants and anti-inflammatory drugs, sodium nitrite, cyclosporine, exenatide, inhibitors of protein kinase C, calcium channel blockers endovascular cooling, hyperbaric oxygen therapy, etc. None has stood the test of time. Translating cardioprotection shown in animal experiments into clinical practice is an arduous task. CAESAR remains the only public network that performed rigorous, multicenter testing of cardioprotective therapies and showed their futility.[23] There is an urgent need for more work and more funding in this direction.

CONCLUSION

- Bedside echocardiography should be performed serially in all patients with acute myocardial infarction following reperfusion therapy.
- Special attention should be paid to those who present with hemodynamic compromise or re-ST-elevation with patent vessel after successful PCI.
- Those who show evidence of significant myocardial edema/regional wall thickening should have a longer hospital stay and intensive cardioprotective therapy.
- If the patient has multivessel disease, intervention in other vessels for complete revascularization should be deferred till there is resolution of reperfusion injury.
- Prophylactic surgery to prevent rupture or development of pseudoaneurysms may have to be considered.
- Intensified follow-up of such patients is imperative.
- Reperfusion injury remains the last frontier that poses a significant challenge, and more work is needed in this area.

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CHAPTER 60

Women and Spontaneous Coronary Artery Dissection: Is it Different?

Lekha Adik Pathak, Ronak V Ruparelia

ABSTRACT

Spontaneous coronary artery dissection (SCAD) is a nonatherosclerotic disease involving coronary arteries, which may lead to acute coronary syndrome (ACS) as well as sudden cardiac death. The incidence of SCAD remains very high among middle-aged women, the average age being 40–50 years. SCAD is many times found to be associated with fibromuscular dysplasia (FMD), postpartum status, and episode of extreme emotional stress or exercise. It is extremely important for an interventionalist to understand the pathophysiology and mechanism of SCAD as the short-term and long-term management strategies differ from conventional strategies being used to treat atherosclerotic coronary artery disease (CAD). This chapter highlights various salient points of SCAD regarding its prevalence among women, presentation, associated conditions, and management strategies.

INTRODUCTION

Spontaneous coronary artery dissection (SCAD) is defined as an epicardial coronary artery dissection that is not associated with atherosclerosis or trauma and is not iatrogenic. After its first description by Pretty in 1932 at an autopsy, SCAD remained a topic of debate for a long time.[1] In the past couple of decades, SCAD is increasingly being reported as one of the causes of myocardial infarction (MI) among middle-aged women as many online registries and studies started reporting it. SCAD MI is caused by partial or complete occlusion of the coronary artery from vessel wall tear and/or hematoma.[2] The diagnosis and management of SCAD remain debatable and challenging despite recent advances.

DEMOGRAPHICS AND PREVALENCE

Originally, SCAD was believed to be a rare entity **(Table 1)**. In literature, the reported incidence of SCAD remained between 0.07 and 1.1%.[4,5,11,12] Although SCAD is likely to be more common than previously thought of, with increasing awareness and use of intravascular imaging, SCAD is being increasingly recognized. High female preponderance has been noted in various studies ranging from 74 to 92%.[4,5,11,13] Up to 10–30% of women, younger than 50 years suffering from MI were also found to have SCAD.[7,13] SCAD remains the most common cause of pregnancy-associated MI.[14] One study reported that men presenting with SCAD are slightly younger (mean age 48.6 years) as compared to women (mean age 52.3 years).[9]

In terms of involvement of coronary arteries, left anterior descending (LAD) artery is the most commonly affected artery (45–61%) followed by left circumflex (LCX) (15–45%) and last, right coronary artery (RCA) (10–39%).[15,16] In the majority of cases, the mid to distal segments are affected. Involvement of the left main coronary artery and multivessel SCAD remains rare.

NATURAL HISTORY

Natural history of SCAD remains obscure. It has been observed to be markedly different from atherosclerotic coronary artery disease (CAD). As the majority of SCAD patients are relatively young women, they are typically found to have no or very little atherosclerotic plaques or traditional risk factors associated with atherosclerotic CAD. Although SCAD MI can be a fatal event, most series suggest good early and long-term survival. In-hospital death is uncommon in SCAD. However, long-term major adverse cardiovascular events (MACE) such as recurrence of SCAD, congestive cardiac failure, MI, and death remain high. Studies showed recurrent MI occurring in 1.6–18% of patients, recurrent SCAD occurring in 4.7–22%, heart failure

TABLE 1: Prevalence of spontaneous coronary artery dissection (SCAD) in acute coronary syndrome (ACS) cohorts.[3]

Reference	Year	Patients with SCAD, n	SCAD prevalence as a proportion of all ACS cases, %	Women among SCAD cases, %	PA-SCAD, %	SCAD prevalence in subgroup with ACS	Methods, population, inclusion criteria
Vanzetto et al.[4]	2009	23	0.2 (0.6 women, 0.07 men)	74	0	8.7% SCAD among ACS in women ≤50 years	• Systematic retrospective review of 11,605 angiograms • Included type 1 SCAD only • Atherosclerosis-related coronary dissection not excluded
Mortensen et al.[5]	2009	22	2.0	77	12	NR	Retrospective search for coded diagnosis in database of 32,969 angiograms reviewed only those with prior SCAD diagnosis
Alfonso and Bastante[6]	2014	27	0.16	85	3.7	NR	Retrospective search for coded diagnoses among 16,813 first angiograms (2004–2010)
Saw et al.[7]	2014	16	NR	100	NR	24.2% SCAD among ACS in women ≤ 50 years	Retrospective review of 177 angiograms in women ≤50 years representing 9% of angiograms (*n* = 7,605) performed during the study period (2009–2011)
Rashid et al.[8]	2016	21	1.7	95.2	NR	22.5% SCAD among ACS in women ≤ 60 years	Retrospective search for coded diagnoses among 1,332 angiograms (2012–2013)
Nakashima et al.[9]	2016	63	0.31	94	8.1	35% SCAD among ACS in women ≤ 50 years	• Retrospective review of 20,195 angiograms (2000–2013) • Excluded atherosclerosis-related coronary dissection • Included type 2 SCAD • Separate analysis for women ≤50 years with ACS (*n* = 45)
Nishiguchi et al.[10]	2016	13	4	53.8	NR	NR	• 326 selected ACS patterns undergoing OCT (2008–2012) • Atherosclerosis-related coronary dissection not excluded

(ACS: acute coronary syndrome; NR: not reported; OCT: optical coherence tomography; PA-SCAD: pregnancy-associated spontaneous coronary artery dissection; SCAD: spontaneous coronary artery dissection)

in 2–3.9%, and death ranging from 0 to 3.1%.[8,17,18] More than half of women complain of having recurrent chest pains, even without demonstrable ischemia or worsening angiographic epicardial coronary appearance.

PRESENTATION AND DIAGNOSIS

Spontaneous coronary artery dissection can have a varied presentation ranging from acute coronary syndrome (ACS) to sudden cardiac arrest. High female preponderance has been noted in various studies with a mean age of 42–52 years.[4,5,11] Although typical presenting symptoms are of ACS, women can have atypical symptoms such as unusual fatigue/lethargy, back pain, light-headedness, diaphoresis, and nausea. These patients being relatively young, many times SCAD is not considered a differential diagnosis. A considerable number of patients are misdiagnosed as myopericarditis, takotsubo cardiomyopathy, gastroesophageal reflux, or gastritis. Investigations such as serial electrocardiogram (ECG) evaluation, regional wall motion abnormality, and raised cardiac biomarkers help in early suspicion. Coronary angiography (CAG) confirms the diagnosis of SCAD in many cases as contrasts fill into the intimal dissection plane (false lumen). Type I SCAD on CAG is defined as arterial wall stain with the appearance of multiple lumens. Type II SCAD is defined as intramural hematoma with diffuse and smooth stenosis. Type III SCAD may mimic atherosclerosis and is difficult to differentiate. However, intramural hematoma may not be visible on conventional CAG and may mimic coronary vasospasm or atherosclerotic disease. The use of intravascular imaging helps in accurate diagnosis in such cases.

ASSOCIATED CONDITIONS

Traditional atherosclerotic risk factors are rarely found in women presenting with SCAD. Association with peripartum

status, predisposing episode of extreme emotional stress or exercise, and connective tissue disorders such as Marfan syndrome, Ehlers–Danlos syndrome, and Loeys–Dietz syndrome were noted in studies.[11] In women, extreme emotional stress acts as a predisposing factor as compared to men in whom extreme physical stress acts as a predisposing factor many times. The high prevalence of young women and association with peripartum status indicates potential hormonal contribution.[11] Mean maternal age of 33 years and mean postpartum period of 38 days were reported in a study by Tweet et al.[11] The same study also revealed that SCAD associated with pregnancy presents more severely than SCAD occurring in nonpregnant women. Pregnancy-associated SCAD has a higher incidence of presentation with ST-segment elevation myocardial infarction (STEMI). CAG in such patients many times revealed SCAD involving the left main coronary artery or multiple vessels SCAD simultaneously. The high association between SCAD and fibromuscular dysplasia (FMD) among women also points toward a systemic vasculopathy distinct from inheritable connective disorders.[19] In a series of 114 SCADs conducted by Mayo Clinic,[8] 66% had detectable extravascular abnormalities (such as FMD, aneurysms, dissections, and aortic tortuosity) with wide anatomical distributions including the abdomen (36%), pelvis (28%), and neck (27%). The most common abnormality was FMD.[8] Whether the presence of FMD is the "missing link" between sex hormone changes and the occurrence of SCAD is an intriguing possibility and warrants further study. Other potential hormone-mediated SCAD triggers such as perimenopausal state, use of hormonal contraceptive pills or hormonal therapy, infertility treatment, and high-dose corticosteroid administrations are also reported in the literature.

SHORT-TERM MANAGEMENT

Being a nonatherosclerotic disease, the management differs in women with SCAD. In a series that retrospectively reviewed short-term management strategies of 19 patients, 50% of patients with SCAD with normal or near-normal coronary blood flow had an unsuccessful coronary intervention and 13% subsequently required subsequent coronary artery bypass graft (CABG).[6] In patients with occluded coronary blood flow, percutaneous coronary intervention (PCI) or CABG can salvage viable myocardium, although the PCI failure rate remains as high as 53%.[11] Hence, conservative management is associated with favorable outcomes in patients with preserved coronary blood flow. Empirical treatment includes single antiplatelet therapy and β-blockers. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) may be added in patients with left ventricular (LV) dysfunction. Symptomatic improvement may be achieved with long-acting nitrates or calcium channel blockers also. Being a nonatherosclerotic condition, there is no role of statin therapy. However, statins may be added to patients with dyslipidemia. Close monitoring is required in the initial period as many women are reported to develop progression of dissection in the first week. However, robust recommendations supported by data or randomized trials for conservative cardiac medications are lacking.

LONG-TERM MANAGEMENT

General Long-term Management

It remains debatable as many patients are at future risk of MACE. Regular follow-up is of utmost importance. A large proportion of women (>50%) report chest pain even after optimal conservative treatment of SCAD. Such patients may require evaluation for ischemia with stress testing and/or CAG. However, in large proportion, the evaluation remains unremarkable. These subgroups usually respond to antianginal therapies such as long-acting nitrates, calcium channel blockers, or β-blockers. Alternatively, ranolazine, gabapentin, antidepressants, or anxiolytics may be tried.

Role of Imaging

Comprehensive imaging of vasculature is recommended in women with SCAD to rule out FMD. Computed tomography (CT) angiography of vasculature from neck to pelvis is recommended in all women with SCAD. Imaging of cerebral vessels can be considered for those with diagnosed FMD. Magnetic resonance imaging (MRI) or ultrasound can also be used as an alternative modality.

Neurological Management

Anxiety and Depression

In a cross-sectional study of 158 SCAD survivors,[18] depression and anxiety were found to be common, especially among young and postpartum women. Hence, long-term assessment of mental health and treatment, if necessary, also plays an important role.

Migraines

Migraines are also common among women with SCAD (lifetime prevalence ~ 40%).[20] Women with SCAD and migraine are more prone to recurrent chest pain, depression, anxiety, and recurrent SCAD as compared to men.[13] Triptans should be avoided in the treatment of such migraine owing to their vasoconstrictive properties. β-blockers may be prescribed in such cases as a preventive measure.

Rehabilitation

Cardiac rehabilitation and patient learning also play a major role in long-term management. However, cardiac rehabilitation participation remains very low among women, which makes them prone to future untoward events. As many SCADs are associated with postpartum status, future pregnancies are discouraged. Furthermore, hormonal contraceptives and therapies are also better avoided. Because of the association of recurrence and resurgence of chest pain with menstruation, one might hypothesize a therapeutic role for exogenous hormone treatment following SCAD. However, evidence is lacking to validate such use. Due to the poorly understood role of the hormonal milieu and the association of SCAD with pregnancy, exogenous hormone use after SCAD may be harmful.[2] As SCAD in women is associated with extreme physical exertion, subsequent participation in competitive sports, prolonged high-intensity activities, and heavy weight lifting are discouraged.

CONCLUSION

Understanding SCAD, a nonatherosclerotic disease spectrum leading to ACS is critical to improving outcomes in women. The utmost care and high suspicion are needed while approaching middle-aged women with angina. CAG with preferably intravascular imaging is required for the diagnosis of SCAD. PCI should be discouraged unless the patient is having life-threatening hemodynamic instability. Conservative medical management remains the cornerstone of treatment. In certain cases, CABG or minimally invasive direct coronary artery bypass (MIDCAB) may be required. Long-term care for SCAD may require a multimodality approach to treat the various associated spectrum of diseases such as migraine, depression, and anxiety. Specialists in cardiology, vascular medicine, genetics, psychiatry, pain management, neurology, cardiac rehabilitation, radiology, and obstetrics can facilitate personalized care.

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CHAPTER 61

STEMI in Women: Is it Different?

Jyotsna Maddury

ABSTRACT

Various large databases from The United States and Europe have shown that women with ST-segment Elevation Myocardial infarction (STEMI) have more mortality as compared to men with STEMI. Most of this has been contemplated due to older age at presentation, higher cardiovascular risk profile, delay in reperfusion, and differences in STEMI pathophysiology in women. However, if all these factors be controlled, question arises: Is Female Sex in itself a bad prognosticator for STEMI outcomes?

INTRODUCTION

Why STEMI requires separate attention in women?

Mortality is high in women than in men with ST-elevation myocardial infarction (STEMI), even in the present era of availability of multiple efficient drug therapies and advanced interventional technologies. The reason for this gender difference is multiple factorial with both correctable (e.g., delay in presentation and treatment) and uncorrectable factors (e.g., older age, multiple comorbidities) along with difference in pathophysiology of acute myocardial infarction (AMI), which are discussed in this chapter. For this reason, women with STEMI require special attention.

STEMI: GLOBAL SCENARIO

Each year, an estimated more than 7 million people in the world are diagnosed with acute coronary syndrome (ACS), including more than 1 million patients hospitalized in the United States.[1] In American women, AMI is one of the leading causes of morbidity and mortality with an annual prevalence of 2.7 million. Of these, more than 53,000 died of a myocardial infarction (MI).[2] According to Framingham Heart Study, the 1-year mortality percentages in women and men were 44% versus 27%. In another study, there was a gender difference in the prehospital and hospital mortality. In females, prehospital mortality was less but higher hospital mortality when compared to men, which balances the overall mortality in both sexes.[3] In addition, increased mortality was demonstrated in female AMI patients for recurrence of MI or heart failure (HF) or death after first MI, even after postpercutaneous coronary intervention (PCI).[4] In a study conducted by Vaccarino et al., the effect of age on the sex differences in mortality was found. Mortality in women <50 years of age with AMI was double than that of men, whereas this tendency was not seen in those <60 years of age.[5]

According to the scientific statement of the American Heart Association (AHA) on AMI in women, an increase in mortality in American women due to cardiovascular disease (CVD) has been noted since 1984; however, a reduction in female mortality was observed in the last decade. The reasons behind this reduction in mortality in females were due to multiple pathway improvements such as increased awareness, better risk factor management, and implementation of evidence-based treatments.[6]

STEMI: INDIAN SCENARIO

Indian women with STEMI has double the risk of Americans and several folds higher than other Asians.[7] Among Indian women, the presence of hypertension, diabetes, low levels of high-density lipoprotein, high levels of total cholesterol, triglycerides, low-density lipoprotein, and lipoprotein(a) [Lp(a)] is correlated with coronary artery disease (CAD) and may lead to MI.[8]

PATTERN OF PRESENTATION

The classical presentation of AMI is central chest pain. On the contrary, females with AMI also present with atypical chest pain and angina-equivalent symptoms such as dyspnea, weakness,

fatigue, and indigestion.[9] High-risk presentations without central chest pain are more frequent in women than in men.[10,11] In the Comprehensive Evaluation of Risk Factors in Older Patients with AMI (SILVER-AMI) study, women reported more symptoms and had significantly more symptom phenotypes than men. Appreciation of the diversity of symptom phenotypes may help clinicians recognize the less common phenotypes that occur more often in women.[12]

PROBABLE CAUSES FOR GENDER DIFFERENCE

Previous multiple studies demonstrated increased mortality and morbidity in women with STEMI. Possible reasons are discussed in the following text **(Fig. 1)**.

Age

In the United States, even though there was a decrease in MI events and related deaths in the past decade, there was no decrease in MI events and outcomes in young women.[4] Troubling trends of worse risk factor profiles and higher mortality among younger women compared with older women persist, with continuing reports of excess in-hospital, early, and late mortality compared with men.[13-20] But there are studies that state that this gender difference disappears once analysis is done with adjusted for age and cardiovascular risk profiles.[21-24] The VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young Acute Myocardial Infarction Patients) study was done in this young women population with AMI (15–55 years). The study found that these women had at least one cardiovascular risk factor but were not informed about the risk and not advised for risk modification.[25] Hence, attention should be paid to early detection and prevention which are essential for this young women population to decrease the morbidity and mortality rates due to AMI.

Racial and Ethical Disparities

Among all the ethnic groups, Black women have the highest risk for the prevalence of MI,[2,26-29] sudden cardiac death (SCD), and as the first manifestation of coronary heart disease (CHD).[29-31] Even their survival rate was one-third that of whites who presented after out-of-hospital arrest.[32] When compared to non-Hispanic white women, Asian Indian women have higher mortality from CHD (proportional mortality ratio, 1.12 vs. 0.92).[33-36] The CHD mortality rates increased in Asian Indians from 2003 to 2010 than in other ethnic groups.[37] According to Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study) registry, Asian Indians have a higher burden of cardiovascular risk factors, especially at a younger age.[38]

Cardiovascular Risk Factors

Women with STEMI tend to be older at presentation, with worse cardiovascular risk profiles, including higher rates of hypertension, diabetes, and dyslipidemia. Among women, a history of an MI or sudden death before the age of 55 years in a sister is more strongly associated with risk of MI than that in a brother or parent. Diabetes is a stronger risk factor for CAD in women than in men, with a three- to sevenfold higher CAD incidence and mortality compared to a two to threefold higher risk in men.[38,39] Obesity is a major risk factor for AMI in women and increases their risk almost threefold.[40] The prevalence of most risk factors is lower in rural than in urban India with exception of smoking/tobacco use (Tobacco Paradox).[41] In the

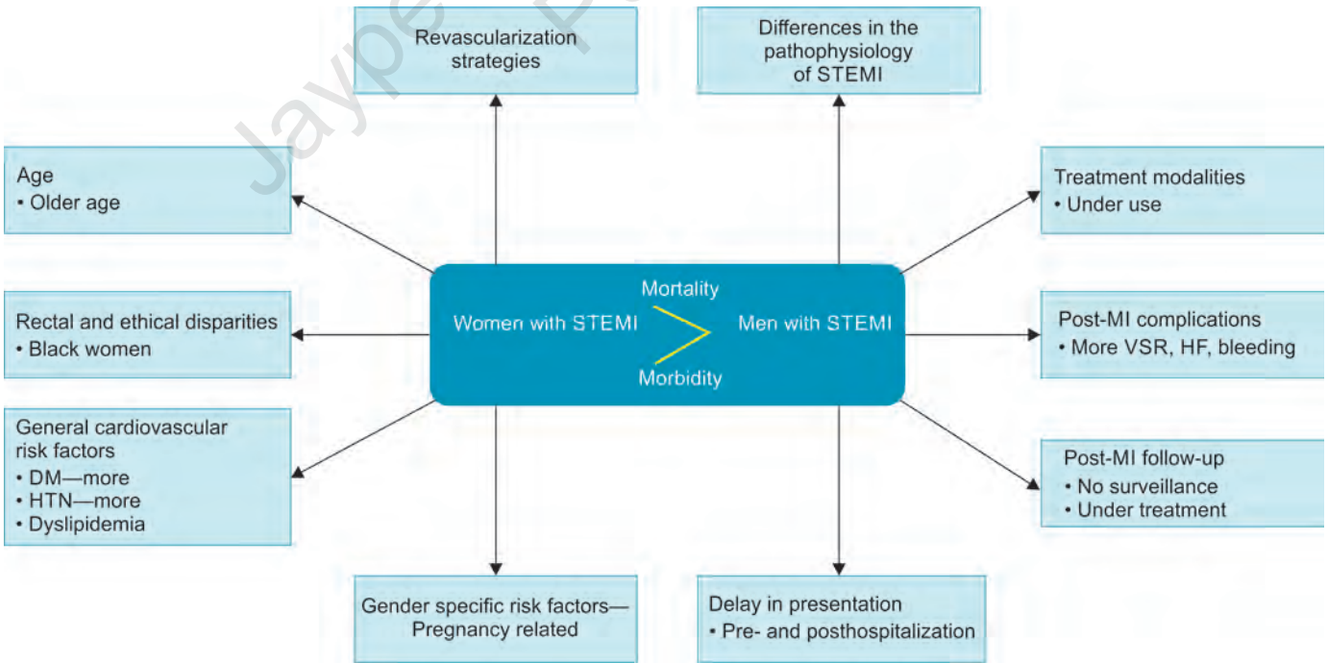

FIG. 1: Probable causes for gender difference.
(DM: diabetes mellitus; HF: heart failure; HTN: hypertension; MI: myocardial infarction; STEMI: ST-elevation myocardial infarction; VSR: ventricular septal rupture)

INTERHEART study, aggregate exposure to psychosocial risk factors, including depression, perceived home, work stress, low locus of control, and major life events, was significantly associated with AMI in women, with an adjusted odds ratio of 3.5.[42] Intense grief over the loss of a significant person may trigger the acute onset of MI.[43]

Delay in Presentation

Prehospital median delay times in seeking treatment for symptoms of AMI have ranged from 1.4 to 53.7 hours.[44,45] However, majority of studies suggest that the median delay ranges from 2 to 5 hours,[46] exceeding AHA recommendations by hours, not minutes.

Revascularization Strategies

Thrombolytic therapy, especially when administered early, reduces mortality regardless of sex and age.[47] In the recent American College of Cardiology (ACC)/AHA STEMI guidelines, thrombolytic therapy is recommended in patients without contraindications who present to a non-PCI-capable hospital, and there is an anticipated delay in performing PCI within 120 minutes of first medical contact (class I, level of evidence A);[48] however, there are no sex-specific recommendations.

Although there have been increases in PCI rates for STEMI and hospitals providing STEMI-related PCI in the United States,[49] sex differences in reperfusion management persist. The Nationwide Inpatient Sample Database study of young adults (age < 60 years) with STEMI from 2004 to 2011 in the United States found that young women with STEMI were less likely to undergo coronary angiography, were less likely to receive revascularization, and experienced more delays in reperfusion than young men; these differences remained despite adjustment for sociodemographics, comorbidities, and clinical factors.[50] More recently, the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With The Guidelines demonstrated that from 2008 to 2014, contact-to-device time remained longer in women than men, and longer reperfusion time was associated with increased mortality for both women and men.[51] This is consistent with the VIRGO analysis, which found that short-term and long-term mortality rates were higher in young patients who exceeded the recommended reperfusion goals (particularly for the PCI transfer patients) compared with patients who met the recommended perfusion guidelines.[52]

Sex Differences in the Pathophysiology of STEMI

Compared with men, women are less likely to have a culprit lesion identified at the time of angiography and more likely to have nonobstructive CAD.[53,54] Myocardial infarction with nonobstructive coronary arteries (MINOCA) is more common in women than men and is associated with a 4.7% all-cause mortality at 1 year.[6,55] Mechanisms of MINOCA include plaque rupture, plaque ulceration, coronary vasospasm, embolism, spontaneous coronary artery dissection (SCAD), and Takotsubo cardiomyopathy.[55] There are currently no national guidelines for the diagnosis and management of MINOCA. The VIRGO investigators found that approximately one in eight young women with AMI are unclassified by the Universal Definition of MI and proposed a new taxonomy for AMI to better phenotype patients and to ultimately determine optimal treatment strategies. The AHA scientific statement on AMI in women also recognized this knowledge gap and recommended sex-specific examination of coronary pathophysiology and optimal diagnostic strategies to close the gap in sex disparities.[6] SCAD has been discussed in the following text.

FALLACIES AND CONTROVERSIES ABOUT STEMI IN WOMEN

One may hypothesize that women should actually have lower STEMI mortality than men because TIMI flow pre PCI is higher in women and because peak cardiac enzymes are lower in women compared with men. In addition, in a study of patients who underwent reperfusion with primary PCI post-STEMI and cardiac magnetic resonance imaging, higher myocardial salvage, smaller percent infarct size, and microvascular damage were observed in women compared with men, suggesting sex-based differences in myocardial response to ischemic injury and reperfusion, possibly due to ischemic preconditioning.[56-60] However, a recent pooled analysis of patients with STEMI demonstrated that percent infarct size does not appear to contribute to long-term prognosis in women versus men after STEMI.[61]

TREATMENT OF ACUTE MYOCARDIAL INFARCTION IN WOMEN

For patients presenting with possible ACS, electrocardiography should be performed immediately (within 10 minutes of presentation) and can distinguish between STEMI and non-ST-segment elevation ACS (NSTE-ACS). STEMI is caused by complete coronary artery occlusion and accounts for approximately 30% of ACS. When electrocardiography suggests STEMI, rapid reperfusion with primary PCI within 120 minutes reduces mortality from 9% to 7%. If PCI within 120 minutes is not possible, fibrinolytic therapy with alteplase, reteplase, or tenecteplase at full dose should be administered to patients younger than 75 years of age without contraindications and at half dose to patients 75 years or older (or streptokinase at full dose if cost is a consideration), followed by transfer to a facility with the goal of PCI within the next 24 hours. High-sensitivity troponin measurements are the preferred test to evaluate for non-ST-elevation myocardial infarction (NSTEMI).[1]

TREATMENT OF ACUTE MYOCARDIAL INFARCTION IN WOMEN: OUTCOMES AND GUIDELINE-BASED RECOMMENDATIONS

STEMI Reperfusion Strategies

Thrombolytics

- Higher risk of mortality and bleeding complications compared with PCI

- Use at non-PCI-capable hospitals when a significant delay to performing primary PCI within 120 minutes of first medical contact is anticipated[48]
- No sex-specific recommendations for utility of agents.

Percutaneous Coronary Intervention

- Primary PCI has a lower 30-day mortality compared with thrombolytics.
- Reduced risk of intracranial bleeding compared with thrombolytics but still high risk of vascular complications.
- Decreased major adverse cardiac events (MACEs) and target vessel revascularization with stenting compared with angioplasty.
- PCI is the preferred reperfusion strategy compared with thrombolytics,[48] but there are no sex-specific recommendations.

Coronary Artery Bypass Graft

- Women have an increased risk of in-hospital mortality compared with men.
- No sex-specific data or recommendations on utility

Medical Management

- Reduced risk of recurrent ischemic events with aspirin
- Reduced risk of thrombotic complications with antithrombotic agents
- Increased bleeding risks in women with antiplatelet and antithrombotic agents; careful attention should be given to weight and renal calculation of doses when indicated.[62]
- Women with NSTEMI should be managed with the same pharmacological therapy [aspirin, P2Y12 receptor inhibitors, anticoagulants, statins, β-blockers, and angiotensin-converting enzyme (ACE) inhibitors] as men in the acute setting and for secondary prevention.[62]
- No sex-specific recommendations for STEMI patients

Aggressive Behavioral Interventions

- Smoking cessation[48,62,63]
- Referral to a comprehensive cardiac rehabilitation (CR) program that includes education on lifestyle and stress management, appropriate weight maintenance, dietary changes, and physical activity[48,62]

The 2014 ACC/AHA NSTEMI guidelines recommend that women with NSTEMI be treated with the same pharmacological agents as those used in men for both acute care and secondary prevention of MI.[62] This is a class I, level of evidence B recommendation that also recommends consideration of weight and renal dosing of antiplatelet and anticoagulant agents because of the higher bleeding risks in women.[64-67] Despite this evidence for efficacy, observational studies show consistent underutilization of these guideline-recommended therapies among women compared with men with AMI.[68,69] Women with nonobstructive CAD and MI are less likely to be prescribed medications for secondary prevention of MI (including antiplatelet agents and statins),[70] and these women have increased rates of readmission, reinfarction, and death in the first year after MI.[71-73] Equally important for women after AMI is the discontinuation of harmful drugs or drugs that are of no benefit. Hormone therapy with estrogen plus progestin or estrogen alone should not be given de novo to postmenopausal women after AMI for secondary prevention of coronary events. Furthermore, postmenopausal women who are already taking estrogen plus progestin or estrogen alone at the time of their MI, in general, should discontinue taking these agents.

POSTMYOCARDIAL INFARCTION COMPLICATIONS

Bleeding

Data from 24,045 patients of the GRACE (Global Registry of Acute Coronary Events) trial indicated that women versus men had a 43% increased risk of bleeding during hospitalization; the risk appears to be even higher in the setting of STEMI (odds ratio 1.71). Women undergoing PCI also showed a significantly higher incidence of in-hospital major bleeding, including access-related complications, compared with men. This increased bleeding risk appears to be related at least in part to inappropriate dosing of antithrombotic therapies.[74] In these analyses, women had a higher risk for bleeding with antithrombotic therapy independent of age, weight, baseline blood pressure, renal function, baseline hematocrit, and other potential confounders. The Study of Access Site for Enhancement of PCI for Women (SAFE-PCI) was the first randomized trial of specific PCI access strategies that were exclusive to women only. The trial demonstrated reductions in bleeding or vascular complications with the radial access approach in women undergoing elective or urgent cardiac catheterization.

Cardiogenic Shock

Women are at an increased risk of developing cardiogenic shock (CS) in the setting of AMI despite presenting with less extensive CAD and smaller infarct size.[75-78] Patient factors that may contribute to the increased prevalence of CS in women with MI include older age, higher rates of diabetes mellitus (DM) and hypertension, and higher incidence of underlying HF.[79-83] According to a study done by Elgendy, women with AMI with CS were less likely to receive guideline-recommended care, including revascularization, and had worse in-hospital outcomes than men. At 1 year, there were no sex differences in the risk of mortality.[84]

Heart Failure

Women are more likely to develop symptoms of HF in the setting of AMI. Several studies have identified that women have a higher Killip class at presentation for AMI.[85] This may be related to higher rates of underlying hypertension, DM, and HF or may be due to longer delay in presentation to the hospital.

Mechanical Complications

Women are at increased risk of developing acute severe mitral regurgitation after AMI.[86] Women, older patients, and nonsmokers are at increased risk of ventricular septal rupture after AMI.[87,88] Left ventricular free wall rupture and tamponade

are more common in women after AMI.[89-91] Older age, anterior AMI, and delayed thrombolysis are additional risk factors.[89,90,92]

Arrhythmias

Women and men appear to be at similar risk for the development of ventricular arrhythmias after AMI.[93]

Subgroup (Age) of Women with STEMI

- *Young women*: This has been discussed under the heading "Age" earlier in the text.
- *During pregnancy and postpartum period*: AMI during pregnancy and postpartum period carries higher mortality when compared to nonpregnant women. There are specific conditions to be considered for AMI causes during this period.
    - *Spontaneous coronary artery dissection*: SCAD is a very rare cause of AMI that occurs more frequently in women and should be suspected in any young woman who presents with an ACS without typical atherosclerotic risk factors.[56] The true prevalence of SCAD is unknown, but available data suggest a prevalence of 0.2–4% of patients undergoing cardiac catheterization, and it is reported to occur in 10.8% of women. In contrast to atherosclerotic AMI, conservative therapy is considered preferable in the acute management of SCAD if clinically possible. Isogai et al. in their study by multivariable logistic regression analysis demonstrated that anterior STEMI, inferior STEMI, and CS were strongly associated with revascularization. Other factors associated with revascularization were DM, dyslipidemia, smoking, renal failure, and pregnancy/delivery-related conditions, whereas known fibromuscular dysplasia and admission to teaching hospitals were associated with conservative therapy. Propensity-score matched analyses (546 pairs) found no significant difference in in-hospital death, 30-day readmission, and recurrent AMI between the groups.[94]
- *Older women*: According to Udell et al.'s study, preexisting frailty in an older patient with AMI had worse in-hospital and long-term cardiovascular outcomes. Frail patients were older, more frequently female, of non-white race and/or ethnicity, and less likely to be treated with guideline-recommended therapies. Increasing severity of frailty by this scale was associated with a step-wise higher risk for in-hospital mortality (p-trend < 0.001).[95]

STUDIES

The clinical presentation of MI in women varies from mild chest discomfort to severe unstable angina. Primary angioplasty is the gold standard treatment for such patients. Data about gender as an independent prognostic factor for death is conflicting. Women usually present at a later age with atypical symptoms and have higher rates of comorbidity, which translate to a worse prognosis post-ACS than men. As this study is based on experience at single center, various biases may be possible.[96]

According to Cenko et al.'s observational study, a disproportionate burden of coronary risk factors and comorbidities is a clear feature of younger women with STEMI but does not account for age-dependent difference in mortality. Younger age was associated with higher 30-day mortality rates in women even after adjustment for medications, primary PCI, and other coexisting comorbidities, but this difference declined after the age of 60 years and was no longer observed in older women. Sex-related pathophysiological differences may contribute to the higher mortality rates in younger women compared with men of the same age category.[97]

A study conducted by Ghaffari et al. in 1,017 patients with STEMI, showed in a center with low rate of primary PCI, crude rates of HF and in-hospital mortality are higher in females; however, the association is lost after adjustment for baseline characteristics.[98] As per the recent PACMAN-AMI randomized clinical trial, among patients with AMI, the addition of subcutaneous biweekly alirocumab, compared with placebo, to high-intensity statin therapy resulted in significantly greater coronary plaque regression in non-infarct-related arteries after 52 weeks.[99]

GAPS IN KNOWLEDGE AND REQUIRED FIELDS OF RESEARCH IN WOMEN WITH STEMI

There are many gaps in knowledge regarding AMI in women, and research should concentrate on the following points **(Fig. 2)**.

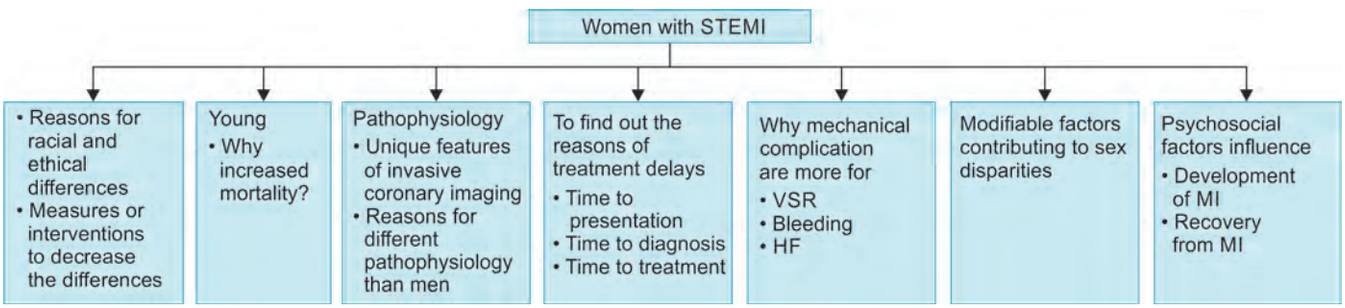

FIG. 2: Fields where research is to be focused.
(HF: heart failure; MI: myocardial infarction; STEMI: ST-elevation myocardial infarction; VSR: ventricular septal rupture)

MEASURES TO IMPROVE THE DISPARITY

In order to decrease this gender disparity, the diagnosis to treatment AMI in women requires special attention **(Fig. 3)**.

CONCLUSION

Cardiovascular disease is an equal-opportunity killer, and since 1984 the mortality burden has been higher in women than men, but a significant decline has occurred since 2000. This dramatic decline may be the result of the application of evidence-based therapies and education to improve the public and medical communities' awareness of heart disease in women. This is encouraging, but there remains an excess in mortality in women that is multifactorial. This document reviews the different factors plausibly responsible in the setting of an AMI. Sex differences occur in the pathophysiology and clinical presentation of MI and affect treatment delays. Recommended perfusion therapies for AMI in women are similar to those in men, yet bleeding risks and other complications remain greater in women. Women are undertreated with guideline-based recommendations, leading to worse outcomes and increased rates of readmission, reinfarction, and deaths in the first year after MI. CR is underused and underprescribed for women, but novel approaches to increase participation by women are promising. To further compound undertreatment, women's adherence to these evidence-based recommendations is suboptimal. There is a need for continued public health messages and interventions to target racial and ethnic minority women, given the burden of risk factors and continued disparity in outcomes. Multidisciplinary research teams are urged to examine innovative secondary prevention models of care that are age appropriate, culturally sensitive, and personalized to women's psychosocial and physiological characteristics. Each year, an estimated more than 7 million people are diagnosed with ACS worldwide. For patients with STEMI, coronary catheterization and PCI within 2 hours of presentation reduce mortality, with fibrinolytic therapy reserved for patients without access to immediate PCI.[1]

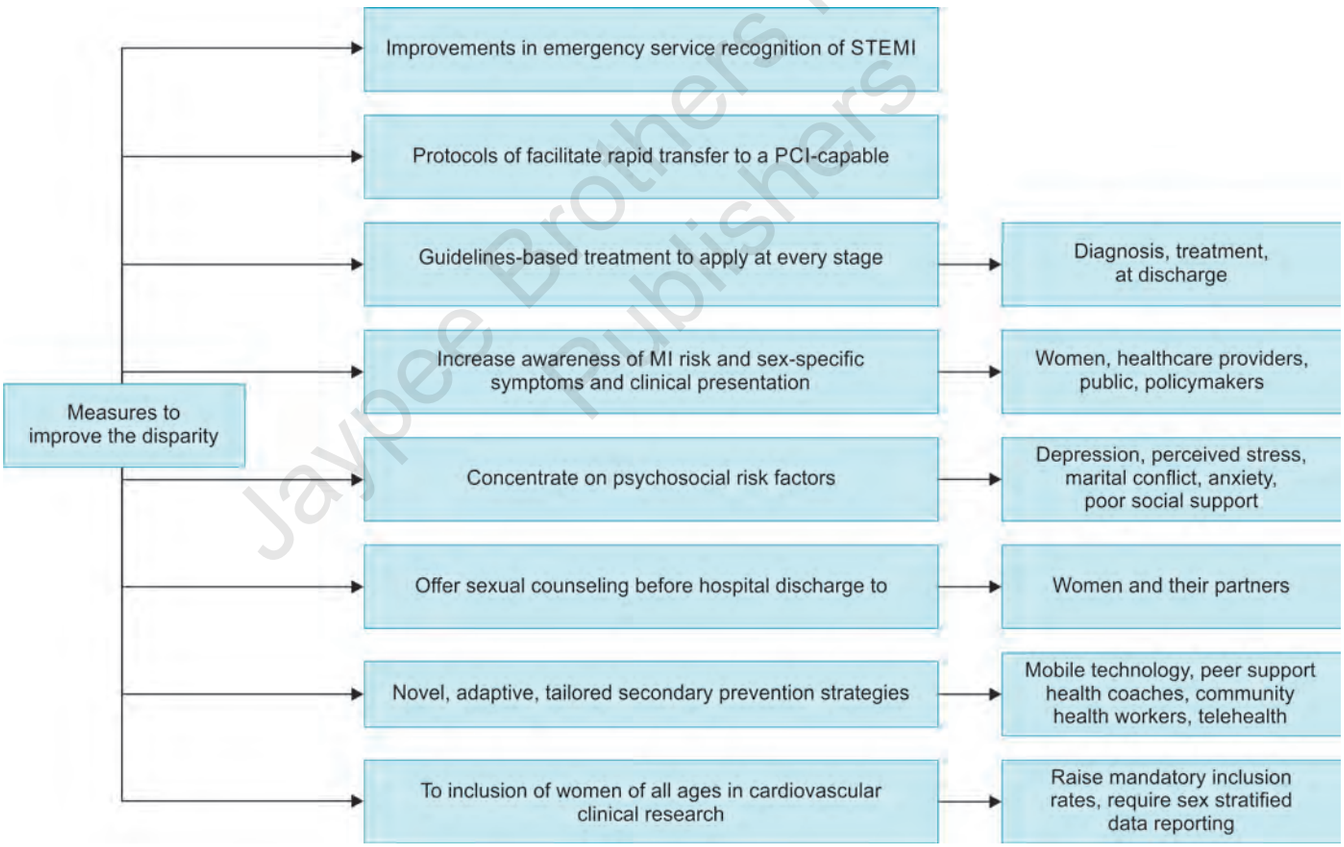

FIG. 3: Proposed methods to decrease the gender disparity in ST-elevation myocardial infarction (STEMI) patients.
(MI: myocardial infarction; PCI: percutaneous coronary intervention)

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CHAPTER 62

An Approach to STEMI: Late Presenters

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ABSTRACT

Patients presenting late (12–48 hours) after ST-elevation myocardial infarction (STEMI) constitute a significant proportion of patients, particularly in low-and-middle-income countries (LMICs). Efforts must be made to reduce delays and ensure early reperfusion in these patients to maximize myocardial salvage. Unstable late presenters should have immediate revascularization, preferably via percutaneous coronary intervention (PCI). Stable late presenters should be stratified to those with viable infarct-related myocardium and undergo revascularization. Late presenters have increased complication rates and reduced thrombolysis in myocardial infarction (TIMI)-III flow rates during PCI. The long-term consequences of large infarcts and left ventricular (LV) dysfunction should be anticipated in these patients and proactively dealt with.

INTRODUCTION

The time window for reperfusion therapy in ST-elevation myocardial infarction (STEMI) is based on the current understanding of the benefits of thrombolytic therapy.[1,2] These studies presuppose that arterial occlusion results in complete necrosis of the perfused myocardium. However, multiple factors can modulate myocardial necrosis including collaterals, preconditioning, and metabolic status of the perfused myocardium.[3] Furthermore, recent registry data has shown that a significant percentage of late presenters have patent culprit vessels.[4]

Contemporary studies and guidelines[5] have defined "late presenters" as patients with STEMI who present beyond 12 hours of the onset of symptoms but not later than 48 hours.[4,6] Developed countries with mature STEMI networks have shown a progressively smaller number of late presenters and these currently constitute <15% of the total STEMI patients.[6,7] Low-and-middle-income countries (LMICs), most of which do not have STEMI networks, see a much larger percentage of late presenters. In India and other LMICs, this could constitute up to 50% of the patients.[8-10] Patients presenting to rural clinics and hospitals without reperfusion capability are likely to suffer further delays before they are transferred to appropriate reperfusion-capable hospitals. Appropriate management strategies and treatment pathways for these patients are imperative. With improvement in access to reperfusion centers and the development of STEMI networks, it is hoped that these numbers will progressively come down and early reperfusion will be the norm in patients with STEMI.

CURRENT GUIDELINES

Guidelines for Thrombolysis in Late Presenters

According to the 2013 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines,[11] in a nonpercutaneous coronary intervention (PCI)-capable facility (where delay from door to transfer to the balloon is >120 minutes), patients with early presentation (<12 hours) should be treated with fibrinolytic [class I, level of evidence (LOE) A].

In latecomers (12–24 hours) with evidence of ongoing ischemia, hemodynamic instability, or those with a large area of myocardium at risk, fibrinolytics are reasonable (class IIa, LOE C).

After administration of thrombolytic therapy, patients should be transferred to a PCI-capable facility.

There is no indication for thrombolysis in asymptomatic latecomers or patients with very late presentation beyond 24 hours from symptom onset.

The European Society of Cardiology (ESC) 2017 guidelines[5] are similar. It emphasizes the maximum benefit of early lytic therapy (<2 hours) and routine transfer of patients for coronary angiography within 2–24 hours of lysis.

Guidelines for Percutaneous Coronary Intervention in Late Presenters

According to the 2013 ACC/AHA guidelines,[11] in a PCI-capable facility, all patients with a STEMI and ischemic symptoms of less than 12 hours from presentation should undergo PCI (class I, LOE A). Latecomers (12–24 hours) with evidence of ongoing ischemia (symptomatic) are to be considered for PCI (class IIa, LOE B). If the patient is in cardiogenic shock, PCI is recommended regardless of the time of symptoms onset (class I, LOE B).

Delayed PCI (>24 hours) in asymptomatic stable patients with one or two diseased vessels and an occluded infarct artery without evidence of ischemia should not be performed because of the risk of harm (class III, LOE B).

The 2017 ESC guidelines[5] recommend PCI in late-presenting patients (>12 hours) with signs or symptoms of ischemia, hemodynamic instability, or life-threatening arrhythmias (class I, LOE C). In patients presenting days later, if symptoms are recurrent or silent ischemia is documented (on stress testing), revascularization may be considered.

The main difference with the ACC/AHA guidelines is that the European guidelines suggest consideration of routine primary PCI in late presenters (12–48 hours) (class IIa, LOE B). These are based on two studies that showed there will be a benefit in late revascularization.[12]

Reasons for Delayed Presentation

"Nonsystem delays" is the delay between symptom onset and call for transport. This delay is multifactorial. The first and foremost is the patient's recognition of symptoms due to myocardial infarction (MI) and thereby delay in seeking care because their symptoms differ from their preexisting bias that a heart attack presents dramatically with severe, crushing chest pain. Approximately one-third of patients with MI experience symptoms other than chest pain, especially women and the elderly. Other reasons for a delay in seeking treatment include inappropriate reasoning that symptoms will be self-limited or are not serious and attributing the symptoms to other preexisting conditions, reluctance to trouble others unless "really sick" or fear of embarrassment should symptoms turn out to be a "false alarm," lack of knowledge of the importance of early reperfusion therapies; and attempted self-treatment with prescription and/or nonprescription medications.

To avoid such delays, healthcare providers could develop public education programs. Family members and close friends should be enlisted as reinforcement for rapid action when the patient experiences symptoms of possible STEMI, particularly in patients with preexisting risk factors.

Lack of developed "STEMI networks" results in patients self-transporting themselves and presenting at hospitals that do not have reperfusion capability. Door-in to door-out (DIDO) time is a new reperfusion performance measure for patients with STEMI who require interhospital transfer for primary PCI. A recent study[13] showed that patients with a DIDO time of 30 minutes or less are more likely to achieve an overall door-to-balloon time of less than 90 minutes and are associated with lower risk-adjusted mortality compared with patients who had a DIDO time more than 30 minutes, thus affirming the importance of DIDO time as a metric for reperfusion quality.

Strategies to Reduce Delayed Presentation

Public education has to be the cornerstone of any attempt to reduce total ischemia time. There have been some studies that have looked at reducing time delays with public education campaigns, however, with limited success.[14,15] A more targeted approach to sensitizing patients in noncommunicable disease (NCD) clinics or those with documented coronary risk factors may yield better results. Utilizing occasions such as World Heart Day to run isolated public education programs may not be adequate. Sustained periodic print, television, radio, and social media campaigns are necessary to make an impact.

Ambulance services with electrocardiogram (ECG) machines and paramedics trained to take ECG and deliver emergency care are critical to any STEMI network. It is also critically important in fostering confidence among the general population to call the ambulance service rather than self-transport themselves to a hospital, which is the predominant current practice. This is a major lacuna in all the current ambulance services.

Tele-electrocardiogram

Studies have shown that prehospital transmission (PHT) significantly reduces reperfusion times.[16] One of the major barriers to starting lytic therapy in smaller hospitals is the delay in ECG confirmation of STEMI. Even in situations where an ECG is done on arrival, lytic therapy is often further delayed until STEMI confirmation by a senior physician who may not be available on-site. Tele-ECG services can obviate this problem.

Pre-hospital (Pre-CCU) Thrombolysis

Very early thrombolysis is an effective strategy for reperfusion. The ambulance could, as in the French "Samu" system include a physician to administer the lytic within the ambulance, with results shown in the FAST-MI to be comparable to primary PCI.[17] Furthermore, prehospital thrombolysis is also associated with a four-fold increase of aborted MI compared with in-hospital treatment.[12]

Designating hospitals as "Heart Attack Ready" hospitals is crucial to ensuring that patients with STEMI do not present to hospitals that do not have reperfusion capability, and the resultant DIDO delay does not contribute to mortality. These designated hospitals should have periodic training and audit to ensure that the protocols are being followed and the critical time intervals maintained.

Finally, developing a STEMI system of care is imperative so that patients have quick access, standardized care, periodic audit, gap analysis, and quality improvement measures. The STEMI India models, appropriate for the manpower and infrastructure availability, can be the solution.[18]

Benefits of Late Reperfusion

Where the exact time of onset of arterial occlusion is unclear or in a "stuttering infarct," the benefit of reperfusion therapy may still be present. However, primary PCI would likely be superior to lytic therapy.

Myocardial salvage has time-independent benefits and could manifest with late reperfusion. Coronary artery occlusion, particularly STEMI, involves both partial occlusion and recanalization. Furthermore, the presence of collateral circulation and ischemic preconditioning will postpone the formation of the necrotic myocardium.[19]

The concept that a patent infarct-related artery (IRA) and myocardial reperfusion confer a benefit beyond that resulting from myocardial salvage has given rise to the "open-artery hypothesis." Possible mechanisms for this benefit include improved infarct healing, and limitation of ventricular remodeling decreased ventricular arrhythmias and reperfusion of hibernating or stunned myocardium. It is postulated that infarct expansion is attenuated by late reperfusion, a process associated with inhibition of collagen breakdown, an intense early inflammatory response, and accelerated scar formation.[20,21]

In an imaging-based study by Busk et al.[22] STEMI patients were evaluated for final infarct size (FIS) and myocardial salvage in early presenters (<12 hours) versus late presenters (12–72 hours) undergoing primary angioplasty in the IRA. Myocardial perfusion imaging (MPI) was performed to assess the area at risk before angioplasty and repeated after 30 days. The percentage area salvaged by PCI was 53% in late presenters versus 66% in early presenters. Salvaged area was 44% even in occluded IRA versus 71% in open IRA. This implies that final myocardial salvage might be obtained beyond the 12 hours limit, even when the IRA is occluded.

Trials of Late Reperfusion

The efficacy of thrombolytic agents is time-dependent and in the pivotal LATE (Late Assessment of Thrombolytic Efficacy) study[23] and the EMERAS (Estudio Multicentrico Estreptoquinasa Republicas de America del Sur) study,[24] thrombolysis showed no benefit in patients when administered beyond 12 hours after symptom onset. Delayed reperfusion is, therefore currently, almost exclusively dealt with by PCI.

Trials of late reperfusion are a heterogeneous group since the studies tested reperfusion therapy at different timelines beyond 12 hours after symptom onset. Some of the important trials are listed below.

BRAVE-2 Trial

The BRAVE-2 (Beyond 12 Hours Reperfusion Alternative Evaluation) trial aimed to evaluate treatment with PCI in patients with STEMI presenting later than 12 hours after symptom onset but without persistent chest pain. This international multicenter open-label randomized controlled trial included 365 patients admitted between 12 and 48 hours after symptom onset.[6] Treatment with an invasive strategy was associated with a reduction in infarct size at 5–10 days compared to a conservative strategy. However, there was no difference in the 30-day clinical composite primary endpoints.

Nepper-Christensen et al.[25]

The study evaluated the effect of primary PCI in STEMI patients with signs of ongoing ischemia presenting 12–72 hours after symptom onset compared with STEMI patients presenting less than 12 hours after symptom onset. STEMI patients with signs of ongoing ischemia treated with primary PCI 12–72 hours after symptom onset had less myocardial salvage and developed larger infarcts. However, a large proportion achieved substantial myocardial salvage indicating some benefit from primary PCI in late-presenting patients.

STOPAMI-3[26]

STOPAMI-3 (Stent or Percutaneous Transluminal Coronary Angioplasty for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Ineligible for Thrombolysis) trial is another randomized, open-label trial that included 611 patients with acute myocardial infarction (AMI) who were ineligible for thrombolysis (lack of ST-segment elevation on the ECG, late presentation >12 hours after symptom onset, and contraindications to thrombolysis) and randomized to percutaneous old balloon angioplasty (POBA) versus stenting. There was no difference in myocardial salvage index by treatment with stent versus POBA though there was a high crossover rate from POBA to stenting (30%). The overall salvage index was substantial in both groups, indicating the benefit of primary PCI even after 12 hours of presentation.

Occluded Artery Trial[27]

The OAT (Occluded Artery Trial) tested the strategy of routine PCI for total occlusion of the IRA 3–28 days after AMI whether it would reduce the occurrence of a composite endpoint. Patients were assigned to routine PCI and stenting with optimal medical therapy versus optimal medical therapy alone. PCI did not reduce the occurrence of death, reinfarction, or heart failure, and there was a trend toward excess reinfarction during 4 years of follow-up in stable patients with occlusion of the IRA 3–28 days after MI. The major drawback of this study is that the median time to revascularization was 8 days post-STEMI, and the exclusion criteria were very broad and so do not reflect the usual population with STEMI.

A meta-analysis of randomized trials on the value of PCI in patients presenting beyond 12 hours after AMI showed that PCI in these patients is associated with a more favorable pattern of left ventricular (LV) remodeling.[28]

Two important registries have looked at reperfusion in late presenters.

PL-ACS Observational Study[29]

The Polish Registry of Acute Coronary Syndrome (PL-ACS) aimed to investigate whether reperfusion by the primary PCI improves 12-month survival in late presenters with STEMI. 2,036 patients out of 23,517 STEMI patients enrolled in the study from June 2005 to August 2006, with STEMI presenting 12–24 hours from onset of symptoms, were included in the

analyses. An invasive approach was chosen for 910 (44.7%) late presenters. Patients with an invasive approach had lower mortality after 12 months than patients with a conservative approach (9.3% vs. 17.9%, $p < 0.0001$).

FAST-MI Program

Bouisset et al.[30] analyzed data from three nationwide observational studies, conducted as part of the FAST-MI program over 1 month in 2005, 2010, and 2015. The investigators assessed 1,169 latecomer STEMI patients (presenting between 12 and 48 hours from symptom onset) compared to the 5,104 early comers with STEMI. Thus, the investigators focused on the remaining 1,077 latecomers STEMI patients, divided into two groups according to whether they received PCI within 48 hours from admission (729) or not (348). All-cause mortality was significantly lower among revascularized patients compared with nonrevascularized patients after a median of 58 months of follow-up.

The results are the basis for the current European guidelines that recommend performing a PCI on STEMI patients up to 48 hours after the onset of chest pain.

MANAGEMENT ALGORITHM IN LATE PRESENTERS

Patients presenting late (12–48 hours) after a STEMI can be divided into those who are stable and those who are unstable.

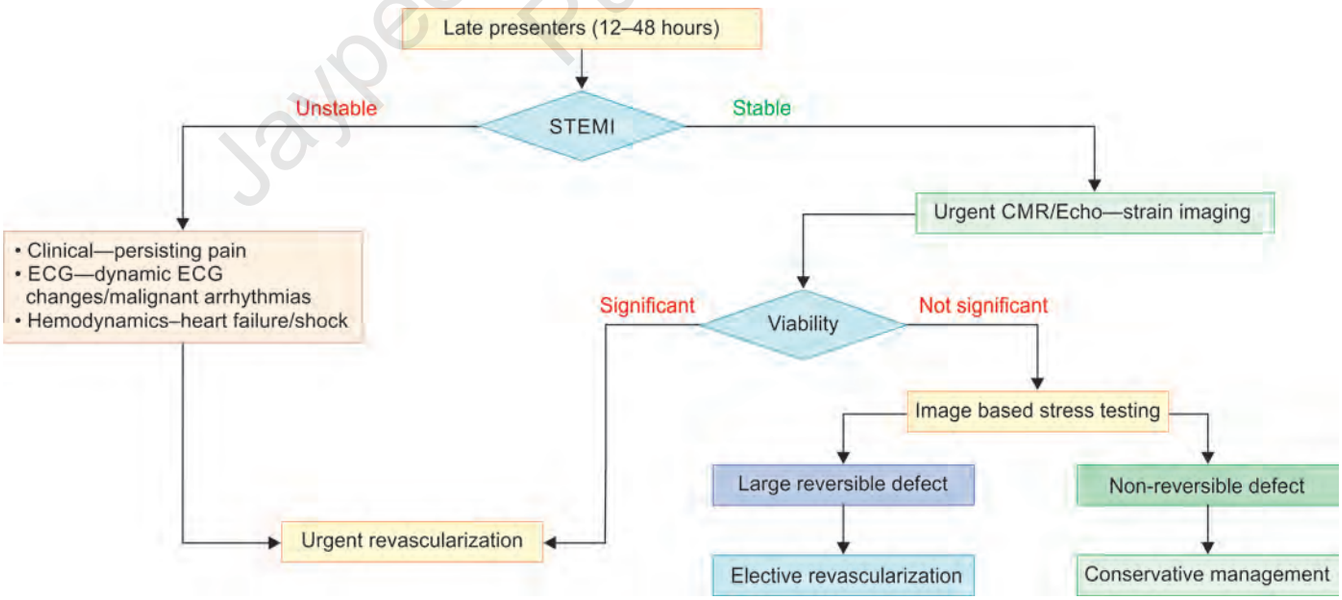
Unstable STEMI is based on clinical presentation and the ECG. Instability is defined as evidence of ongoing ischemia, ongoing, or recurrent pain with or without symptoms or signs of shock, heart failure, or malignant arrhythmias. All late presenters with unstable STEMI should undergo immediate cardiac catheterization and revascularization.

In stable patients, imaging can help to stratify patients quickly so that they can be moved from the emergency room to the imaging room and, if appropriate, moved to the catheterization laboratory for immediate reperfusion. Two modalities of imaging have recently been shown to quickly and reliably diagnose viable and recoverable myocardium in the infarcted territory.

Cardiac magnetic resonance (CMR) imaging mapping techniques reflect myocardial composition, with changes in relaxation times reflecting the pathological processes. These mapping techniques can characterize injured myocardium and their potential for recovery.[25,31] A recent study showed that in late presenters, there was a significant degree of salvageable myocardium 0.58 (0.39–0.71) with two-thirds of patients achieving a myocardial salvage index ≥ 0.5, highlighting the potential benefits of PCI in this group. Progress in the CMR technology and availability may eventually lead to CMR characterization as an ideal tool in stable late presenters to decide the place for immediate revascularization.

Myocardial deformation imaging by either tissue Doppler or speckle tracking 2D-strain has been used to accurately predict viability in ischemic LV dysfunction. There have been a few recent trials that have looked at viability in akinetic segments during STEMI using global longitudinal strain (GLS) and territorial longitudinal strain (TLS). The cutoff value that identified large MI was –13% for GLS, identified large infarct size, and the cutoff for viability with TLS was –9.6%.[32]

Stable late presenters in whom acute imaging is not possible should have ischemia-guided revascularization based on a nuclear stress test **(Flowchart 1)**.



FLOWCHART 1: Management algorithm for late presenters with ST-elevation myocardial infarction (STEMI).
(CMR: cardiac magnetic resonance; ECG: electrocardiogram)

COMPLICATIONS IN LATE PRESENTERS

Cardiogenic Shock

Cardiogenic shock after MI constitutes the most common cause of death after MI. It is caused by LV or right ventricular failure. Although uncommon, mechanical complications of STEMI increase significantly the in-hospital mortality to more than 40%. In the current era, it occurs in around 0.27–0.9% of patients with STEMI and is associated with higher rates of acute kidney injury, hemodialysis, a longer length of stay, and use of mechanical circulatory support in up to 50% of patients.[33] Late presentation and late revascularization were associated with a higher incidence of deleterious complications. Rupture of the LV free wall, rupture of the interventricular septum, and acute mitral regurgitation due to papillary muscle necrosis are three potentially lethal mechanical complications of AMI and are more common in late presenters. Evidence that thrombolysis in late presenters is a cause of myocardial rupture is inconclusive with conflicting studies.[34]

No-reflow

No-reflow is defined as inadequate coronary flow [thrombolysis in myocardial infarction (TIMI) grade ≤ 2] despite successful dilatation in the absence of dissection, thrombus, spasm, or high-grade residual stenosis at the original target lesion after the procedure. The mechanism of no-reflow after primary PCI in patients with STEMI is complex. The most common cause is a late presentation and organized thrombus dislodging into coronary microcirculation.[35]

Reperfusion Injury

Lethal reperfusion injury can occur during the restoration of blood flow to the damaged myocardium, which triggers further ischemic cellular damage and is most commonly seen in late presentation acute coronary syndromes.[36] This paradoxical effect is known as reperfusion injury and is due to a complex interaction between oxygen-free radicals and intracellular calcium, leading to acceleration of myocardial damage followed by death, microvascular dysfunction, and fatal arrhythmias.

Microvascular Obstruction

Microvascular obstruction (MVO) is also known as the "inability to revascularize a previously ischemic region." The major contributing factors include microembolization of friable material released from the atherosclerotic plaque, platelet microthrombi, the release of soluble vasomotor and thrombogenic substances, and neutrophil plugging. This manifests as sluggish coronary blood flow, and impaired myocardial blush grade most commonly during late than early presentation.[37] Other complications are stunned myocardium, resulting in brady or tachyarrhythmia and sudden cardiac death.

CONCLUSION

STEMI patients with signs of ongoing ischemia treated with primary PCI 12 to 72 hours after symptom onset have less myocardial salvage and develop larger infarcts. However, a large proportion can achieve substantial myocardial salvage indicating a benefit from primary PCI in late-presenting patients. Myocardial salvage and infarct size may in addition to duration of ischemia be affected by periprocedural events, such as distal embolization, no-reflow phenomenon, or lethal reperfusion injury. However, various trials indicate a benefit from primary PCI in those STEMI patients presenting ≥12 hours who have signs of ongoing ischemia.

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CHAPTER 63

Culprit Vessel or Multivessel PCI during PAMI: Which One to Adopt?

Dev B Pahlajani

ABSTRACT

Primary percutaneous coronary intervention (PPCI) is the treatment of choice in patients presenting with ST-segment elevation myocardial infarction (STEMI). In contemporary practice, among patients who present to the hospital with STEMI, around 40% and 65% have concurrent multivessel (MV) coronary artery disease (CAD), which is a combination of a thrombotic culprit lesion and one or more significant (50% or more diameter stenosis) nonculprit lesions on coronary angiography. Optimal management of these nonculprit lesions in this setting is still a matter of debate. On one hand where STEMI patients with MV CAD are at higher risk of recurrent cardiovascular events, PCI of bystander lesions during PPCI can be a harbinger of potential complications. Thus, the presence of MV CAD in STEMI patients often poses a therapeutic dilemma for interventional cardiologists. As the burden of cardiovascular disease affects hospital systems throughout the world, there is a growing interest to examine and improve the various treatment strategies involved in the management of STEMI with multivessel CAD.

INTRODUCTION

Percutaneous coronary intervention (PCI) of infarct-related coronary artery performed within recommended window period is considered as the standard of care for ST-elevation myocardial infarction (STEMI).[1] Multivessel disease defined as >50% diameter stenosis in at least one nonculprit artery is present in 40–50% of patients presenting with acute myocardial infarction (AMI) and it negatively affects the short- and long-term outcomes.

The optimum reperfusion strategy during primary angioplasty in myocardial infarction (PAMI) has been a matter of debate and subject of various randomized trials and registries **(Boxes 1 to 3)**.

One could perform:

- Only culprit vessel PCI during index procedure
- Perform complete revascularization during index procedure
- Perform culprit vessel PCI during index procedure and stage nonculprit vessel PCI during index hospitalization
- PCI of noninfarct artery after discharge from hospital

Decision to perform nonculprit vessel PCI could be based on evidence of ischemia either by symptoms or myocardial perfusion scan studies. Recently, several studies have highlighted the importance of fractional flow reserve (FFR) in evaluating the nonculprit vessel during hospital admission since FFR is a very reliable indicator of myocardial ischemia. Strategy of revascularization during PAMI could also depend on the hemodynamic status during presentation.

BOX 1 Risk factors for contrast nephropathy.

- Pre-existing renal impairment
- Congestive heart failure
- Mitral regurgitation
- Acute myocardial infarction
- Dehydration
- Gender (female > males)
- Diabetes (probably dependent on coexistent renal damage)
- Elderly
- Concurrent use of NSAIDs and other nephrotoxic drugs
- Widespread evidence of arterial disease
- Hypotension
- Hypoalbuminemia

(NSAIDs: nonsteroidal anti-inflammatory drugs)

PATIENTS WITHOUT CARDIOGENIC SHOCK

Conventional training and guidelines have recommended to perform culprit-only PCI during index procedure and decision to perform PCI for nonculprit vessel is often taken after demonstrating ischemia either by symptoms, nuclear studies, or FFR. However, some of the recent trials have reported better outcomes with complete revascularization. While European Society of Cardiology has given IIa for PCI of noninfarct artery as a staged procedure it also gives IIb to PCI during index procedure. American College of Cardiology/American Heart Association upgraded recommendation for noninfarct-related artery either at index procedure or staged PCI from class III to IIb.[1,2]

BOX 2 The case for performing multivessel PCI.

- Flow in non-IRA vessels is not normal and is worse in vessels with >50% stenosis
- Slow flow in the non-IRA is associated with reduced non-IRA territory wall thickening, which improves when flow returns to normal
- Enhanced function in the non-IRA territory confers a survival advantage
- Patients often have multiple complex plaques
- Coronary plaque instability can be a multifocal process
- Patients with MVD have higher event rates
- Treatment of additional unstable plaques may be beneficial
- May be crucial in patients with cardiogenic shock
- Simultaneous multivessel PCI may reduce vascular access and anticoagulant-related complications and reduce costs

(IRA: infarct-related artery; MVD: multivessel disease; PCI: percutaneous coronary intervention)

BOX 3 Costs and psychological factors.

- Multivessel PCI is more costly to the provider and the patient
- Psychological and logistic problems
- Staged PCI in the same hospital admission only attracts a single procedural cost

(PCI: percutaneous coronary intervention)

Preventive angioplasty in acute myocardial infarction (PRAMI) trial enrolled 465 patients with AMI and randomized them to undergo culprit versus complete revascularization—preventive PCI.[3] Among these, 234 patients were randomized to preventive PCI for nonculprit vessel and 231 to undergo culprit-only PCI. The primary endpoint was death from cardiac cause, nonfatal MI, or refractory angina. At 23 months, there was absolute risk reduction of 14% in cardiac death, nonfatal MI, or refractory angina in patients who underwent preventive PCI. There was no difference in all-cause mortality between two arms. The trial was prematurely terminated since the results were overwhelmingly in favor of preventive PCI. However, the trial was not designed to answer whether complete revascularization needs to be performed during index procedure or hospitalization.

In complete versus lesion-only primary PCI trial (CvLPRIT) 296 patients were randomized to culprit-only PCI (146 patients) versus complete revascularization (15 patients). Among complete revascularization arm 64% patients received nonculprit vessel PCI during index procedure, 36% were staged during index hospitalization. The primary endpoints were all-cause mortality, recurrent MI, heart failure, and ischemia driven revascularization. Major adverse cardiac events (MACE) were significantly lower in patients who received complete revascularization as compared to those who received culprit vessel PCI. Total MACE at 12 months' time occurred in 10% patients with complete revascularization versus 21% in culprit-only PCI group **(Fig. 1)**. The trial concluded that in most STEMI

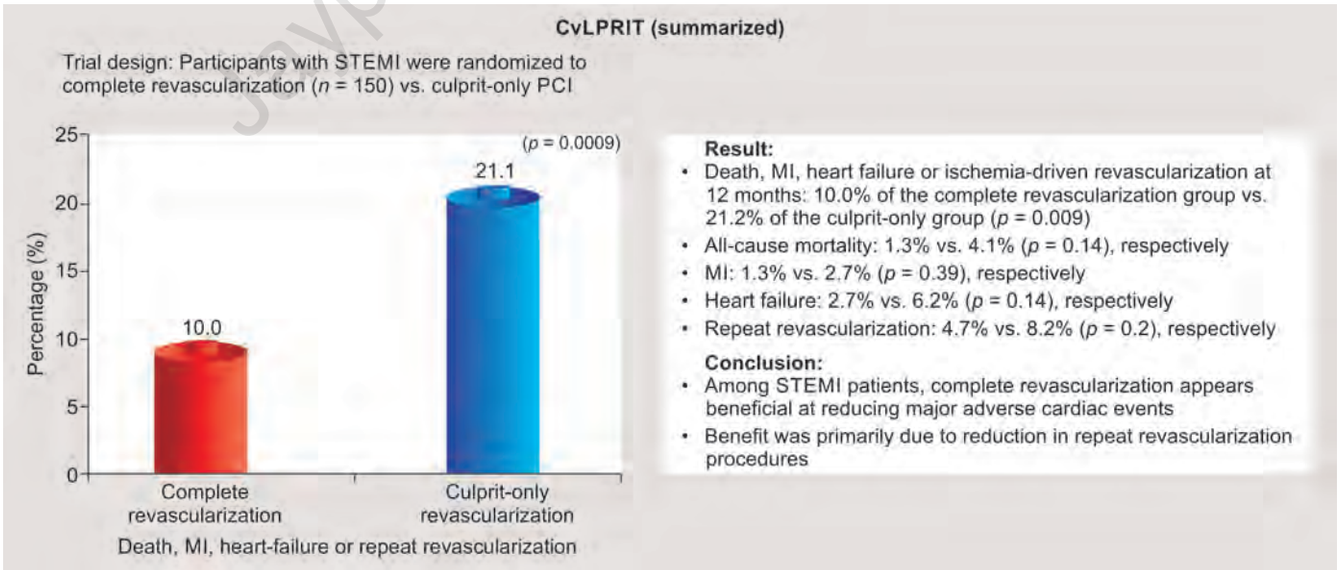

FIG 1: Complete versus Lesion-only PRimary PCI Trial - CvLPRIT (Summarized).

(MI: myocardial infarction; STEMI: ST-segment elevation myocardial infarction)

Source: Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol. 2015;65:963-72.

patients complete revascularization appears better as compared to culprit-only PCI. Benefit of complete revascularization was driven mainly by repeat revascularization.[4] However, both these trials did not use FFR during PCI of nonculprit vessel.

Subsequently, DANAMI-3 trialists planned their strategy based on the results of FFR for nonculprit artery.[5] The trial enrolled 627 patients and randomized 330 to culprit-only PCI versus 314 to FFR-guided complete revascularization. The primary endpoint was all-cause mortality, nonfatal MI, and ischemic driven revascularization. While all-cause death, nonfatal MI was not significantly different in two groups; complete revascularization patients had lower risk of ischemia driven revascularization (17% vs. 5%; $p = <0.001$).

In the DANAMI-3 PRIMULTI magnetic resonance study, the investigators studied the effect of culprit vessel PCI versus FFR-guided complete revascularization on infarct size, left ventricular (LV) function, and LV remodeling by cardiac magnetic resonance.[6] These patients were enrolled from the FFR-guided complete revascularization versus culprit-only PCI. FFR-guided complete revascularization in patients with multivessel disease did not affect final infarct size, LV function or remodeling as compared to culprit-only PCI.

While these recently conducted trials have shown the superiority of complete revascularization, the timing of achieving complete revascularization has not been clearly defined. Some of the recent studies have attempted to address this issue. Bilal Iqbal and coworkers published their data from British Columbia Cardiac Registry.[7]

They studied the outcome of culprit versus complete revascularization at index procedure versus staged complete revascularization in 6,503 patients. The authors concluded that at 30 day, 1 and 2 years mortality consistently was lowest in the culprit vessel intervention with staged PCI as compared to culprit only or complete revascularization at index procedure. At 2 years, the event rates were 9.1% for culprit only, 5.6% for staged complete revascularization, and 12.6% for complete revascularization at index procedure. A recent trial, COMPARE-ACUTE, addressed this issue by enrolling 885 patients with STEMI to see if FFR-guided PCI of nonculprit vessel could result in better outcomes.[8] Investigators enrolled 885 patients and randomized them in 2:1 fashion to FFR-guided complete revascularization. They assigned 295 patients to FFR-guided complete revascularization and 590 patients to culprit-only revascularization. Complete revascularization was performed in 83.4% during index procedure. At 12 months primary endpoint of all-cause mortality, nonfatal MI, any revascularization, and cerebrovascular accident were significantly lower in FFR-guided complete revascularization [23 vs. 121 hazard ratio (HR) 0.35 ($p < 0.001$)]. The benefit was mainly driven by reduced risk of repeat revascularization.

Recently, a meta-analysis of randomized controlled trials that compared the outcomes of multivessel intervention as staged versus complete revascularization at index procedure was studied by Nayan Agarwal et al.[9] The primary outcome was composite of death or MI. The meta-analysis included six randomized studies totaling 1,162 patients. At mean follow-up of 13 months patients who underwent staged multivessel PCI had better outcomes than that performed at index PCI. Composite of MI or death occurred in 7.2% in staged PCI versus 11.7% in index PCI respectively. All-cause mortality, cardiovascular mortality, and <30 days mortality were lower in staged versus index multivessel PCI. MACE, repeat MI, and repeat revascularization were similar in both the groups. The investigators concluded that as compared to multivessel PCI during index procedure, staged multivessel revascularization is associated with reduced mortality without an increase in repeat MI or repeat revascularization patients with STEMI.

Results of COMPLETE trial (complete vs. culprit-only revascularization to treat multivessel disease after early PCI for STEMI) that compared the outcomes of infarct-related artery (IRA) PCI versus complete revascularization have recently been published. The trial also compared the results of timing of staged PCI of nonculprit artery.[10,11] The trial enrolled 4,041 patients with STEMI undergoing PAMI with 70% disease in nonculprit vessel or 50–69% stenosis with FFR of <0.8. Their average age was 62 years and 19% had diabetes. Patients with prior coronary artery bypass graft surgery or those with prior intention of complete revascularization were excluded.

Complete enrolled patients from 140 centers from 31 countries. Patients were randomized to:

- Two thousand sixteen patients were randomized to complete revascularization either during index hospitalization (1,353 patients median 1 day) or within 45 days after discharge (663 patients median 23 days)
- Culprit-only PCI—2,025 patients
- Duration of follow-up was 3 years.
- Primary outcome of cardiovascular death or MI occurred in 7.8% in patients who underwent compete revascularization versus 10.5% in those in the infarct artery PCI group ($p = 0.004$)
- Secondary endpoint that was defined as cardiovascular death, MI, or ischemia driven revascularization, which occurred in 8.9% in the complete revascularization group versus 16.7% in infarct artery PCI group ($p = 0.001$).
- Major bleeding was not significantly different in two groups (2.9% in complete and 2.2% in IRA PCI).
- Contrast-induced kidney injury was 1.5% with complete and 0.9% in IRA PCI ($p = 0.11$)

The trial concluded that complete revascularization was superior to IRA PCI only irrespective of the investigator determined timing of nonculprit lesion intervention.

STEMI WITH COMPROMISED HEMODYNAMICS AND CARDIOGENIC SHOCK

Acute myocardial infarction complicated by cardiogenic shock is a serious medical condition encountered in approximately 10% of patients and is associated with about 80% mortality. Conventional treatment of STEMI presenting with cardiogenic shock has been to perform complete revascularization.[1] This has been based on certain observational studies. It has been argued that complete revascularization will result in overall improvement in the blood supply to all myocardial segments and result in improved LV function. However, recently 30 days and 1-year follow-up data from CULPRIT-SHOCK trial is available.[11] It randomized 706 patients to immediate complete or culprit-only revascularization with hypothesis that culprit only is superior to complete revascularization in STEMI or

BOX 4 The case against performing multivessel PCI.

- Every PCI for every lesion carries a finite risk
- Nonculprit lesion severity is often exaggerated during AMI
- State of vasoconstriction
- Enhanced thrombotic and inflammatory state persists for some time after an AMI
- Longer more complex procedures (contrast nephropathy, hemodynamic instability)
- Additional time, more radiation exposure
- Additional cost of the index procedure
- Benefits not proven

(PCI: percutaneous coronary intervention)

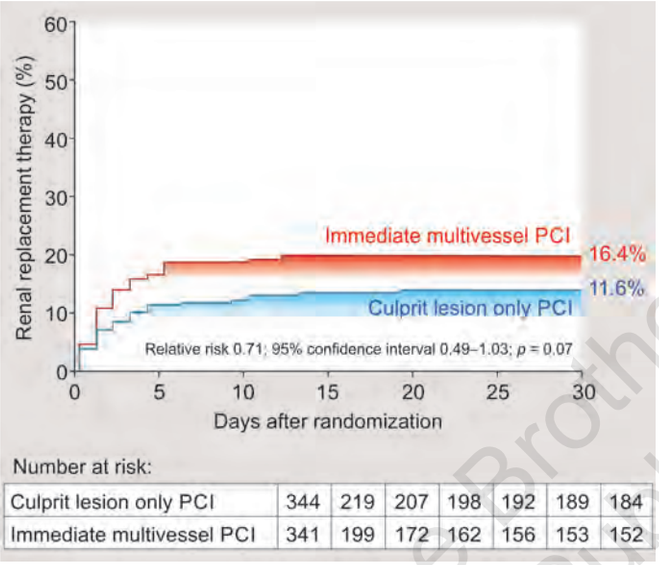

FIG. 2: Renal replacement therapy.
(PCI: percutaneous coronary intervention)
Source: Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, et al. PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock. N Engl J Med. 2017;377:2419-32.

NSTEMI with cardiogenic shock. It was a multicentral trial and patients were randomly assigned to either PCI of culprit lesions only or immediate multivessel PCI. Culprit-only patients were encouraged to undergo ischemia-guided staged PCI of nonculprit arteries. The primary endpoint was composite of death, severe renal failure leading to renal replacement therapy **(Box 4)**. The safety endpoints were stroke at 30 days. At 30 days, the primary endpoint of death or renal replacement occurred in 138 of 334 (45.9%) in the culprit lesion only and 189 of 341 patients (55.4%) in the multivessel PCI group **(Fig. 2)**. Further the authors reported 1 year outcomes.[11] At 1 year, the death occurred in 172 of 344 patients (50.0%) in the culprit lesion only and 194 of 341 patients (56.9%) in the multivessel PCI group. Repeat revascularization occurred more frequently with culprit lesion only as compared to complete PCI (33.2% vs. 9.4%). The rehospitalization for heart failure also occurred more frequently in the culprit lesion only versus complete revascularization (5.2% vs. 1.2%). While mortality was not significantly different between the two arms, repeat revascularization and cardiac failure occurred more frequently in culprit-only arm. However, patients who underwent complete revascularization had higher risk kidney injury renal replacement.

CONCLUSION

Looking at the current data from various trials, it appears that there is compelling evidence that the earlier recommendations based on observational studies are perhaps not completely valid.[12]

There is overwhelming data from the recently conducted randomized trials that complete revascularization in STEMI without shock can be performed with safety and better outcomes. Death, MI, and recurrence of ischemic events are significantly lower in patients subjected to complete revascularization as compared to infarct artery PCI only. It is operator choice whether the PCI of noninfarct artery is performed at index procedure. However, it should be performed preferable during index hospitalization or within 4–6 weeks after hospital discharge **(Box 3)**. The current data also suggests that noninfarct artery PCI should preferably be performed a day after PAMI or during index hospitalization or within 45 days after PAMI. There is a temptation to perform noncritical lesions in noninfarct artery which many times look critical due to vasoconstriction and inflammation during AMI **(Box 4)**.

Current evidence encourages staged nonculprit PCI with FFR during index hospitalization and would be more scientific and could avoid many procedures for nonsignificant lesions.

When it comes to STEMI with cardiogenic shock, again the old conventional guidelines are challenged by the CULPRIT-SHOCK trial. Benefit if any is achieved at the cost of renal injury leading to higher risk of renal replacement therapy. This perhaps is related to prolonged procedure time and larger quantity of contrast needed to achieve complete revascularization. Most of these patients in cardiogenic shock are elderly, associated with several comorbidities such as hypertension and diabetes. Their vessels are more diffusely diseased with calcified coronary arteries and high SYNTAX score. Attempting complete revascularization could result in renal dysfunction and greater risk of renal replacement therapy.

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CHAPTER 64

Plaque Rupture versus Erosion: Common Consensus in ST-elevation Myocardial Infarction

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ABSTRACT

Plaque rupture (PR) causing ST-elevation myocardial infarction (STEMI) is a well-established event. Owing to development of intracoronary imaging, the incidence of plaque erosion (PE) is an increasingly recognized phenomenon. With recent studies, difference between PR and PE in pathophysiological mechanisms, biomarkers, and clinical outcomes are evident. So accurate diagnosis and specific management are the need of the hour in STEMI patients. In this review, we have portrayed recent studies showing distinct contrast between PR and PE from clinicopathological and radiological aspects to guide us for further management.

INTRODUCTION

The ST-elevation myocardial infarction (STEMI) is a significant health problem in industrialized countries and is becoming an increasingly significant problem in developing countries. It is familiar that atherosclerotic plaque rupture (PR) is the primary pathological cause of STEMI.[1] Progress has been made in uncovering of the etiopathogenesis and progression of preventive procedures against "vulnerable plaques."[2,3] By using intraluminal imaging, specifically optical coherence tomography (OCT), it was distinguished that plaque erosion (PE) is likewise a vital mechanism underlying STEMI.[4] Evidences show that those with eroded plaques are unlike the ones having traditional ruptured plaques in the pathophysiological mechanisms, prognostic biomarkers, and prognosis.[5,6] Atherosclerosis is universally the foremost reason of death at the current time and infirmity with the majority of diseases in the emerging world.[7]

CAUSES

An increased blood level of apolipoprotein B—containing lipoproteins, especially low-density lipoprotein (LDL) typically the most prevalent, is a constant factor for atherosclerosis, such as in familial hypercholesterolemia (FH) and other hereditary hyperlipidemias (monogenic disease). Nevertheless, the ailment progresses at lesser levels of LDL in amalgamation with other risk elements that enable atherosclerosis (multifactorial disease).[8,9] These consist of smoking, diabetes mellitus, hypertension, male gender, and an intricate heritable predilection to the disease.

MECHANISM OF FORMATION OF PLAQUE

Low-density lipoprotein and the additional influential factors are multifaceted as concerning lipoprotein retaining, inflammatory cell recruitment, production of foam cells, natural cell death (apoptosis) and pathological cell death (necrosis), creation of smooth muscle cell (SMC) and matrix, deposition of calcium salts leading to calcification, formation of new blood vessels, arterial makeover, fibrous cap rupture, thrombosis, etc. Most plaques are symptomless (subclinical ailment), some become obstructive (stable angina), and some incite acute thrombosis and may give rise to acute coronary syndrome (ACS).

Predilection Site

Atherosclerosis is a multifactorial disease that targets the reproducible areas of the arterial hierarchy. Sites having less or oscillatory endothelial shear stress, positioned adjoining the division points and along internal curvatures, are utmost predisposed areas,[10] and the abdominal aorta, coronary arteries, iliofemoral arteries, and carotid bifurcations are classically the majorly affected. Preceding to the development of atherosclerosis, these proclivity sites are demonstrated

by vagaries in endothelial turnover and the manifestation of genetic characteristics,[10] the occurrence of subendothelial dendritic cells,[11] and, in humans, the existence of adaptive intimal thickening.[12] Adaptive intimal thickenings develop extemporaneously after birth and may grow as broad as the underlying media. They may offer a soil for preliminary lesion progression,[12] and the rate of development remains astronomical here than at other arterial sites. Nevertheless, with time, the disease stretches to adjoining intima,[13] and in aged patients having myocardial infarction (MI) as a cause of death, most of the epicardial coronary arteries are distressed by plaques.[14]

Mechanisms of Plaque Rupture

Plaque rupture transpires at the thinnest cap area and is frequently insinuated by foam cells (macrophages),[15] and fibrous caps are at the vulnerability of breaking. As discovered by microscopic investigation in a postmortem study of abrupt cardiac death, the average thickness of ruptured caps was found to be only 23 μm, and 95% of ruptured fibrous caps (RFC) were under 65 μm.[16] Based on these annotations, Virmani et al.[17] presented the term thin-cap fibroatheromas (TCFAs) meant for coronary fibroatheromas with a fibrous cap thickness of <65 μm, which can thus be presumed to incorporate the majority of plaques at risk for rupture.[17]

Diminishing or thinning of the fibrous cap undoubtedly comprises two contemporaneous mechanisms. First being the slow loss of SMCs from the fibrous cap. Ruptured caps comprehend fewer SMCs and reduced collagen than the intact caps,[18] and SMCs are typically not present at the real site of rupture;[18,19] infiltrating macrophages destroy the collagen-rich cap matrix. Ruptured caps that were scrutinized at postmortem are generally profoundly insinuated by macrophage foam cells[19] that produce proteolytic enzymes such as plasminogen activators, cathepsins, and matrix metalloproteinases (MMPs). The MMPs are released as latent zymogens that necessitate extracellular initiation, following which they are competent of disintegrating all components of the extracellular matrix fundamentally. Whether thinning of the fibrous cap takes years to grow or is much more dynamic is yet unknown. Yet, the fact that fibroatheromas are frequently noticed from 30 years of age,[20] where ACS is exceptionally sporadic, seems to designate that it is a sluggish, smoldering process.

The rupture of a thin cap and consequent thrombosis may take place suddenly, but in few cases, a momentary upsurge in emotional or physical stress delivers the ultimate trigger of the event. Documented triggers are physical and sexual activity, anger, anxiety, work stress, earthquakes, war and terror attacks, temperature changes, infections, and cocaine use.[21] Likewise, elementary daily activities or the quotidian rhythm of biological pathways may regulate the onset of ACS, which are most common in the morning.[22] The activating pathways may include initiation of the sympathetic nervous system with augmented heart rate and blood pressure, leading to PR, or amplified coagulability and platelet responsiveness, leading to an emphasized thrombotic response on already ruptured plaques.[23]

Mechanisms of Plaque Erosion

The mechanism leading to thrombus without rupture is one of the most imperative unanswered questions within atherosclerosis research. The surface endothelium under the thrombus is typically not present; nonetheless, no diverse morphological features of the underlying plaque have been recognized. Eroded and thrombosed plaques instigating sudden cardiac death are often barely calcified, frequently allied with negative remodeling, and less inflamed than ruptured plaques.[17,24] Some, but not all, have reported focused inflammation proximately underneath the overlaid thrombus.[17] Vasospasm has been proposed as the origin of endothelial damage and succeeding thrombosis.[25] Unswerving with this theory, PE lesions archetypally show unbroken internal and external elastic laminas and a mature media with contractile SMCs contrasting to lesions of PR where the whole internal lamina is often disrupted and the underlying media thin and muddled.[26]

Remarkably, morphology matching to that of PE (endothelial stripping over pathological intimal thickening and fibroatheromas with thick cap) can frequently be found in segments up- or downstream of PR with a lethal superimposed thrombus.[17] This exemplifies the prerequisite for tightly spaced sectioning to diagnose erosion (by exclusion of rupture). It might also propose that injury or loss of endothelium can occasionally happen secondarily to thrombus creation, on condition that one assumes that the bordering rupture in these cases is the solitary triggering cause. Autopsy studies direct that only a smaller number of ruptures lead to clinical symptoms, although the others heal silently with only mural thrombus.[27-29] Putatively, loss of the antithrombotic characteristics of the plaque surface, which in its extremity may present as PE, could be an influential factor among these results, concurrently with circulating thrombogenic factors **(Fig. 1)**.

CLINICAL STRATEGIES AND OUTCOMES IN PATIENTS WITH PLAQUE EROSION

The introduction of OCT immensely guides us to appraise the clinical treatment approaches and consequences in patients with PE. The current standard of care dictates instantaneous stenting for STEMI, and usually an early invasive strategy with stenting for many cases of non-STEMI, which is called a "one-size-fits-all" clinical strategy.[30] Though, bearing in mind the distinct demographic features and pathologies of PE and PR, customized treatment strategies are of utmost importance.

An evaluation of the angiographic features of patients with PE and PR revealed that patients with PE had scarcer multivessel lesions, lesser Gensini risk scores, more preserved vascular structure, and a greater lumen.[31] All of these discoveries suggests that PE may not unavoidably require stent implantation **(Table 1)**. A single-center, unrestrained, prospective, proof-of-concept study was completed to gauge the practicability and safety of long-term antithrombotic therapy without stenting in patients with ACS caused by PE. Patients with residual diameter stenosis <70% on coronary angiography and identified with PE by OCT were treated with antithrombotic therapy without stent

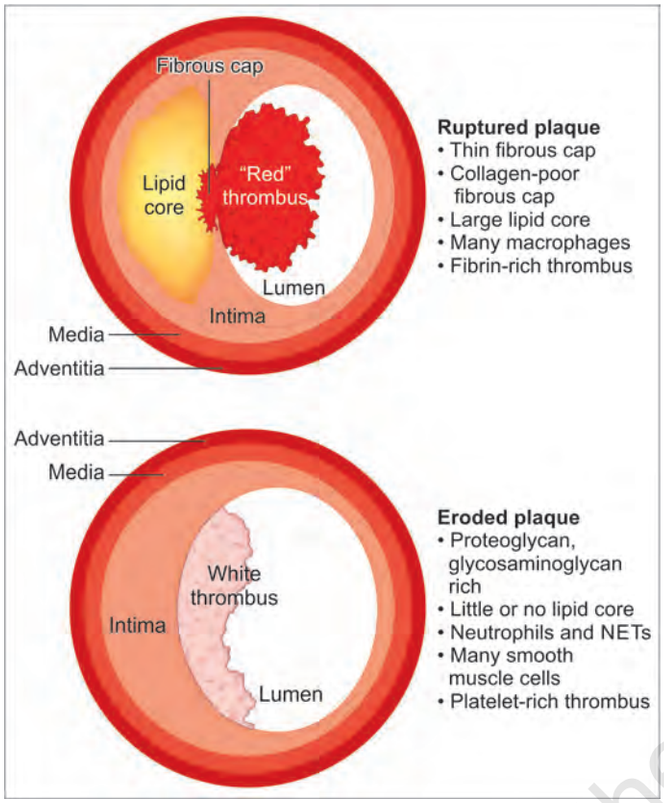

FIG. 1: Comparison of the characteristics of human atheromata complicated by thrombosis because of plaque rupture (top) or superficial erosion (bottom). The text highlights some of the characteristics demonstrated by analyses of human coronary arterial lesions that have undergone thrombosis by these two diverse mechanisms.

(NETs: neutrophil extracellular traps)

Source: Libby P, Pasterkamp G, Crea F, Jang IK. Reassessing the mechanisms of acute coronary syndromes: the "vulnerable plaque" and superficial erosion. Circ Res. 2019;124:150-60.

implantation.[32] Thrombus volume decreased from 3.7 (range: 1.3–10.9) mm^3 to 0.2 (range: 0.0–2.0) mm^3.[32] At 1-year follow-up, OCT confirmed that the median residual thrombus volume lessened meaningfully from 1 month to 1 year (0.3 mm^3 vs. 0.1 mm^3).[33] The majority (92.5%) of patients with ACS caused by PE managed with antithrombotic therapy without stent implantation continued free of major adverse cardiovascular events for up to 1 year.[33] Sugiyama et al. estimated whether tirofiban, a glycoprotein IIb/IIIa inhibitor, had supplementary benefits in ACS patients with PE treated with antiplatelet therapy without stent implantation. The tirofiban group had lesser residual thrombus volume, thrombus burden, and superior reduction of thrombus volume at the 1-month follow-up. These differences were maintained for up to 1 year. There was no difference in the 1-year major adverse cardiovascular event rate between the two groups.[34] Above all, the results proposed that antithrombotic as an alternative of stent implantation may be innocuous and effective for partial patients with PE.

Prati et al. executed OCT after aspiration thrombectomy and recognized 31 PE patients presenting with STEMI. 40% of patients with nonobstructive lesions were treated with antiplatelet strategy alone, and the remaining 60% underwent angioplasty and stenting. At a median follow-up of 753 days, all patients were symptomless, regardless of stent implantation. They have confidence that if intracoronary imaging can authenticate intact fibrous cap (IFC) or PE with nonobstructive lesions precisely, the safety and efficiency of these substitute methods could be considered, unswerving with the EROSION (Effective Anti-thrombotic Therapy without Stenting: Intravascular Optical Coherence Tomography-based Management in Plaque Erosion) study.[35] Souteyrand et al. showed a two-step strategy of invasive management without stenting in ACS patients, guided by OCT. Up to 46 patients were treated with antithrombotic therapy and completed delayed angiography and OCT in a median period of 6 (3–10) days. PE was noticed in 54.3% of patients, PR in 39.1%, and calcified nodule in 6.5%. Up to 23 patients, who had a rise in minimal lumen area, profited from methodical delayed OCT over a median period of 171 days. They believe that it might be a steadfast option to choose conventional treatment without stenting in a designated population (PE or nonvulnerable PR without significant stenosis).[36] It might be an unfailing option to choose conventional treatment without stenting in a nominated population.

On the contrary, a prospective multicenter study demonstrated that STEMI patients who underwent primary percutaneous coronary intervention (PCI) and received everolimus-eluting stent (EES) were separated into IFC and RFC groups. Saia et al. exhibited that IFC and RFC unveiled analogous degrees of stenosis and an elevated occurrence of residual endoluminal thrombus after manual thrombectomy and that the vascular response to the EES was admirable and comparable in the two groups.[37] Roule et al. equated the characteristics of plaques and thrombi between PR and PE in STEMI patients efficaciously treated with fibrinolysis by intracoronary optical frequency domain imaging. PE had a lesser thrombus volume and burden equated to PR at baseline, while there was no noteworthy variance in thrombotic volume, burden, and its dispersal, as well as angiographic estimators of myocardial reperfusion between the two groups after stenting.[38] Of note, 52 patients in the EROSION study completed a 4-year follow-up. All patients were free from hard endpoints, while 11 patients underwent elective target lesion revascularization (TLR) due to a lesser amount of enhancement in diameter stenosis.[39] Consequently, whether plaque morphology underlying STEMI should lead to a diverse therapeutic method remains hypothetical. Future studies are needed to corroborate this therapeutic tactic.

Plaque erosion equated with PR had quite dissimilar pathological features that may lead to unlike consequences. Hu et al. retrospectively appraised 141 patients with ACS who underwent OCT of the culprit lesion prior to stent implantation. Compared with PR, patients with PE had a lesser frequency of distal embolization, higher baseline thrombolysis in myocardial infarction (TIMI) flow grade, and lesser incidence of TIMI flow grade ≤2 after stenting. Besides, the rate of revascularization in patients with PE was arithmetically lesser than that in patients with PR, even though no statistical difference was found. OCT analysis revealed a higher occurrence of malapposition, thrombus, and protrusion in the rupture group equated to the erosion group.[40]

TABLE 1: Representative studies of the clinical strategies and prognosis of the patients caused by plaque erosion.

References	Number in study	Strategy	Follow-up time	Endpoint	Key observations
Jia et al.[32]	55 patients with ACS caused by PE	Residual diameter stenosis <70% on coronary angiogram were treated with antithrombotic therapy without stenting	1 month	The primary endpoint was >50% reduction of thrombus volume at 1 month compared with baseline. The secondary endpoint was a composite of cardiac death, recurrent ischemia requiring revascularization, stroke, and major bleeding	47 patients met the primary endpoint, and 22 patients had no visible thrombus at 1 month
Prati et al.[35]	31 patients with STEMI	40% of patients with subcritically occlusive plaque were treated with dual antiplatelet therapy without PCI, and the remaining 60% of patients underwent angioplasty and stenting	753 days	Myocardial infraction, heart failure, or deaths	All patients were asymptomatic, regardless of stent implantation
Souteyrand et al.[36]	46 patients with ACS, 39.1% of PR and 54.3% of PE	Medical therapy treatment alone without stenting in case of absence of vulnerable plaque rupture and <70% stenosis	12 months	MACE	23 patients benefited from systematic delayed OCT over a median period of 171 days, showing an increase in minimal lumen area
Hu et al.[40]	141 patients with ACS, 79 of PR and 62 of PE	Stent implantation was performed in 77 (97.5%) patients with PR versus 49 (79.0%) in those with PE	12 months	MACE	OCT showed a higher incidence of malapposition (37.5% vs. 7.3%, $p < 0.001$), thrombus (59.4% vs. 14.6%, $p < 0.001$), and protrusion (93.8% vs. 73.2%, $p = 0.008$) in the rupture group compared with the erosion group
Saia et al.[37]	32 plaques (33.0%) with an IFC, 63 (64.9%) plaques with a RFC	Primary PCI with everolimus-eluting stent implantation	2 years	MACE	At the 9-month OCT, IFC and RFC had similar high rates of stent strut coverage (92.5% vs. 91.2%; $p = 0.15$) and similar percentage of volume obstruction (12.6% vs. 10.2%; $p = 0.27$). No significant differences in clinical outcomes were observed up to 2 years
Higuma et al.[42]	112 patients with STEMI, 64.3% of PR and 26.8 of PE	Primary PCI	No follow-up visits	–	PE had a lower incidence of no-reflow phenomenon after PCI than PR and associated with less microvascular damage after PCI
Niccoli et al.[44]	139 patients with ACS, 82 of PR and 57 of IFC	Primary PCI	31.58 + 4.69 months	MACE	Major adverse cardiac events occurred more frequently in patients with PR when compared with those having IFC (39.0% vs. 14.0%, $p = 0.001$)

(ACS: acute coronary syndrome; IFC: intact fibrous cap; MACE: major adverse cardiac event; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; PE: plaque erosion; PR: plaque rupture; RFC: ruptured fibrous cap; STEMI: ST-elevated myocardial infarction)

Previous studies have revealed that patients with PE have scarcer lipid plaques, heavier fibrous caps, slighter lipid arcs, and petite lipid lengths than those with PR.[1,4,41] Besides, ruptured plaques release highly thrombogenic substrates, encouraging repeated local thrombosis and distal embolization. These discoveries suggest that PE may be related with more promising outcomes. Higuma et al. compared the postprocedure results of PR and PE. The study unveiled that PE had a superior plaque eccentricity index and a lesser occurrence of the no-reflow phenomenon after PCI than PR. In addition, PE was allied with less microvascular injury after PCI.[42] Dai et al. described that STEMI patients with PE were linked with improved myocardial perfusion than those with PR.[43] Recently, Niccoli et al. assessed the prognostic value of PR and IFC in patients with ACS. Equated to patients with IFC, major adverse cardiac events happened more often in patients with PR. Patients with PR as offender

lesions by OCT have a worse prognosis after a 3-year follow-up compared to those with IFC.[44] Though, White et al. conjectured that a higher frequency of the residual incidence of MI and stroke was the outcome of erosion.[45] These conflicting verdicts divulge that more clinical trials were desired to reconnoiter the connotation among clinical outcome and criminal plaque morphology.

Hayashi et al. studied 107 patients with acute MI (PR: 44; PE: 28; unclassified: 35) by means of coronary angiography and intravascular ultrasound instantly before PCI. Patients with eroded plaques had additional pre-infarction angina, less STEMI, lesser peak creatine kinase level, less distal embolization after PCI, and less Q-wave MI 1 month after the onset of MI than those with ruptured plaques. Patients with eroded plaque lesions had reduced infarctions than those with ruptured plaque lesions, demonstrating that eroded lesions were less thrombogenic than ruptured lesions.[46]

A 3-vessel OCT study was accomplished to examine the nonculprit plaque phenotype in patients with ACS based on culprit lesion pathology (PE: 17; PR: 34). None of the PE patients had nonculprit PR, whereas 26% of PR patients had nonculprit PR. The culprit PE group had a lesser number of nonculprit plaques per patient and a reduced prevalence of PR, macrophage gathering, microvessels, and spotty calcium in the nonculprit lesions compared with the culprit PR group, which established that PR and PE had dissimilar pathophysiological mechanisms.[3,47] Several reports propose more extensive inflammation and unsteadiness in culprit PR patients versus PE patients.[5,48,49] Sugiyama et al. endorsed that PE might involve local endothelial damage rather than prevalent coronary arterial inflammation, leading to ACS.[50] These consequences help us to better understand the phenomenon that patients with PE are characteristic with better clinical outcomes compared with PR **(Fig. 2)**.

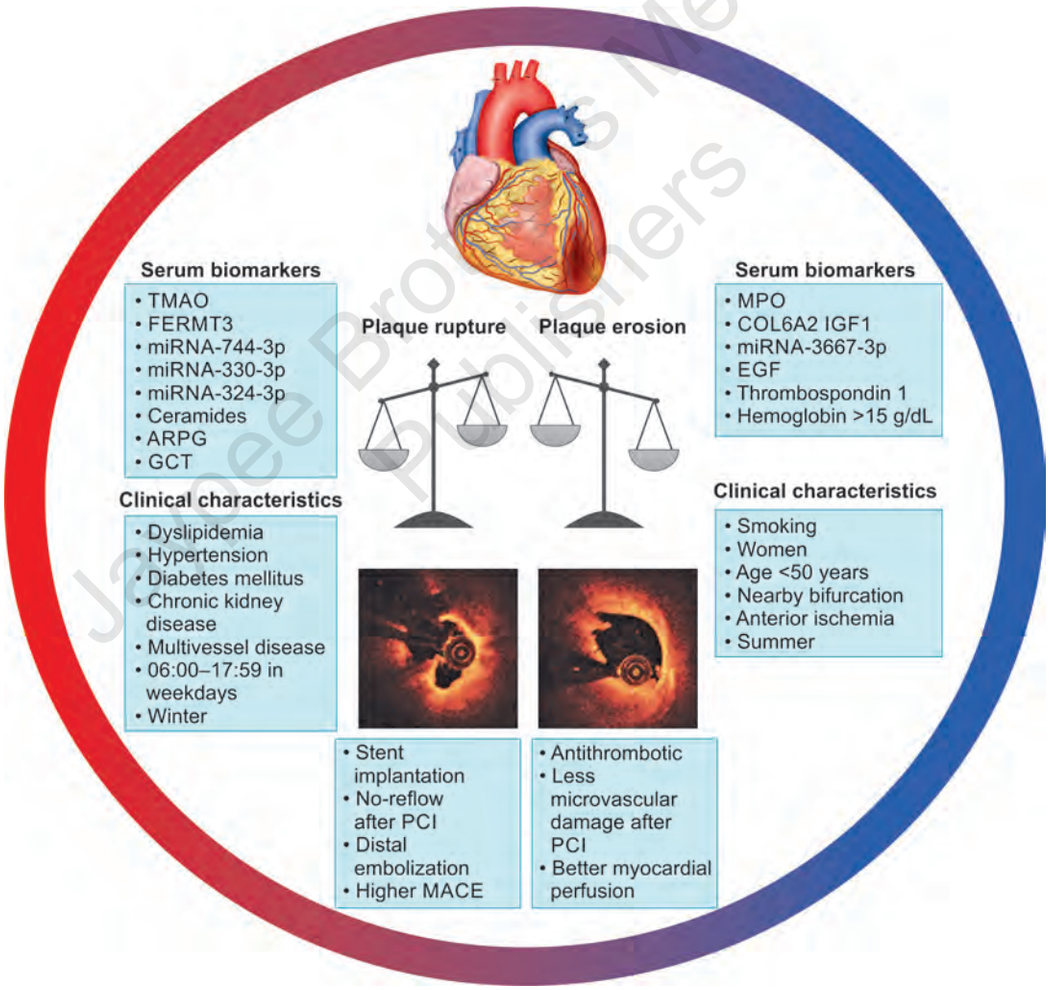

FIG. 2: The prediction and clinical outcome of plaque erosion and plaque rupture.

(ARPG: random plasma glucose on admission; COL6A2: collagen type VI α-2 chain; EGF: epidermal growth factor; FERMT3: fermitin family homolog 3; GCT: glucose challenge test; IGF-1: insulin-like growth factor 1; MACE: major adverse cardiac event; miRNA: microribonucleic acid; MPO: myeloperoxidase; PCI: percutaneous coronary intervention; TMAO: trimethylamine *N*-oxide)

Source: Luo X, Lv Y, Bai X, Qi J, Weng X, Liu S, et al. Plaque erosion: a distinctive pathological mechanism of acute coronary syndrome. Front Cardiovasc Med. 2021;8:711453.

CONCLUSION

Plaque erosion is a common and vital pathological mechanism of ACS, and its pathological features and mechanisms are quite diverse from those of PR. The mechanism of eroded plaque is still abstruse and requires further study. PE is a foreseeable clinical entity different from PR in STEMI patients. Antithrombotic therapy alone may be safe and effective for some patients with eroded plaques but then needs more clinical trials to sustain this concept. The long-term prognosis of patients with eroded plaques might be improved than that of patients with ruptured plaque.

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CHAPTER 65

Colchicine and Cardiology: What is New?

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ABSTRACT

Though atherosclerosis starts with the deposition of lipid-rich particles in vessel walls, progression of atherosclerosis leading to ischemia and plaque rupture causing acute coronary syndromes (ACS) has largely been attributed to be related to inflammation in the plaque. This inflammation is mediated by interleukin (IL)-1β, IL-18, and tumor necrosis factor α (TNF-α)-like substances. Nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome has been found mainly responsible for atherosclerosis progression and plaque rupture through IL-1β and IL-18 release. The drugs which antagonize this cytokine release, such as colchicine, have been extensively studied in various clinical trials and have been found to be effective in atherosclerosis progression and prevention of adverse cardiovascular events after the first ACS. This review briefly discusses the potential role of inflammation and its modulation in the secondary prevention of cardiovascular disease. This review does not discuss the guidelines-approved role of colchicine in acute pericarditis.

INTRODUCTION

Colchicine is an alkaloid derived from the plant *Colchicum autumnale*. Its medicinal value as a treatment of joint pain was described as far back as 1500 BC. In cardiology, colchicine is the recommended treatment for acute and recurrent pericarditis. The anti-inflammatory properties of colchicine have prompted an investigation into its potential usage in the management of acute coronary syndrome (ACS) and acute heart failure. Rupture of a nonflow-limiting plaque is the predominant pathology in ACS. This rupture is caused primarily by stress and inflammation. Various factors such as diabetes, smoking, and hyperlipidemia, potentiated by inflammation, ultimately lead to plaque instability. Thus, controlling or modulating inflammation can have potential roles in preventing plaque rupture.

EVIDENCE THAT INFLAMMATION TRIGGERS ACUTE CARDIOVASCULAR EVENTS

Influenza Vaccine in Secondary Prevention of Cardiovascular Disease

Annual influenza vaccine has shown to significantly reduce all-cause mortality, cardiovascular mortality, and major recurrent cardiovascular events in patients with coronary artery disease (CAD).[1] Administering this vaccine early post-acute myocardial infarction (MI) resulted in a significant reduction in all-cause mortality, stent thrombosis, and cardiovascular events.[2] The reduction in acute MI has been reported to be in the range of 15–45%, which is almost similar to the use of other preventive strategies such as statins.[3] The potential mechanism of beneficial effects is through the prevention of the release of inflammatory cytokines.

It is a common observation that incidences of ACS and its mechanical complications, new-onset heart failure or worsening of existing chronic heart failure (CHF), new-onset atrial fibrillation (AF) or worsening of preexisting AF, and ischemic stroke occur more from August to March in the Northern Hemisphere which coincides with influenza season. Inflammation appears to trigger these acute events.

Systemic Inflammatory Disorders are Associated with Higher Cardiovascular Disease Risk

Chronic inflammatory disorders such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, systemic sclerosis, and ankylosing spondylitis increase the risk of cardiovascular disease (CVD) and CVD-related deaths in affected individuals.[4]

The prevalent concept of lipid deposition dependence of atherosclerosis and CVD is challenged in such conditions. The higher prevalence is probably due to the activation of the immune system, causing inflammatory responses at various stages of plaque formation and disease progression. In addition to atherovascular disease, chronic inflammation plays an important role in myocarditis and cardiomyopathy. The QRISK®-3 risk score includes systemic lupus erythematosus and rheumatoid arthritis in the risk assessment for CVD in the United Kingdom.

COVID-19 and Cardiovascular Disease

During the severe acute respiratory syndrome (SARS) COVID-19 pandemic, the Centers for Disease Control and Prevention[5] (CDC), United States, reported a significant increase in cardiovascular mortality from 161.5 deaths per 1 million population in 2019 to 168.2 deaths per million population in 2020. Apart from pulmonary complications, SARS COVID-19 has been reported to cause acute myocardial ischemia in 0.9–11%, ventricular dysfunction in 10–41%, and acute heart failure in 3–33% of patients. The causative mechanisms include direct angiotensin-converting enzyme (ACE)-2 mediated cardiac injury, hypoxemia, microvascular thrombosis, and inflammatory cytokine-mediated injury. Cytokine storm is one of the reasons for the sudden deterioration or cardiovascular collapse in SARS COVID-19 patients.

Inflammation has a Key Role in Atherosclerosis Leading to Acute Coronary Syndrome

Atherosclerosis has been considered to be a disease primarily caused by an accumulation of lipid-rich substances in the subendothelium of vessel walls. However, subsequent research has shown that in addition to lipid deposition, the progression of atherosclerotic plaque is largely a product of inflammation and autoimmunity. The presence of thin fibrous caps with a few smooth muscle cells, large lipid or necrotic core, large areas of foam cells, abundant intimal inflammatory cells, and spotty or microscopic calcification are the hallmarks of a vulnerable plaque. The fibrous caps of plaque are collagenous and undergo continuous remodeling. Low-density lipoprotein (LDL) undergoes oxidation in subintima, and this oxidized LDL particle triggers inflammation.

Collagen turnover is controlled mainly by matrix metalloproteinases (MMPs) secreted by macrophages within the plaque. Plaque inflammation leads to an increase in collagen degradation, resulting in the formation of thin fibrous caps or vulnerable plaques. Various markers of inflammation such as interleukin (IL)-6, IL-18, MMP-9, and factors produced by cells of the adaptive immune system, such as soluble CD40 ligand (sCD40L), and tumor necrosis factor alpha (TNF-α) have been studied and found to promote plaque rupture. Studies have found that IL-6 and high-sensitivity C-reactive protein (hs-CRP) correlate well with adverse cardiovascular events, independent of cholesterol. The intracellular mechanism for protection against infection or any other threat is mediated through nucleotide-binding and oligomerization NOD-like receptors (NLRs). The NLRP3 inflammasome is responsible for the release of IL-1β and IL-18, which play an important role in the progression of atherosclerosis and myocardial ischemia and reperfusion injury after acute MI.[6] The NRLP3 have three main components—NLRP3, apoptosis speck-like protein (ASC), and caspase-1. Caspase activation triggers microtubule polymerization and activation of pro-IL-18 and pro-IL-1β, which in turn form active inflammatory molecules IL-18 and IL-1β. This leads to a marked inflammatory response by releasing IL-1β, IL-6, and IL-18. IL-6 further triggers the release of CRP from the liver. Drugs such as colchicine, canakinumab, and anakinra target inflammatory cytokines (IL-1β and IL-18) released from NLRP3 inflammasomes.[7] Statins exert a beneficial effect not only by lowering cholesterol but also by reducing plaque inflammation **(Table 1)**.

TABLE 1: Various circulating inflammatory substance and their potential antagonists.

Inflammatory molecule	Source	Inhibitor
IL-1β, IL-18	NLRP3 inflammasome	• Colchicine • Canakinumab • Rilonacept • Anakinra
TNF-α	• Adipose tissue • Macrophage/ monocyte	• Adalimumab • Infliximab
IL-6	• Macrophage/ monocyte • Adipose tissue	• Tocilizumab • Sarilumab • Low-dose methotrexate
Lp-PLA2	Macrophage/ monocyte	• Darapladib • Varespladib

(IL: interleukin; Lp-PLA2: lipoprotein-associated phospholipase A2; NLRP3: nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3; TNF: tumor necrosis factor)

COLCHICINE AS AN ANTI-INFLAMMATORY AGENT

Colchicine is a relatively inexpensive, reliable, less toxic, age-old anti-inflammatory molecule used in various conditions such as gout and Behçet's disease. Its mode of action as an anti-inflammatory agent has been explored in clinical trials for various other indications such as ACS, stable CAD, AF, heart failure, percutaneous coronary interventions (PCI), and stroke. Colchicine works mainly to prevent NLRP3 caspase-1 activation and prevents microtubule polymerization. This in turn prevents IL-1β, IL-18, and IL-6 release, which helps to prevent an unwanted inflammatory response **(Table 2)**.

CLINICAL TRIAL EVIDENCE OF COLCHICINE IN CARDIOLOGY

Clinical Trials of Colchicine after Acute Coronary Syndrome

The LoDoCo-MI Study[8]

Low-Dose Colchicine after Myocardial Infarction (LoDoCo-MI) pilot study[8] investigated low dose of colchicine (0.5 mg daily) in patients with acute MI and elevated hs-CRP levels. It tested

TABLE 2: Mechanisms of colchicine in cardiovascular diseases.

Potential mechanisms of action	Observed clinical effect
Microtubule depolymerization	• Treatment of acute pericarditis • Prevention of recurrent pericarditis • Prevention of postcardiotomy syndrome after cardiac surgery
Inhibition of NLRP3 inflammasome leading to reduction in IL-1β, IL-6, IL-8, CRP, and TNF-α	• Prevention of AF after pulmonary vein ablation/isolation • Prevention of atherosclerosis progression and ACS
Inhibition of macrophages release of reactive oxygen species (ROS), TNF-α, nitric oxide, and IL-1β	Reduction in plaque inflammation, rupture, and ACS
Inhibition of neutrophil activation, and release of IL-1β, IL-8, superoxide, chemotactic factors, and L-selectin	Prevention of restenosis and adverse cardiovascular events after percutaneous coronary interventions

(ACS: acute coronary syndrome; AF: atrial fibrillation; CRP: C-reactive protein; IL: interleukin; NLRP3: nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3; TNF: tumor necrosis factor)

the ability of colchicine to reduce hs-CRP levels compared to its placebo. Out of a total of 237 patients, low-dose colchicine was able to lower hs-CRP < 2 mg/L in 56% compared to 50% in the placebo group at 30-days post-acute MI. It was well tolerated during that period.

The COLCOT Trial[9]

Low-dose colchicine in the prevention of adverse cardiovascular events was evaluated in this landmark trial.[9] The COLCOT (Colchicine Cardiovascular Outcomes Trial) enrolled 4,745 patients (colchicine group 2,366; placebo group 2,379) within 30 days of acute MI and were followed for a median of 22.6 months. The primary endpoint was a composite of death from cardiovascular causes, resuscitated cardiac arrest, acute MI, stroke, or urgent revascularization. There was a significant reduction in the primary endpoint (7.1% in the placebo group vs. 5.5% in the colchicine group, $p = 0.02$). Low-dose colchicine significantly reduced adverse ischemic cardiovascular events in post-acute MI patients.

The Australian COPS Randomized Clinical Trial[10]

In this multicenter trial[10] in Australia, 795 patients with ACS were evaluated (396 in the colchicine group and 399 in the placebo group). Patients received 0.5 mg colchicine twice daily for 1 month, followed by 0.5 mg once daily for 11 months in addition to standard therapy. Primary endpoint events occurred in 6.1% in colchicine group versus 9.5% in placebo group ($p = 0.09$, not significant). There was a higher rate of death in the colchicine group (2.2% vs. 0.25% in the placebo group, $p = 0.017$, significant). The majority of the deaths in the colchicine group were noncardiac. There was no benefit of colchicine over standard medical therapy in ACS patients at 12 months.

Clinical Trials of Colchicine in Stable Coronary Artery Disease

The LoDoCo1 Trial[11]

This LoDoCo-1 (Low-Dose Colchicine 1) is a small randomized study[11] from Australia and Canada. It enrolled 532 patients with stable CAD on antiplatelets and statins further treated with low-dose colchicine, 0.5 mg daily ($n = 282$) or no colchicine ($n = 250$). In this study, primary endpoint events occurred in 5.3% of colchicine group patients versus 16.0% in the noncolchicine group ($p < 0.001$, number to treat 11). This trial showed a marked benefit of low-dose colchicine in patients with stable CAD added to standard treatment.

The LoDoCo2 Trial[12]

This randomized trial[12] from Australia and New Zealand assessed the efficacy of low-dose colchicine in reducing adverse cardiovascular events in chronic CAD patients. It enrolled 5,522 patients; 2,762 in the colchicine group; and 2,760 in the placebo group. The median follow-up was 28.6 months. The primary endpoint occurred at 6.8% in the colchicine group and 9.6% in the placebo group ($p < 0.001$). There was a significant reduction in primary endpoints in stable CAD patients receiving low-dose colchicine.

Meta-analysis

A meta-analysis of 13 randomized trials[13] of colchicine in stable CAD or ACS by Kofler et al. involving 13,125 patients found that colchicine reduced the risk of MI or stroke, but there was no effect on all-cause mortality or cardiovascular mortality. There was a higher rate of gastrointestinal side effects in colchicine-treated patients.

Another meta-analysis by Grajek et al.[14] of 14 clinical trials with 13,186 patients showed that low-dose colchicine reduced the risk of primary endpoints by 30%. The authors strongly recommended low-dose colchicine for the prevention of future CVD.

Colchicine in the Prevention of Brain Stroke in Patients with Coronary Artery Disease

A meta-analysis[15] of clinical trials of colchicine showed that daily intake of low-dose colchicine reduced the incidence of stroke by 51%. This was equivalent to one stroke prevention per 218 treated patients with a follow-up of 2 years.

Colchicine in Percutaneous Coronary Interventions

The COLCHICINE-PCI Randomized Trial[16]

Percutaneous coronary intervention may cause vascular inflammation and myocardial injury. This trial[16] tested whether prevention of inflammation can lead to a better outcome. It enrolled 400 patients (colchicine = 206, placebo = 194). The colchicine group patients received 1.8 mg of colchicine within 1 hour of PCI. The composite primary event of death, nonfatal MI, and target vessel revascularization at 30 days occurred in 11.7% in the colchicine group versus 12.9% in the placebo group ($p = 0.82$). PCI-related MI occurred in 2.9% in the colchicine

group versus 4.7% in the placebo group (p = 0.49). However, there was significant attenuation in IL-6 and hs-CRP level rise in colchicine-treated patients though it did not lower PCI-related myocardial injury.

Colchicine in Stable Heart Failure

The FINER Trial[17]

This prospective randomized trial[17] from Greece evaluated colchicine 0.5 mg twice daily (0.5 mg once daily for body weight <60 kg) versus placebo in stable CHF patients. Of a total of 267 patients, primary endpoint events occurred in 11% in the placebo group versus 14% in the colchicine group (p = 0.365). A composite of death or hospitalization due to heart failure occurred in 9.4% in the placebo group versus 10.1% in the colchicine group (p = 0.839). Colchicine, though able to reduce inflammatory markers, did not influence cardiovascular events in stable heart failure.

Colchicine in the Prevention of Postoperative Atrial Fibrillation

Inflammation plays an important role in the postoperative period after major cardiac surgeries. It may cause pericarditis, postpericardiotomy syndrome, and AF. Colchicine has been evaluated for the prevention of postoperative atrial fibrillation (POAF).

The COPPS POAF Sub-study[18]

In the COPPS POAF sub-study,[18] 336 postcardiac surgery patients in sinus rhythm were subjected to either placebo (n = 167) or colchicine 1 mg twice for the first day, followed by 0.5 mg twice daily (half dose in patients with weight <70 kg) for 1 month. There was a significant reduction in POAF in colchicine-treated patients (12.0% vs. 22.0%, p = 0.021, number needed to treat 11) with a significantly shorter hospital stay and better rehabilitation. Both groups had similar side effects.

The COPPS-2 Trial[19]

In the COPPS-2 trial,[19] colchicine 0.5 mg twice daily (0.5 mg once daily for body weight <70 kg) (n = 180) was evaluated against placebo (n = 180) in 360 consecutive patients started 48–72 hours after cardiac surgery and continued for 1 month in 11 Italian centers. There was a significant reduction in postpericardiotomy syndrome in the colchicine-treated group (19.4% in the colchicine group vs. 29.4% in the placebo group, absolute difference of 10.0%). However, colchicine could not significantly reduce POAF (33.9% in the colchicine group vs. 41.7% in the placebo group).

In another 2014 study from Iran,[20] 216 patients undergoing coronary artery bypass graft (CABG) received colchicine 1 mg the night before surgery and the morning before surgery, followed by 0.5 mg twice daily for 5 days after surgery. The authors reported a significant reduction in POAF (14.8% in the colchicine group vs. 30.6% in the placebo group) **(Table 3)**.

Colchicine in Prevention of Recurrence of Atrial Fibrillation after Radiofrequency Ablation or Pulmonary Vein Isolation

Atrial fibrillation has been correlated with an enhanced inflammatory response, which is primarily mediated through the NLRP3 inflammasome. This in turn activates caspase-1 and IL-1β and causes IL-18 release. Additionally, NLRP3 inflammasome directly promotes ectopic firing in the atrium, triggering and maintaining AF. Colchicine acts to block NLRP3 inflammasome.[23] Colchicine was evaluated for its potential usefulness in patients with paroxysmal AF who underwent a successful pulmonary vein isolation (PVI) procedure. In a study by Deftereos et al., 223 patients scheduled for PVI procedure for paroxysmal AF received colchicine 0.5 mg twice daily or placebo for 3 months prior to the procedure and were followed up for 15 months. AF recurred in 31.1% in the colchicine group versus 49.5% in the placebo group (p = 0.01, relative risk reduction of 37%, number needed to treat 6) after a single PVI procedure for paroxysmal AF **(Table 4)**.

Ongoing Clinical Trials of Colchicine in Cardiology

Colchicine and Spironolactone in Patients with MI/SYNERGY Stent Registry, Organization to Assess Strategies for Ischemic Syndromes (CLEAR SYNERGY OASIS 9)[27] is a phase III trial by the Canadian Institutes of Health Research. It is a four-intervention arm trial in patients with acute MI being treated by Synergy® bio-absorbable polymer drug-eluting stent. It is

TABLE 3: Summary of clinical trials of colchicine in prevention of atrial fibrillation after cardiac surgery.

Study	N	Type of cardiac surgery	Median follow-up	Outcome
Imazio et al. 2011 COPPS trial	336	CABG, valvular, others	1 month	Colchicine superior to placebo
Imazio et al.[19] COPPS-2 trial	360	CABG, valvular, others	3 months	Neutral, no benefit of colchicine
Sarzaeem et al.[20]	216	CABG	NA	Colchicine superior to placebo
Tabbalat et al.[21] END-AF trial	360	Cardiac surgery	8 days	Neutral, no benefit of colchicine (17.5% in colchicine group vs. 20.5% in no colchicine group, p = 0.14)
Zarpelon et al.[22]	140	CABG	14 days	Neutral, no benefit of colchicine (7.04% in colchicine group vs. 13.04% in placebo group, p = 0.271)

(CABG: coronary artery bypass graft)

TABLE 4: Summary of clinical trials of colchicine in the prevention of atrial fibrillation after pulmonary vein isolation/ablation.

Study	*n*	Follow-up	Outcome
Deftereos et al.[24]	170	3 months	Colchicine superior to placebo
Deftereos et al.[25]	206	12 months	Colchicine superior to placebo
Egami et al.[26]	62	2 weeks 2 months	Colchicine superior to placebo at 2 weeks but neutral at 2 months

studying colchicine, spironolactone, colchicine-placebo, and spironolactone-placebo in the long-term management of MI. The results are likely to be published in 2025. The Colchicine in STEMI patients study (COVERT-MI)[28] is a phase II trial sponsored by the French Ministry of Health. It is evaluating colchicine versus placebo in the first ST-elevation myocardial infarction (STEMI) episode with initial thrombolysis in myocardial infarction (TIMI) ≤1 flow, referred for primary PCI. The patients will receive an oral bolus of 2 mg colchicine followed by 0.5 mg twice daily for 5 days. The primary endpoint is the reduction in infarct size on cardiac magnetic resonance imaging (MRI). COPMAN (Colchicine Prevents Myocardial Injury After NonCardiac Surgery Pilot) study[29] is evaluating colchicine 0.6 mg 1 hour prior to noncardiac surgery followed by 0.6 mg twice daily for 7 days (once daily if weight is <60 kg). Primary outcome measure is the determination of incidence of myocardial injury after 7 days, apart from side effects of medication, including sepsis. The COP-AF (Colchicine for the Prevention of Perioperative Atrial Fibrillation in Patients Undergoing Thoracic Surgery)[30] trial is an ongoing placebo-controlled trial that will enroll 2,800 patients undergoing cardiac surgery. The participants will receive 0.5 mg twice-daily dose of colchicine versus placebo for 10 days. The primary outcome measure is the incidence of POAF at 14 days. It is likely to be completed in 2022.

CONCLUSION

Colchicine has been studied extensively in various cardiac conditions such as post-ACS, stable CAD, stable heart failure, postpericardiotomy syndrome, postoperative atrial fibrillation (POAF), and recurrence of AF after radiofrequency ablation (RFA) or PVI. Data in ACS, CAD, POAF, and post-RFA or PVI AF are encouraging but not so in stable heart failure. Colchicine being a cheap and relatively safer anti-inflammatory agent holds a promise in prevention. Do we have to use both statin and colchicine in secondary prevention? It looks like an interesting concept at the moment but needs more robust evidence. Moreover, many commonly used cardiac drugs such as digoxin, spironolactone, carvedilol, ticagrelor, ranolazine, amiodarone, and statins may increase the serum concentration of colchicine and cause adverse effects.[31]

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CHAPTER 66

Mechanical Complications of Acute Myocardial Infarction: Diagnosis and Management

P Rajendra Kumar Jain, Mohammed Sadiq Azam

ABSTRACT

Mechanical complications of acute myocardial infarction (AMI) include left ventricular free wall rupture, ventricular septal rupture (VSR), papillary muscle rupture (PMR) leading to acute mitral regurgitation (MR), pseudoaneurysm, and true aneurysm. With the introduction of early reperfusion therapies, these complications now occur in <0.1% of patients following an AMI. However, mortality rates have not decreased significantly, and mechanical complications remain an important determinant of outcomes after myocardial infarction. Early diagnosis of mechanical complications and management is crucial to improving outcomes. The care for patients with mechanical complications is complex and requires a multidisciplinary approach for prompt recognition, diagnosis, hemodynamic stabilization, and decision regarding definitive therapies or palliation.

INTRODUCTION

Acute myocardial infarction (AMI) is a potentially life-threatening condition that has myriad clinical presentations ranging from being as innocuous as a silent myocardial infarction (MI) to being as devastating as cardiogenic shock. For the purpose of this chapter, MI refers to ST-segment elevation myocardial infarction (STEMI). Left ventricular free wall rupture, interventricular septal rupture, and acute mitral regurgitation (MR) due to papillary muscle necrosis are three potentially lethal mechanical complications of STEMI which often present with circulatory collapse and shock. Each of these complications has a common pathophysiological mechanism that centers around myocardial necrosis because of prolonged ischemia and is hence more common in patients who have delayed presentation after STEMI.

INCIDENCE

The overall prevalence of AMI is 3% in the United States with a significant decline seen in the past decades due to advances in primary prevention strategies.[1] Large infarcts, delayed presentation, incidence of no reflow, or distal microvasculature choking with thrombus post percutaneous coronary intervention (PCI) have remained risk factors that contribute to a low but persisting incidence of mechanical complications after AMI.[2] Mechanical complications after AMI are more common after STEMI than non-STEMI and have been reported to occur in about 3 per 1,000 patients. Ventricular septal rupture (VSR) is the most reported, with a frequency of 1 in 1,000, while free wall rupture is the least common.[3,4]

The introduction of fibrinolytic therapy for STEMI, which heralded the era of reperfusion therapies, has led to a 40% reduction in overall mortality from STEMI.[5] The incidence of free wall rupture has reduced from around 4% in the prefibrinolytic era (1977–1982) to about 2% in the fibrinolytic era (2001–2006).[6] In recent times, <1% patients after successful fibrinolysis developed mechanical complications.[7] The time to reperfusion is an important predictor of the probability of developing a mechanical complication with the incidence rising as the time window to reperfusion becomes greater. It is equally important to identify and treat noncardiac causes of shock and pump failure, which can confound and influence appropriate management.

CLINICAL PRESENTATION

Patients presenting with mechanical complications are usually older, female, with a history of chronic kidney disease or heart failure, and are usually those presenting with their first MI.[8-10]

Socioeconomic factors have also been reported to play a role in health outcomes after an AMI.[11]

The clinical presentation of patients with mechanical complications of AMI is summarized in **Table 1**.

Acute Mitral Regurgitation

The incidence of acute MR secondary to papillary muscle rupture (PMR) (complete or partial) in AMI has decreased in the reperfusion era with a reported incidence of 0.05–0.26%; however, the associated in-hospital mortality continues to be as high as 10–40%. The anterolateral papillary muscle by virtue of its dual blood supply from the left anterior descending (LAD) and left circumflex (LCx) arteries is protected from ischemia when compared to the posteromedial papillary muscle which has a single source of blood supply from the LCx artery or the right coronary artery (RCA) (depending on dominance). Posteromedial PMR and acute MR usually occur with inferior or lateral STEMIs. PMR usually occurs within days of AMI, and around 50% of patients present with pulmonary edema and cardiogenic shock.[3] There is usually no audible MR murmur in patients with acute MR due to PMR due to the rapid equalization of pressures between the left ventricle (LV) and left atrium (LA). Bedside transthoracic echocardiography helps to make a rapid diagnosis; however, a transesophageal echocardiography (TEE) has greater sensitivity for partial PMRs.

Invasive ventilation for respiratory support and vasopressors is integral to initial management of pulmonary edema and shock. Use of positive pressure ventilation helps improve gas exchange and hemodynamics by reducing LV preload and afterload leading to a reduction in MR and a consequent increase in the cardiac output.[12]

Vasodilators such as nitroglycerine and nitroprusside can be used in hemodynamically stable patients to reduce the afterload and augment forward flow, which leads to a reduction in effective regurgitant volume of MR. The American Heart Association (AHA) recommends norepinephrine or dopamine as a good initial vasoactive agent for hemodynamic support. However, once pressures stabilize, it is recommended to add an inotrope for patients with pump failure.[13] It is important to remember that even patients who do not present with cardiogenic shock initially can rapidly deteriorate. In studies, around 70% of patients who presented with acute MR secondary to PMR required mechanical circulatory support (MCS).[14]

Surgical repair of acute MR had a markedly improved survival rate compared to medical management (69% vs. 33%) in the APEX-AMI (Assessment of Pexelizumab in Acute Myocardial Infarction) trial. Even though the IABP-Shock II (Intra-aortic Balloon Pump in Cardiogenic Shock II) trial did not demonstrate a survival benefit from the use of an IABP in AMI with cardiogenic shock, it is prudent to remember that this study had excluded patients with mechanical complications, and it is still recommended by guidelines due to its potential to reduce afterload, as a bridge to definitive therapy.[15]

Free Wall Rupture

Since free wall rupture **(Figs. 1 and 2)** usually presents as out-of-hospital sudden death, the true incidence of this complication is unknown. Post the reperfusion era, the incidence of free wall rupture has dramatically decreased. Delayed reperfusion with thrombolytics carries an increased risk of free wall rupture because of intramyocardial hemorrhage and myocardial dissection leading to rupture. When diagnosed early by bedside echo, it warrants early surgical correction. Surgery though lifesaving still carries an in-hospital mortality of >35%.

Myocardial rupture can be classified into three types by Becker and van Mantgem **(Fig. 1 and Table 2)**.[16]

Ventricular Septal Rupture

The incidence of post-MI VSR reported in the literature is 0.3%.[17,18] Advanced age, female sex, and delayed reperfusion are risk factors for VSR. The usual timeline for the occurrence of VSR is 3–5 days post-MI. Patients usually present with acute dyspnea and orthopnea with a harsh systolic murmur heard on clinical

TABLE 1: Clinical characteristics of patients presenting with mechanical complications of acute myocardial infarction (AMI).

Papillary muscle rupture	Ventricular septal rupture
• Acute pulmonary edema • Cardiogenic shock • Eccentric/Broad jet of severe MR • Mobile mass in LV, prolapsing into LA	• Asymptomatic to circulatory collapse • Left-to-right shunt
Pseudoaneurysm	**Free wall rupture**
• Asymptomatic • Chest pain or HF • Small neck communication • To-and-fro blood flow through rupture	• Circulatory collapse • Pericardial effusion or tamponade • Electromechanical dissociation

(HF: heart failure; LA: left atrium; LV: left ventricle; MR: mitral regurgitation)

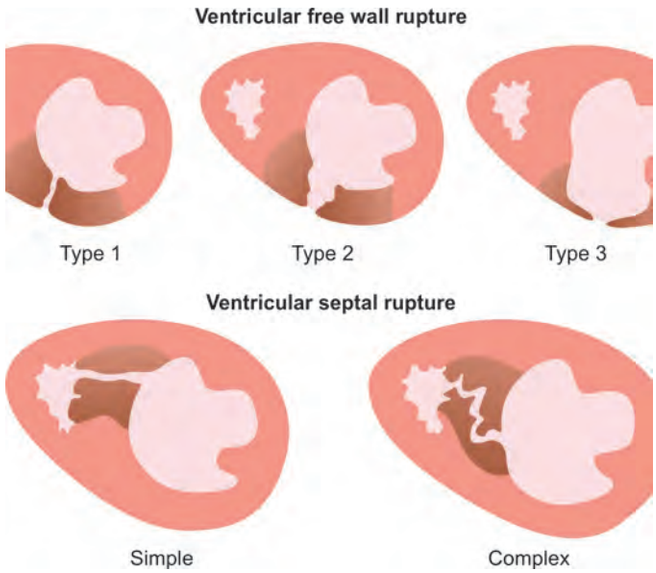


FIG. 1: Diagrammatic representation of types of myocardial free wall rupture and ventricular septal rupture.

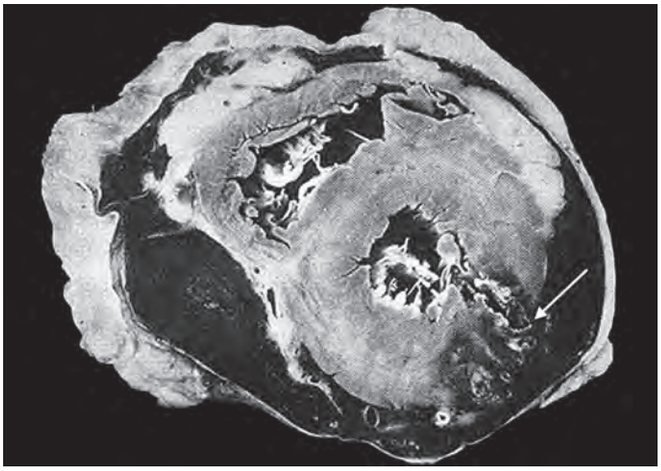


FIG. 2: Pathologic specimen showing free wall rupture (arrow) and hemopericardium after a myocardial infarction.

Source: Edwards WD. Applied anatomy of the heart. In: Brandenburg RO, Fuster V, Guiliani ER, McGoon DC (Eds). Cardiology: Fundamentals and Practice. Chicago: Year Book; 1987. p. 47.

TABLE 2: Becker and van Mantgem classification of myocardial rupture.[16]

Type 1	Abrupt slit-like tear that generally occurs within 24 hours of acute myocardial infarction (without thinning)
Type 2	Erosion of the infarcted myocardium, which is suggestive of a slow tear of the dead myocardium and typically occurs >24 hours after the infarction. The infarcted myocardium erodes before rupture and is covered by a thrombus
Type 3	Early aneurysm formation and subsequent rupture, i.e., perforation of a previously formed aneurysm

examination. Cold and clammy extremities, hypotension, acidosis, oliguria, and signs of pulmonary congestion are usually present. Transthoracic echocardiography is diagnostic for evaluating the size and location of the VSR (left-to-right shunt), MR, pericardial effusion (which might indicate free wall rupture), and assessment of LV and right ventricle (RV) function.

Right heart catheterization, if performed, shows a step up at the ventricular level due to the left-to-right shunt with an increase in the pulmonary blood flow (Qp), up to eight times over the systemic flow. Coronary angiography can guide the revascularization strategy in such patients. VSR is more commonly seen with anterior wall MIs; however, VSRs seen in inferior MIs are usually more complex. LAD territory-related infarcts are usually apical and anteriorly located, whereas posterior VSRs are usually seen in inferior infarcts. Inferior infarcts are also frequently associated with serpiginous defects. Posterior VSRs are usually accompanied by MR because of ischemic tethering, while RV dysfunction associated with VSRs usually points to a proximal RCA culprit.

The 30-day mortality for an AMI-related VSR is close to 80%; hence, conservative medical therapy alone is not recommended unless there is a prohibitive surgical risk or a hemodynamically insignificant shunt.[17,19,20]

Management of Ventricular Septal Rupture

Surgery is usually delayed until after stabilization in patients with VSR, except in patients with early shock and no evidence of end organ involvement, who are usually the best surgical candidates. In others, initial management centers around hemodynamic stabilization. Afterload reduction strategies, both pharmacological and mechanical, are employed to improve forward flow into the aorta and reduce shunt across the VSR. An IABP is the most used cost-effective measure to reduce afterload [up to 75% of post-infarct VSRs in the SHOCK trial had an IABP]. IABP with pharmacotherapy (IV nitroprusside) is used in >80% of emergency and 65% of urgent repairs.[21,22] Post initiation of IABP, there was a mean increase of around 40 mm Hg in the mean systolic blood pressure (BP) (81–102 mm Hg) in 30 minutes. Extracorporeal membrane oxygenation (ECMO) may be considered as a bridge to surgery in patients with multi-organ involvement/failure. ECMO, Impella, and TandemHeart have been shown to be as effective as each other in providing hemodynamic support as a bridge to definitive therapy. In the absence of end organ failure, a delayed surgery will allow scar formation resulting in a better anchor for suture material resulting in a lesser risk of patch dehiscence. Lower mortality is reported when surgery is delayed a week after diagnosis, although selection and survival bias may explain these reported outcomes. In patients with cardiogenic shock and refractory pulmonary edema despite MCS, emergency surgery is indicated, albeit at a high perioperative mortality risk.[15]

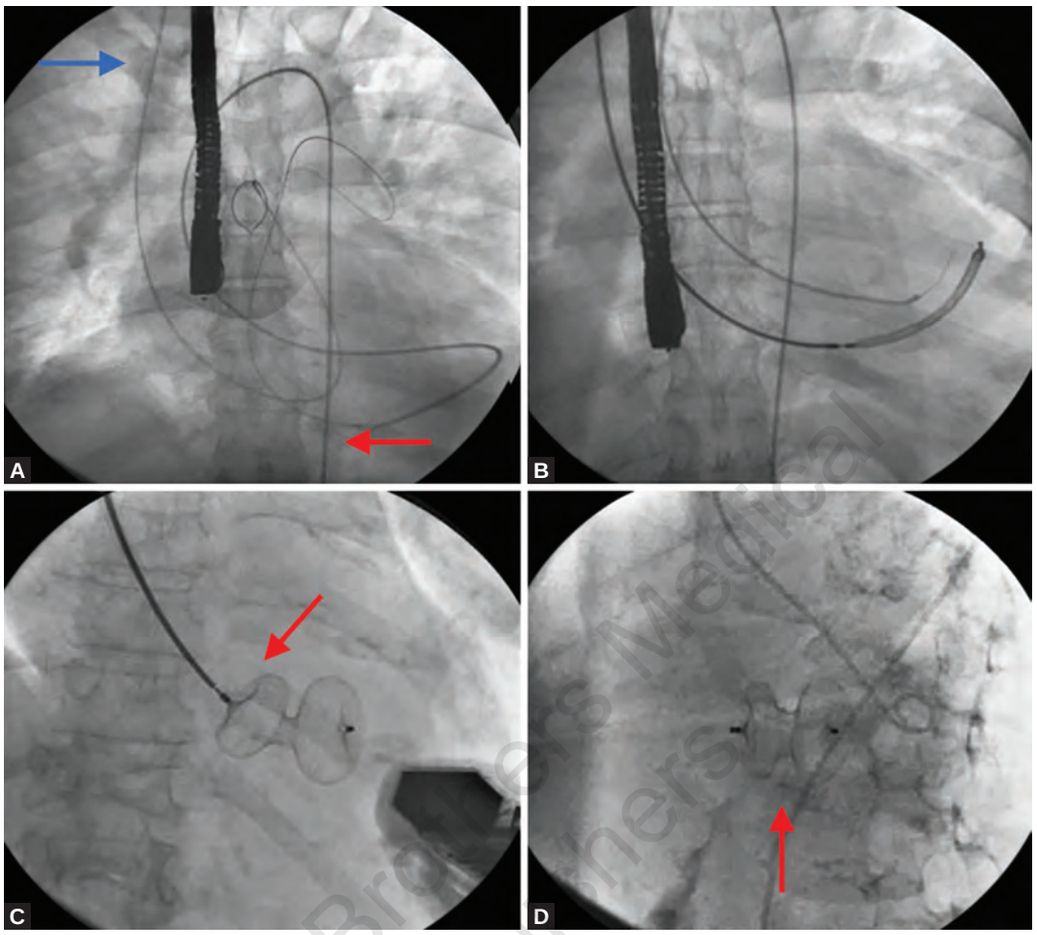
Cardiac Surgery

Bypasses are performed first with a view to protect the myocardium and reduce cardiac handling post VSR repair. Primary repair (Daggett technique) and infarct exclusion (David technique) are the most common surgical repairs. A patch repair using pericardium or synthetic material is performed by placing the pressurized patch on the LV side with pledgeted sutures on the RV side. True apical defects are repaired by amputating the apex. Operative mortality of VSR has been around 40% over the last few decades. Poor LV function, cardiogenic shock, inferior MI, need for inotropes, and total occlusion of the infarct-related artery are poor prognostic factors.[15]

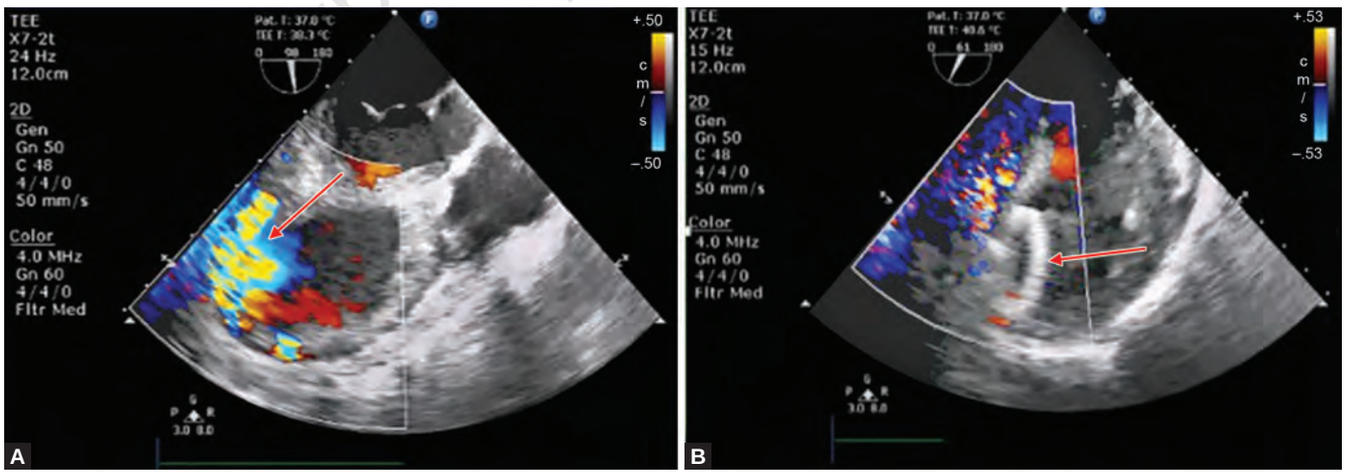
Transcatheter Closure of Ventricular Septal Rupture

Percutaneous closure of post-MI VSR has traditionally been reserved for patients not suitable for surgical closure due to high risk. However, it presents a viable option in many patients, especially with anterior MI and mid-muscular defects, for early closure. Procedure is done under general anesthesia (GA) with TEE guidance for appropriate sizing of device. Arteriovenous (AV) loop is created by crossing, using a hydrophilic wire from left to RV into the pulmonary artery (PA). Sheath is advanced over this loop, and device is deployed **(Figs. 3 and 4)**. Even though there is a high procedural success reported ranging from 80 to 100% in centers of excellence worldwide, hospital mortality remains very high and procedural complications are commonly encountered. High MELD (model for end-stage liver disease) score, high Qp/systemic flow (Qs) at closure, and presence of residual defect are predictors of adverse outcomes.

Cardiac transplant or long-term MCS or total artificial heart is the last resort in patients with refractory shock and



FIGS. 3A TO D: Steps of percutaneous device closure of acute myocardial infarction (AMI) ventricular septal rupture (VSR). (A) Creation of an arteriovenous loop (red arrow arterial end, blue arrow venous end); (B) device across the defect; (C) deploying device; (D) final position of device across defect.



FIGS. 4A AND B: (A) Pre and (B) post transesophageal echocardiographic images showing (A) ventricular septal rupture (VSR) and (B) device across defect with no residual shunt.

(TEE: transesophageal echocardiography)

TABLE 3: Our experience with percutaneous closure of ventricular septal rupture (VSR) due to acute myocardial infarction (AMI) at Krishna Institute of Medical Sciences (KIMS), Secunderabad.

Total cases with VSR	16
Territory • Anterior MI • Inferior/Posterior MI	 13 3
Mean duration from diagnosis to procedure	6.3 days (range 3–10 days)
Cardiogenic shock on admission	9
Procedural success • Anterior MI ○ Inferior/posterior MI ○ Total	12/13 (*92.3%*) 0/3 12/16 (*75%*)
Survival to discharge (all cases) • Anterior MI ○ Inferior/posterior MI ○ Total	 8/13 0/3 8/16 (*50%*)
Survival to discharge (post successful closure) • Anterior MI	8/12 (*66.7%*)
3-month survival post discharge	7/8 (*87.5%*)

(MI: myocardial infarction)

biventricular failure, which deems them high risk for surgical/transcatheter closure.

Our experience at Krishna Institute of Medical Sciences, Secunderabad, with percutaneous closure of ventricular septal rupture due to acute myocardial infarction.

We have been performing device closure for patients with VSR due to AMI at our center since December 2005. The findings of our case series are summarized in **Table 3**. We have found that, generally, patients with anterior MI do well with device closure with us achieving procedural success (defined as successful deployment of device with no complication and no significant residual shunt) in 12 out of 13 cases with anterior MI and muscular defects. In patients with inferior MI, we have found that the defect is usually serpiginous which makes it less amenable to closure and the procedure more likely to fail in such cases. Patients with cardiogenic shock do worse than those with hemodynamic stability. Even after successful closure, these patients tend to have a stormy in-hospital course with most requiring prolonged intensive care unit (ICU) stay to tackle the multiorgan dysfunction. Those who succumb post successful closure do so mostly due to multiorgan failure. Those who stabilize to discharge generally do well on follow-up. Out of 12 successful device closure patients, one patient had a persistent atrial flutter on day 2 post closure, which was successfully cardioverted with ibutilide.

A total of eight patients made it to discharge. Of the eight discharged, one was readmitted after 45 days with severe sepsis, left ventricular failure (LVF), and ventricular tachycardia (VT) and eventually succumbed; seven patients are alive and doing well on regular follow-up.

PROGNOSIS

Even though science and management options have grown by leaps and bounds over the past few decades, the outcomes and overall prognosis for patients with mechanical complications post AMI remain grave. Cardiogenic shock which results because of a decreased cardiac output (consequent to widespread myocardial necrosis) triggers a vicious cycle of systemic hypoperfusion, which further fuels maladaptive cycles of myocardial ischemia, inflammation, vasoconstriction, and volume overload leading to multisystem failure and death.[23]

Despite advances in management for patients presenting with mechanical complications and cardiogenic shock, most studies have shown that the mortality rates have remained largely unchanged despite the use of MCS devices, percutaneous therapies, and improvements of surgical techniques and outcomes over time.[7,15] There is no proven significant difference in this subset of patients presenting with mechanical complications of primary PCI versus fibrinolysis combined with adjunctive medical therapy.[24]

Majority of studies have shown an incidence of shock in about 75% of patients with mechanical complications with most requiring multiple vasopressors or a ventricular circulatory support device—either a balloon pump or a percutaneous device.[25]

Left Ventricular Pseudoaneurysm

Cardiac rupture contained by pericardial adhesions results in the formation of LV pseudoaneurysms. Etiology of pseudoaneurysms is most commonly post-AMI; however, they have also been reported post chest trauma (blunt/penetrating) infective endocarditis-related sequelae as well as postcardiac surgery. When compared to true aneurysms, pseudoaneurysms are more often seen involving the lateral or inferior wall. Acute anterior MI leading to rupture is usually immediately fatal; however, pseudoaneurysms can remain undiagnosed for several months or more.

Most of the patients are usually asymptomatic at diagnosis, though some may present with features of congestive cardiac failure, chest pain, or breathlessness. Symptomatic arrhythmias, systemic embolism, and sudden death may also be present in rare cases. A high index of suspicion is needed to look for and diagnose pseudoaneurysms. They usually have a narrow neck and lack the normal structural elements found in an intact cardiac wall.

Left ventricular pseudoaneurysms are surgical emergencies due to their high propensity for progressive rupture. Primary repair with pledgeted sutures using polytetrafluoroethylene felt as well as Gore-Tex patches can be performed. Autologous pericardial or Dacron double patches can also be used to repair pseudoaneurysms. Percutaneous repair of LV pseudoaneurysm using a retrograde approach across the aortic valve has been described.[15] The procedure is usually done under GA with TEE guidance. In our experience, we have had two cases for which percutaneous closure of pseudoaneurysm was done and are doing well on follow-up.

DIFFERENTIAL DIAGNOSIS OF MECHANICAL COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

Differential diagnosis of mechanical complications of AMI is given in **Box 1**.

Decision-making

In all patients with mechanical complications post MI, a heart team discussion and integrated planning and approach are essential. Often, these patients have multiorgan involvement, and hence a multidisciplinary team (shock team/heart team) approach is often needed. Critical care support is paramount in the stabilization of these patients who often need mechanical ventilation, high inotropes, MCSs, and renal replacement therapies. Issues such as palliative care, role of transplant, and long-term MCS need to be discussed with family as and when relevant.

A suggested treatment pathway for management of stable and unstable mechanical complications of AMI is summarized in **Flowchart 1**.[15]

CONCLUSION

Mechanical complications occurring in patients with AMI are usually critical time-sensitive events. They are associated with high mortality and morbidity despite best efforts and available treatment strategies. Early diagnosis and prompt hemodynamic support with a multidisciplinary approach are essential to improve outcomes.

BOX 1 **Differential diagnosis of mechanical complications of acute myocardial infarction (AMI).[15]**

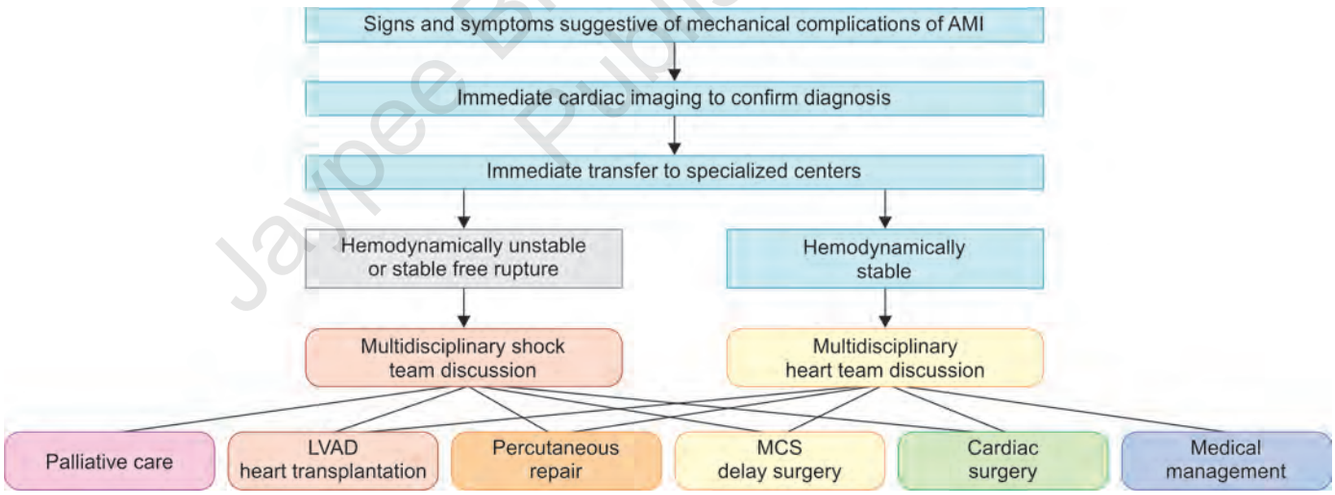
Unrelated to AMI

- Dynamic LVOTO
- Acute pulmonary thromboembolism
- Acute valvular emergency
  - Acute severe MR
  - Acute severe AR
  - Acute prosthetic valve failure
- Cardiac tamponade
- Septic shock
- Acute aortic dissection

Related to AMI

- LV predominant cardiogenic shock
- RV predominant cardiogenic shock
- Dynamic LVOTO
- Occult blood loss
- Drug related
  - Overzealous use of BB or ACE inhibitor if NTG in a preload sensitive/intravascularly depleted state

(ACE: angiotensin-converting enzyme; AR: aortic regurgitation; BB: β-blockers; LV: left ventricle; LVOTO: left ventricular outflow tract obstruction; MR: mitral regurgitation; NTG: nitroglycerin; RV: right ventricle)



FLOWCHART 1: Suggested treatment pathway for management of stable and unstable mechanical complications of acute myocardial infarction (AMI).

(LVAD: left ventricular assist device; MCS: mechanical circulatory support)

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CHAPTER 67

Free Wall Rupture, Can We Mend the Broken Heart?

Ashesh Halder, DP Sinha

ABSTRACT

Free wall rupture (FWR) is one of the devastating mechanical complications of acute myocardial infarction. The incidence of FWR has declined over the years, especially with the introduction of primary percutaneous coronary intervention. FWR may be presented acutely with tamponade and electromechanical dissociation, and subacute rupture and pseudoaneurysm formation are not seen infrequently nowadays. Despite the high mortality rate, surgical repair is the treatment modality of choice, and satisfactory outcomes can be achieved with sutureless technique in the "oozing" type of rupture.

INTRODUCTION

It is considered that the first report of myocardial rupture was recorded by William Harvey in 1649.[1] Subsequently, Morgagni collected 10 cases. Morgagni himself was supposed to have died of cardiac rupture (CR) at the age of 79 years.[2] Richard Quain is the one who correlated this condition with the obstruction of the respective coronary artery in 1851.[3] The initial reports on CR, beginning in the mid-17th century, focused primarily upon the dramatic findings of hemopericardium and the rent or tear of the heart wall. During the 250 years that followed through the last half of the 19th century, careful observations and more detailed accounts gradually established myocardial infarction (MI) caused by coronary artery obstruction as the principal underlying reason for this catastrophic event.[1]

CAUSES OF CARDIAC RUPTURE

Acute MI is by far the most common cause of myocardial rupture. Other causes include blunt cardiac trauma, especially in the setting of automobile accidents as a result of cardiac compression between sternum and spine, and direct impact to the heart by sternum or deceleration injury. Penetrating cardiac trauma by stab injury or gunshot also causes CR.

Other rare causes of myocardial rupture are myocardial abscess following infective endocarditis, particularly prosthetic valve endocarditis, myocardial necrosis due to myocarditis, tuberculosis, sarcoidosis, primary cardiac tumors, or secondary cardiac malignant deposits. Takotsubo cardiomyopathy has rarely been reported to be associated with myocardial rupture.

Despite progressive lowering of mortality in the era of reperfusion, MI still carries a significant risk of in-hospital death (10.4% in 1994 to 6.3% in 2006 in USA and similar results were seen across countries).[4] Early hospital death is most commonly due to arrhythmia or pump failure.

In the era of mechanical reperfusion, mechanical complications such as left ventricular free wall rupture (LVFWR), ventricular septal rupture (VSR), or papillary muscle rupture (PMR)/dysfunction leading to severe mitral regurgitation are uncommon.

The incidence of rupture has decreased from 1970s and 1980s to 1–3% in current reports.[5] However, the consequences of rupture remain catastrophic, and it is the proximate cause of death in 15% of patients in hospitals.[6] In this context, it should be remembered that the true incidence of LVFWR may be underestimated as many out-of-hospital sudden cardiac deaths may be due to LVFWR. Before the era of fibrinolytic reperfusion, VSR or PMR complicated 6% of MI.[7]

Figueras et al.[7] in an overview of CR in a single hospital during a 30-year period, reported an initial prevalence of 6% before 1982, with a progressive decline to 3.2% during 2001–2006, despite a trend toward increasing age (one of the most powerful risk factors for CR). With use of thrombolytics, primary percutaneous coronary intervention (PPCI) and modern therapeutics, the incidence of VSR and free wall rupture (FWR) was further reduced.[8] In MI patients without

reperfusion therapy, mechanical complications typically occur within the first 2 weeks after MI, peaking 3–7 days from the onset of symptoms.[9] It usually does not occur after 10 days.[10] Left ventricular free wall is more commonly involved compared to right ventricular free wall. A trial wall rupture is rarely seen.

In the initial hours after MI, there are few neutrophil migrations into the infarcted tissue; however, coagulative necrosis starts and early rupture occurs in places with large intramural hematoma that penetrates heart tissues and dissect left ventricular walls. Exuberant inflammatory response, coagulation necrosis, neutrophilic predominance, and eosinophilic infiltrations are intricately related to FWR in 1–4 days. Increased matrix metalloproteinase activity is also implicated in such a scenario. Though the classical site of rupture is the border zone of infarct area and the viable myocardium, it is not uncommon to find the rupture site at the center of the necrosis after few days.[10] Undue wall stress on the infarcted tissue, and the mechanical stress on the infarcted segment by the surrounding viable myocardium predisposes to rupture. Smaller transmural infarct in combination with relatively preserved left ventricle (LV) systolic function increases the propensity of rupture as it generates higher intracavitary pressure compared to larger transmural infarct with significant impairment of systolic function where the proneness of rupture is low. Acute rupture is commonly observed in anterior and lateral walls, but subacute rupture usually involves the inferior–posterior wall as there is increased likelihood of clot formation, which can adhere to the ruptured site and may prevent overt bleeding into the pericardial cavity.[11]

Although thrombolysis is necessary to reduce infarct size, in some cases, it is believed that late thrombolysis promotes hemorrhagic dissection of the infarcted wall, thereby accelerating the rupture of free wall. However, in GRACE (Global Registry of Acute Coronary Events) registry, although late thrombolysis was associated with higher risk of heart rupture in univariate analysis, neither use of thrombolysis nor its timing was significant in multivariate analysis.[8]

Based on the pathological criterion, FWR was divided into the following:

- *Blow out type*: A sudden fissure rupture in the myocardium occurring within 24 hours of index MI
- *Oozing type*: With an erosion of the infarct zone with gradual worsening of tear and leakage into pericardium
- *Pseudoaneurysm type*: When pericardial adhesion is sufficient to prevent free rupture for 2 weeks or more12

The risk factors for FWR have been studied. In GRACE registry[8] of 60,198 patients, incidence of heart rupture was 0.45% (273 patients), of which FWR occurred in 118 patients. In the multivariate analysis, the following factors were associated with an increased risk of heart rupture: ST elevation MI/left bundle branch block (LBBB) [odds ratio (OR) 2.10; confidence interval (CI) 1.49–2.97], acute coronary syndrome (ACS)/non-ST-elevation myocardial infarction (NSTEMI) (OR 1.66; CI 1.12–2.46), female gender (OR 1.54; CI 1.18–2.01), past stroke (OR 1.5; CI 1.01–2.22), positive initial enzymes (OR 1.44; CI 1–1.94), age per extra 10 years (OR 1.36; CI 1.22–1.52), heart rate (HR) per extra 30 bpm (OR 1.32; CI 1.13–1.54), and systolic blood pressure (SBP) per 30 mm drop (OR 1.17; CI 1.07–1.27).

Conversely, use of low-molecular-weight heparin (OR 0.62; CI 0.48–0.84), use of β-blockers in the first 24 hours (OR 0.62; CI 0.47–0.82), and history of previous MI (OR 0.45; CI 0.31–0.66) were negatively associated with risk of CR. The GRACE risk score was higher in patients with CR in the GRACE registry; however, in multivariate analysis, it was not found to be significant.

In the SHOCK registry, the incidence of LVFWR or cardiac tamponade occurred in 2.7% of overall cohort with cardiogenic shock.[12] Prior MI, diabetes, previous congestive heart failure, and peripheral vascular disease were less commonly seen in patients with rupture/tamponade.

Despite current advances in management, LVFWR was associated with hospital mortality exceeding 80% and together with VSR account for 5.6% of all deaths in GRACE registry.[8]

CLINICAL PRESENTATION

Typical presentation of myocardial rupture is electromechanical dissociation often preceded by nausea, vomiting, restlessness, precordial pain, and abrupt bradycardia and/or hypotension, which may be transient, in case the rupture is temporarily sealed by pericardium.[13] Rupture accounts for 95% of deaths due to electromechanical dissociation after MI.

Most patients succumb almost instantaneously, but others may present in less acute conditions, mostly with hypotension and cardiogenic shock similar to other patients presenting with cardiogenic shock. In patients with cardiogenic shock due to LVFWR or due to pump failure, there was no significant difference in the time of onset of cardiogenic shock from index MI or in the use of thrombolytic therapy.

So, presentation of FWR can be "acute" with features of tamponade and electromechanical dissociation leading to death in most of the cases. In "subacute" rupture, there is moderate-to-severe pericardial effusion, but the breach on the wall is *temporarily* sealed by the clot or pericardial adhesions, and it may also progress to tamponade. Sometimes, there is slow leakage of blood and the site of rupture is plugged by the hematoma and thrombus, thus impeding overt bleeding into the pericardial cavity; with time, this will lead to pseudoaneurysm formation where the wall is formed by the organized thrombus and fibrous pericardium. Typically, pseudoaneurysm has a narrow neck and has a tendency to rupture **(Figs. 1 and 2)**.[14,15]

DIAGNOSIS OF FREE WALL RUPTURE

Prompt echocardiography should be done in highly suspected cases of FWR (signs of tamponade, hypotension, cardiogenic shock, sudden electromechanical dissociation, junctional rhythm, etc.). Multidetector computed tomography (CT) can be helpful in doubtful cases. Cardiac magnetic resonance (CMR) should be reserved for the clinically stable patients, especially to differentiate aneurysm from pseudoaneurysm and for the surgical planning.[16]

MANAGEMENT

Left ventricular FWR is associated with high risk of mortality (75–90%) without surgical repair. The acute rupture is invariably fatal and makes every resuscitative effort futile; subacute rupture

provides a window of opportunity for surgical intervention. Elective surgery is also mandatory in pseudoaneurysm as the risk of rupture is quite high, around 50% in untreated cases.[17]

It is utmost important to stabilize the patient as far as possible depending on the clinical scenario before the definitive surgical repair is undertaken.

Fluid replacement should be done preferably using colloid/crystalloid, and it should be used along with the dobutamine infusion (5–10 μg/kg/min) to maintain the peripheral perfusion and adequate urine output. Mechanical circulatory support by means of an intraaortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO) can be used whenever

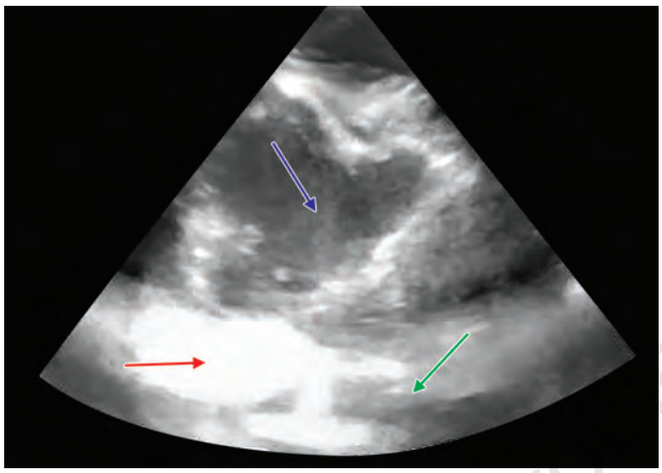


FIG. 1: A 68-year old gentleman presented late in hospital with inferolateral wall myocardial infarction. During in-hospital stay, he developed recurrent hypotensive episodes responding to intravenous fluid, bilateral pleural effusion, and acute kidney injury. Red arrow: Left ventricle (LV) cavity in parasternal short-axis (PSAX) view. Blue arrow: Left ventricular free wall rupture (LVFWR) involving lateral wall, the ruptured site is contained by possible clot. Green arrow: Hemopericardium. This patient never had any evidence of tamponade.

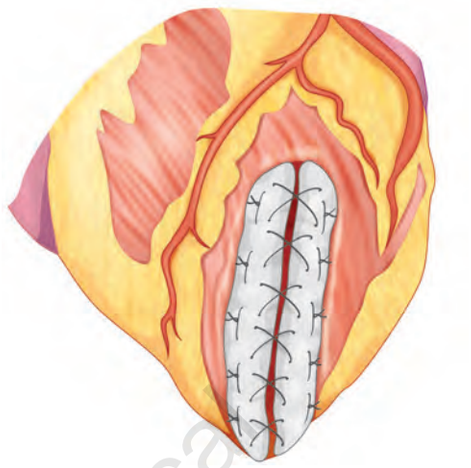


FIG. 3: Linear closure with the Teflon felt.

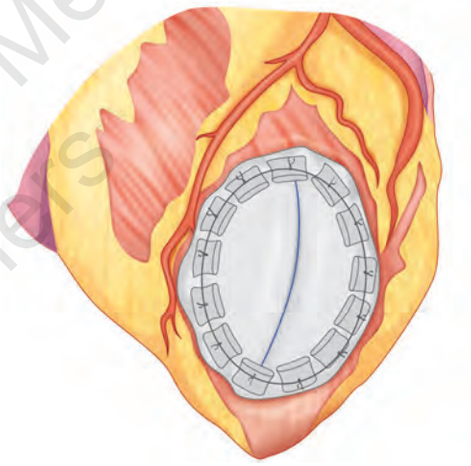


FIG. 4: Infarctectomy and prosthetic patch placement.

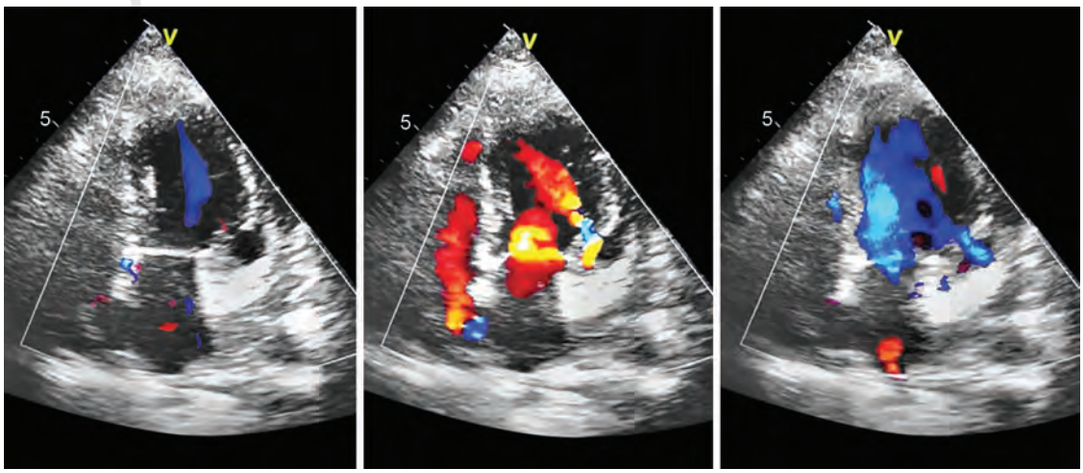
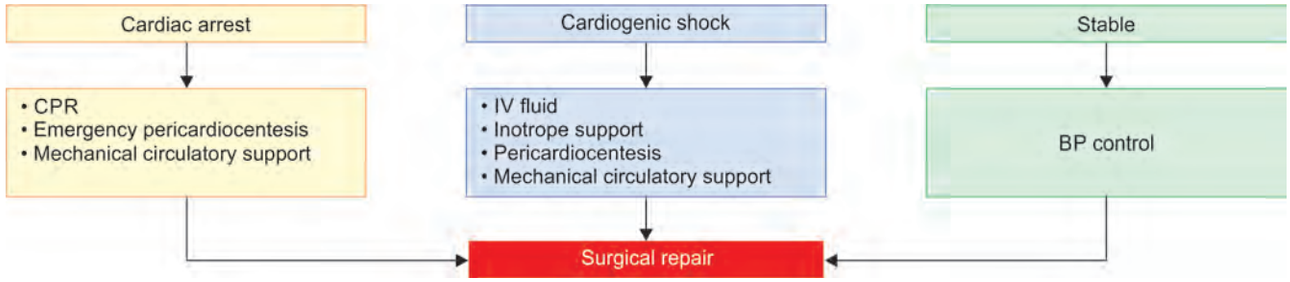
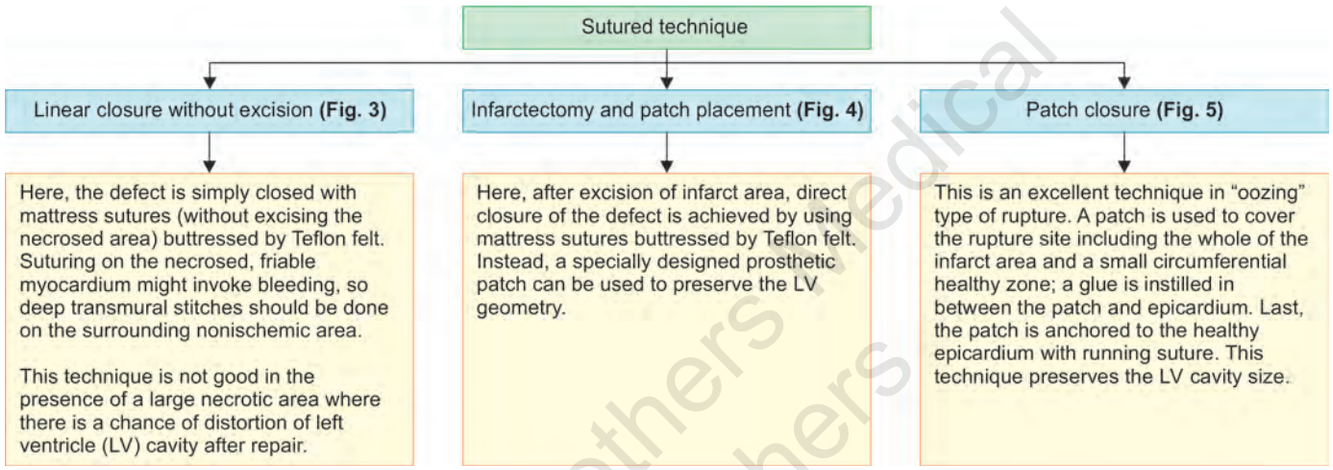


FIG. 2: A 78-year-old lady presented late in hospital with nonanginal chest pain and breathlessness; she was hemodynamically stable otherwise. She had a recent inferolateral wall ST-elevation myocardial infarction (STEMI) and was managed with optimal medical therapy. Echocardiography (A4C view) revealed a small pseudoaneurysm with mild pericardial effusion without any evidence of tamponade involving the lateral wall of LV.



FLOWCHART 1: Management of free wall rupture.
(BP: blood pressure; CPR: cardiopulmonary resuscitation; IV: intravenous)



FLOWCHART 2: Surgical repair techniques of free wall rupture.

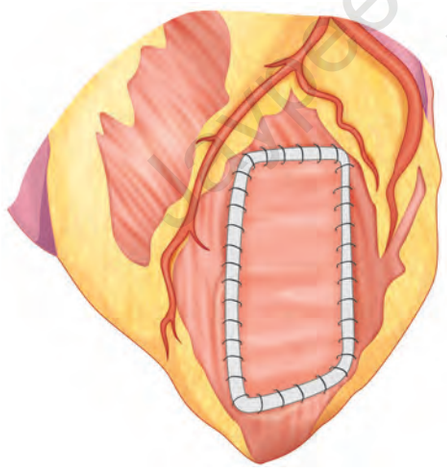


FIG. 5: Patch closure with glue and running suturing over the healthy tissue.

feasible. Pericardiocentesis should be done only in the presence of tamponade, that too in small quantity (10–50 mL) just to stabilize the patient temporarily while preparing for surgery.[18] Pericardiocentesis in the presence of LVFWR may paradoxically deteriorate the clinical picture by dislodging the clot from the ruptured site and thus disrupting the contained rupture; it may also be ineffective sometimes because of presence of clot. Subxiphoid drainage or drainage through sternotomy may be required in a case-to-case basis **(Flowchart 1)**.

The treatment of choice in FWR is surgery despite the fact that it is associated with high mortality (40–50%). Two surgical techniques are commonly employed—sutured and sutureless techniques.[19] Performing coronary angiogram is controversial, but it is worthwhile to mention that it should not delay the life-saving surgery **(Flowchart 2)**.

Sutureless technique (Fig. 6)

In this technique, a prosthetic patch (pericardium, Dacron, Teflon, Goretex, etc.) is secured to the epicardium at ruptured site, infarcted area, and a small peri-infarcted healthy tissue with the use of biological (fibrin based, gelatin hydrogels) or synthetic glue. It is preferable to use this method in "oozing" type of rupture. Using sutureless technique in "blowout" rupture increases the propensity of rerupture, aneurysm, or pseudoaneurysm formation as the glued patch may not withstand the high intraventricular pressure.

More recently, collagen sponge patch (TachoSil) has been used with promising result.

A sutureless technique does not lead to any ventricular cavity distortion and avoids suture-related injury to the peri-infarct healthy myocardium but it is worthwhile to restrict its use in "oozing" type of rupture.

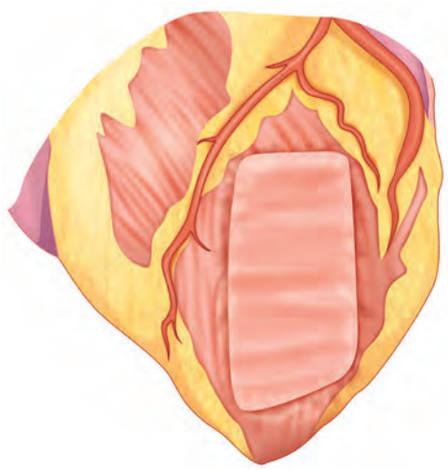


FIG. 6: Sutureless technique.

Postoperative management is also crucial:

- Strict control of blood pressure (BP) and HR
- Alleviation of anxiety
- Extended bed rest for 4–8 days
- Maintaining adequate peripheral perfusion: Inotrope, IABP
- Avoidance of any undue physical strain

Percutaneous procedures

Percutaneous intrapericardial fibrin-glue injection therapy (PIFIT) has been used as a new therapeutic option to treat FWR. Follow-up echocardiography did not show any constrictive physiology with such therapy. This can be used in high surgical risk situations.[20]

Percutaneous closure of pseudoaneurysm can also be done with devices such as Amplatzer septal occluder.[21]

Repair of pseudoaneurysm

Management of asymptomatic pseudoaneurysm of <3 cm without any evidence of expansion is controversial; conservative approach might be reasonable. Apart from this, all other pseudoaneurysms irrespective of their symptom status require surgical correction by means of direct linear closure or patch closure as they are associated with sudden cardiac death and high-risk rupture.

Percutaneous device closure is also an option.

In a recent meta-analysis,[22] outcomes of surgical treatment of LVFWR were assessed: oozing type versus blowout type [risk ratio (RR) 0.47; 95% CI 0.33–0.67; $p < 0.0001$ in favor of oozing type with respect to operative risk] and sutured repair versus sutureless repair (RR 0.59; 95% CI 0.41–0.83; $p = 0.002$ in favor of sutureless technique) **(Table 1)**. There was no significant difference between these two techniques on whether a concomitant IABP was used **(Table 1)** or on the location (anteroapical vs. posterolateral wall) of rupture. Use of ECMO was associated with worse prognosis **(Table 2)**. Use of cardiopulmonary bypass or concomitant bypass surgery had no significant effect on the prognosis **(Table 3)**.

PROGNOSIS

Patients who were treated conservatively had a very high mortality rate (90%) compared to mortality rate of around 40–50% with surgical repair.[19] In-hospital survival after surgery depends on several factors such as cardiac arrest at presentation and type of rupture ("blowout" vs. "oozing"). In one study: in-hospital, 5- and 10-year survival was around 83%, 69%, and 63%, respectively; a sutureless technique was used exclusively, and "oozing" type of rupture was present in 94% of patients. They did not use cardiopulmonary bypass in any patient.[23] In another single-center study: in-hospital, 5- and 10-year survival was 66%, 53%, and 49%, respectively; almost 45% of patients had "blowout" rupture, and both "direct suture" and "patch and glue" techniques were used in this study.[24] Type of rupture and technique of repair might have an impact on the overall short- and long-term prognoses.

Is there any role of conservative treatment in FWR?

In selected patients, long-term survival has been documented with conservative treatment. It may be helpful in "oozing" type of rupture and in elderly patients having very high surgical risk. But surgery is unquestionably the treatment of choice.[25] If conservative treatment is the only available option (such as in a very elderly frail patient or, if surgery is declined) then the following flowchart can be followed.[18,26]

Cardiopulmonary resuscitation (CPR), oxygenation/ventilation, IV fluids, dobutamine infusion, pericardiocentesis in selected cases.

↓

With hemodynamic improvement, dobutamine infusion should be replaced with β-blocker with an aim to maintain the systolic blood pressure (SBP) 100–120 mm Hg.

↓

Extended bed rest, avoidance of undue physical effort, and follow-up echocardiography.

Note: Presence of electromechanical dissociation at presentation does not mean that the patient could not be saved without emergency surgery.

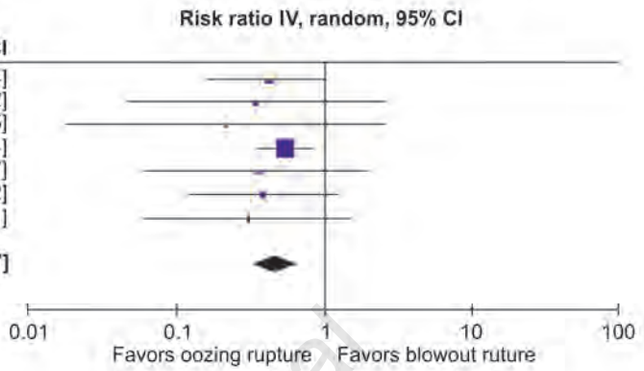
CONCLUSION

Left ventricular FWR is a dreadful mechanical complication of acute MI. Acute FWR is invariably fatal because of insufficient time for surgical intervention whereas surgical repair is the treatment of choice in subacute and chronic FWR. Refinement of surgical techniques and introduction of sutureless methods have made an impact on the overall prognosis and outcome of LVFWR.

TABLE 1: Forest plots of comparison: (A) Oozing rupture versus rupture; (B) Sutureless repair versus sutured repair; (C) Preoperative intraaortic balloon pump (IABP) support versus no IABP support; outcome of interest: operative mortality.

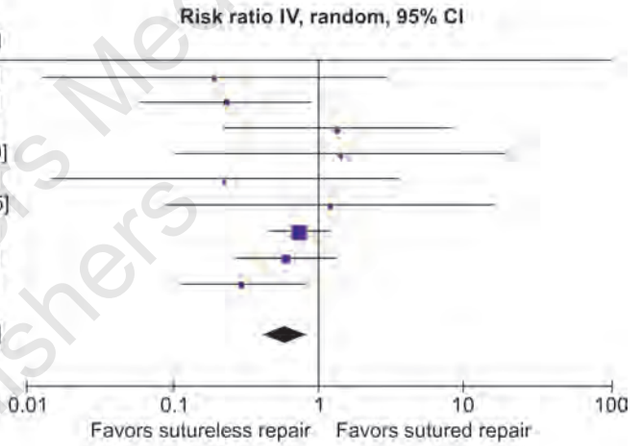
Study or subgroup	Oozing rupture Events	Total	Blowout rupture Events	Total	Weight	Risk ratio IV, random, 95% CI
Formica et al. 2017	4	19	8	16	12.7%	0.42 [0.16, 1.14]
Haddadin et al. 2009	1	8	4	11	3.2%	0.34 [0.05, 2.52]
Iemura et al. 2001	1	14	1	3	2.1%	0.21 [0.02, 2.55]
Matteucci et al. 2020	21	79	30	61	63.5%	0.54 [0.35, 0.84]
McMullan et al. 2001	1	4	10	14	4.2%	0.35 [0.06, 1.97]
Okada et al. 2005	2	6	7	8	9.4%	0.38 [0.12, 1.22]
Okamura et al. 2019	5	33	1	2	4.9%	0.30 [0.06, 1.51]
Total (95% CI)		**163**		**115**	**100.0%**	**0.47 [0.33, 0.67]**
Total events	35		61			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.43$, df = 6 ($p = 0.96$); $I^2 = 0\%$
Test for overall effect: Z = 4.19 ($p < 0.0001$)



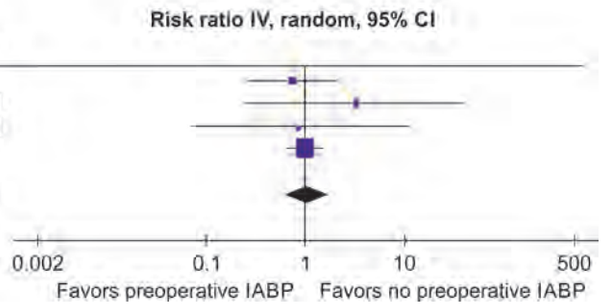
Study or subgroup	Sutureless repair Events	Total	Sutured repair Events	Total	Weight	Risk ratio IV, random, 95% CI
Flajsig et al. 2002	0	5	8	19	1.6%	0.20 [0.01, 2.92]
Formica et al. 2017	2	16	10	19	6.4%	0.24 [0.06, 0.93]
Haddadin et al. 2009	1	3	4	16	3.6%	1.33 [0.22, 8.16]
Iemura et al. 2001	1	7	1	10	1.8%	1.43 [0.11, 19.20]
Kacer et al. 2020	0	5	5	14	1.6%	0.23 [0.01, 3.51]
Mantovani et al. 2002	0	1	3	16	1.8%	1.21 [0.09, 15.95]
Matteucci et al. 2020	16	54	35	86	50.9%	0.73 [0.45, 1.18]
Okada et al. 2005	4	8	5	6	19.6%	0.60 [0.28, 1.31]
Okamura et al. 2019	6	35	4	7	12.7%	0.30 [0.11, 0.79]
Total (95% CI)		**134**		**193**	**100.0%**	**0.59 [0.41, 0.83]**
Total events	30		75			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.93$, df = 8 ($p = 0.54$); $I^2 = 0\%$
Test for overall effect: Z = 3.04 ($p = 0.002$)



Study or subgroup	Preoperative IABP Events	Total	Preoperative IABP Events	Total	Weight	Risk ratio IV, random, 95% CI
Formica et al. 2017	4	14	8	21	16.3%	0.75 [0.28, 2.02]
Iemura et al. 2001	1	4	1	13	2.5%	3.25 [0.26, 41.01]
Kacer et al. 2020	0	1	5	18	2.6%	0.86 [0.07, 10.54]
Matteucci et al. 2020	19	51	32	89	78.6%	1.04 [0.66, 1.63]
Total (95% CI)		**70**		**141**	**100.0%**	**1.01 [0.67, 1.50]**
Total events	24		46			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.19$, df = 3 ($p = 0.76$); $I^2 = 0\%$
Test for overall effect: Z = 0.03 ($p = 0.97$)

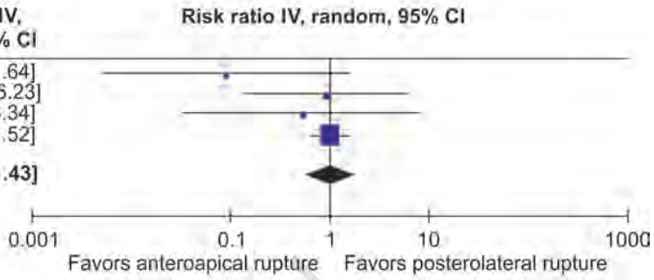


Source: Adapted from Matteucci et al.[22]

TABLE 2: Forest plots of comparison: (A) Anteroapical rupture versus posterolateral rupture; (B) Concomitant coronary artery bypass grafting (CABG) versus no CABG; (C) Postoperative extracorporeal membrane oxygenation (ECMO) support versus no ECMO support; outcome of interest: operative mortality.

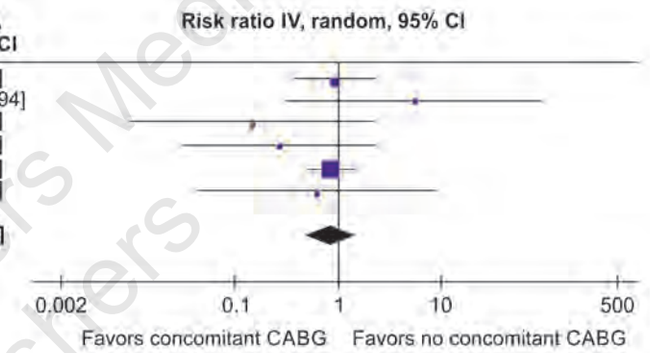
Study or subgroup	Anteroapical rupture Events	Total	Posterolateral rupture Events	Total	Weight	Risk ratio IV, random, 95% CI
Iemura et al. 2001	0	12	2	5	2.3%	0.09 [0.01, 1.64]
Kacer et al. 2020	1	4	4	15	5.4%	0.94 [0.14, 6.23]
Mantovani et al. 2020	0	3	3	14	2.6%	0.54 [0.03, 8.34]
Matteacci et al. 2020	17	47	34	93	89.7%	0.99 [0.62, 1.52]
Total (95% CI)		**66**		**127**	**100.0%**	**0.92 [0.59, 1.43]**
Total events	18		43			

Heterogeneity: Tau² = 0.00; Chi² = 2.69, df = 3 (p = 0.44); I² = 0%
Test for overall effect: Z = 0.38 (p = 0.71)



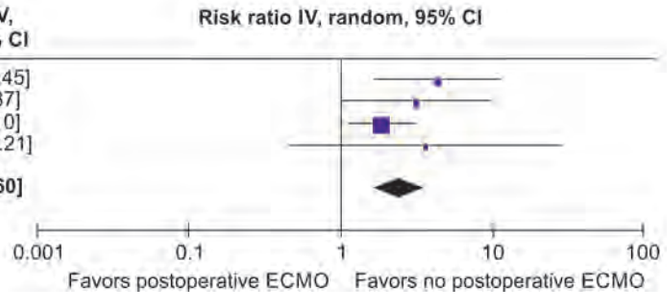
Study or subgroup	Concomitant CABG Events	Total	No concomitant CABG Events	Total	Weight	Risk ratio IV, random, 95% CI
Formica et al. 2017	5	15	7	20	22.4%	0.95 [0.37, 2.42]
Iemura et al. 2001	2	8	0	9	2.3%	5.56 [0.31, 100.94]
Kacer et al. 2020	0	7	5	12	2.6%	0.15 [0.01, 2.33]
Mantovani et al. 2002	1	11	2	6	4.1%	0.27 [0.03, 2.42]
Matteucci et al. 2020	11	34	40	106	65.9%	0.86 [0.50, 1.48]
Okamura et al. 2019	0	3	6	32	2.7%	0.63 [0.04, 9.28]
Total (95% CI)		**78**		**185**	**100.0%**	**0.83 [0.53, 1.29]**
Total events	19		60			

Heterogeneity: Tau² = 0.00; Chi² = 4.29, df = 5 (p = 0.51); I² = 0%
Test for overall effect: Z = 0.83 (p = 0.41)



Study or subgroup	Postoperative ECMO Events	Total	No postoperative ECMO Events	Total	Weight	Risk ratio IV, random, 95% CI
Formica et al. 2017	8	11	4	24	18.0%	4.36 [1.66, 11.45]
Kacer et al. 2020	1	1	4	18	13.0%	3.17 [1.02, 9.87]
Matteucci et al. 2020	7	11	64	129	65.2%	1.87 [1.12, 3.10]
Zoffol et al. 2012	1	3	2	22	3.9%	3.67 [0.46, 29.21]
Total (95% CI)		**26**		**193**	**100.0%**	**2.39 [1.59, 3.60]**
Total events	17		54			

Heterogeneity, Tau² = 0.00; Chi² = 2.81, df = 3 (p = 0.42), I² = 0%
Test for overall effect: Z = 4.17 (p < 0.0001)

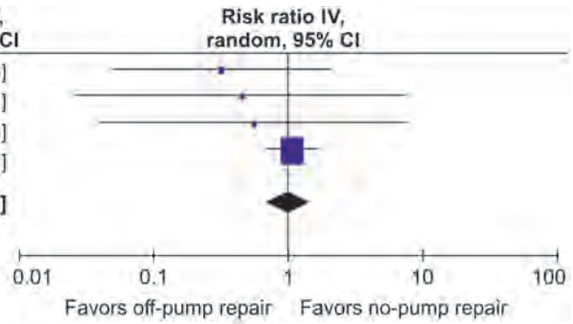


Source: Adapted from Matteucci et al.[22]

TABLE 3: Forest plots of comparison: (A) On-pump repair versus off-pump repair; (B) Postoperative intraaortic balloon pump (IABP) support versus no IABP support; outcome of interest: operative mortality.

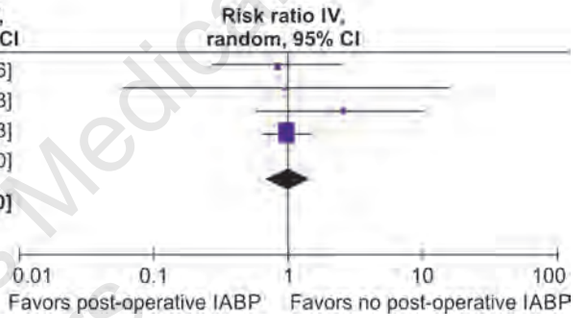
Study or subgroup	Off-pump repair Events	Total	On-pump repair Events	Total	Weight	Risk ratio IV, random, 95% CI
Formica et al. 2017	1	8	11	27	5.0%	0.31 [0.05, 2.03]
Iemura et al. 2001	0	5	2	12	2.1%	0.43 [0.02, 7.71]
Kacer et al. 2020	0	2	5	17	2.6%	0.55 [0.04, 7.53]
Matteucci et al. 2020	21	56	30	84	90.3%	1.05 [0.67, 1.64]
Total (95% CI)		**71**		**140**	**100.0%**	**0.95 [0.63, 1.45]**
Total events	22		48			

Heterogeneity: Tau² = 0.00; Chi² = 2.03, df = 3 (p = 0.57); I² = 0%
Test for overall effect: Z = 0.22 (p = 0.82)



Study or subgroup	Postoperative IABP Events	Total	No postoperative IABP Events	Total	Weight	Risk ratio IV, random, 95% CI
Formica et al. 2017	3	10	9	25	12.8%	0.83 [0.28, 2.46]
Iemura et al. 2001	2	15	0	2	1.9%	0.94 [0.06, 15.03]
Kacer et al. 2020	2	4	3	15	7.5%	2.50 [0.61, 10.23]
Matteucci et al. 2020	24	67	27	73	77.7%	0.97 [0.62, 1.50]
Total (95% CI)		**96**		**115**	**100.0%**	**1.02 [0.69, 1.50]**
Total events	31		39			

Heterogeneity: Tau² = 0.00; Chi² = 1.75, df = 3 (p = 0.63); I² = 0%
Test for overall effect: Z = 0.10 (p = 0.92)



Source: Adapted from Matteucci et al.[22]

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CHAPTER 68

ECG Localization of Culprit Artery in Acute Myocardial Infarction

Dipak Sarma, MS Chaliha, Shekharjyoti Gogoi

ABSTRACT

The ECG is a vital tool in diagnosis of myocardial infarction (MI) and identification of the culprit artery. In general, depending on the coronary artery dominance, ECG changes in leads I, aVL, and V_1–V_6 signify involvement of left anterior descending (LAD) artery. Changes in V_5, V_6, and V_7–V_9 denote involvement of left circumflex (LCx) artery. Right coronary artery (RCA) involvement is usually reflected in leads II, III, aVF and also V_7–V_9 and in special leads V_3R and V_4R. There are, however, some pitfalls in cases where there are anatomical variations of coronary arteries, presence of collaterals, previous coronary artery disease and coronary artery bypass graft (CABG), etc. In spite of these pitfalls the ECG still remains the main preliminary diagnostic tool to identify the culprit artery in acute myocardial infarction.

INTRODUCTION

Culprit artery localization in a patient of acute myocardial infarction [ST-elevation myocardial infarction (STEMI)] is pivotal for providing valuable prognostic information and guiding further therapeutic approach in emergency settings. According to current guidelines,[1] along with the typical ischemic chest pain, the initial 12-lead ECG is the decisive tool to identify the infarct-related artery, predict the amount of myocardium at risk and guiding urgent revascularization. The sensitivity and specificity of ECG in acute myocardial infarction is influenced by the anatomic variations of coronary arteries, presence of collaterals, previous coronary artery disease, previous bypass surgery, and technical limitations. Due to all these pitfalls, at times, the 12-lead surface ECG may not provide accurate information regarding the "culprit artery". An easy-to-use, methodical, and sequential algorithm-based ECG approach is the cornerstone to avoid all these caveats. In this article, we have reviewed the several algorithm-based ECG approaches to delineate the exact "culprit artery" in a setting of acute STEMI. We also have reviewed few novel ECG features that might help to identify the infarct-related artery in acute non-STEMI.

ANATOMY OF CORONARY ARTERY (FIG. 1 AND TABLE 1)

Coronary Artery Dominance[3]

The *right dominant circulation*: In 85% of cases, right coronary artery (RCA) supplies the posterior descending artery (PDA) and at least one posterolateral branch. This type is present in around 85% of patients.

Left dominant circulation: Distal left circumflex (LCx) supplying a left PDA and left posterolateral branches is seen in around 7.5% of patients. Here, RCA is very small, ends before reaching the crux, and does not supply any blood to the left ventricular myocardium.

Balanced/codominant circulation: RCA giving rise to the PDA and LCx artery providing all the posterolateral branches. It comprises the half of the all non-RCA dominant cases.

Coronary artery dominance has great impact on culprit artery localization in a case of myocardial infarction (MI), especially in cases of inferior wall MI, as the infarction area may vary according to the coronary dominance, hence the ECG findings **(Fig. 2)**.

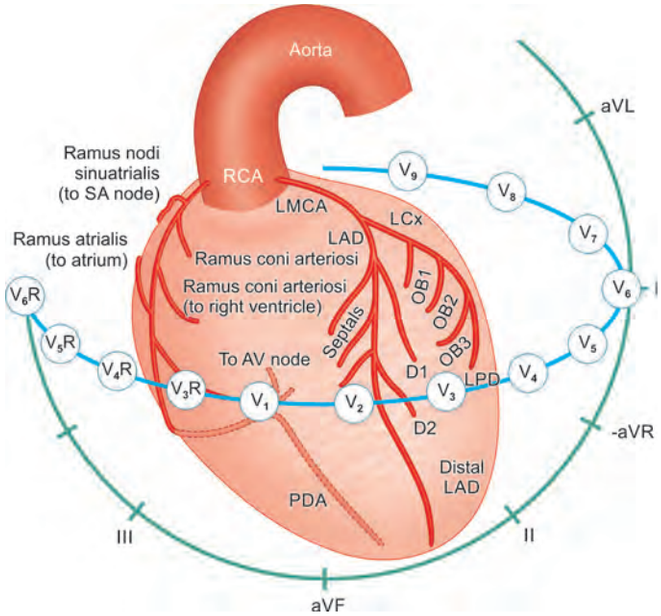

FIG. 1: Schematic overview of coronary arteries and their relation to the ECG leads.[2]

[RCA: right coronary artery; PDA: posterior descending artery; LMCA: left main coronary artery; LAD: left anterior desceding artery; D: diagonal branches (D1, D2); Septals: septal branches; LCx: left circumflex artery; OB: obtuse marginals (OB1,OB2, OB3); LPD: left posterior descending artery]

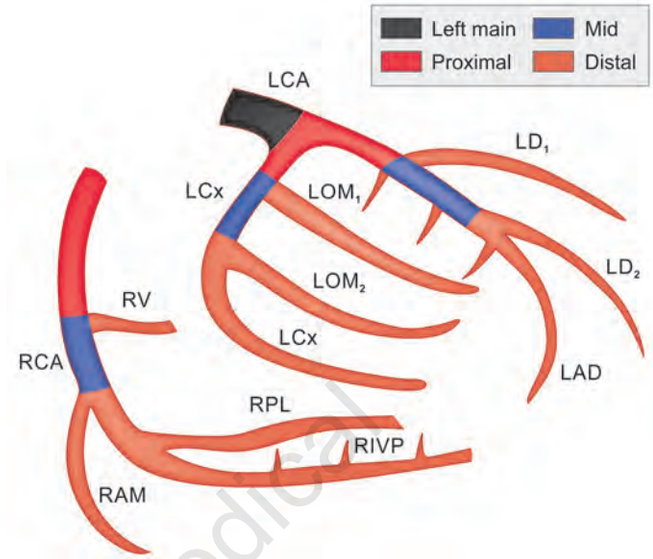

FIG. 2: Segmental anatomy of the coronary circulation.[4]

(LAD: left anterior descending coronary artery; LCA: left main coronary artery; LCx: left circumflex coronary artery; LD_1, LD_2: left diagonal branches; LOM_1, LOM_2: left obtuse marginal branches; RAM: right acute marginal branch; RCA: right coronary artery; RIVP: right interventricular posterior branch; RPL: right posterolateral branch; RV: right ventricular branch)

TABLE 1: Anatomy of coronary artery in relation with area supplied and ECG representation.[3]

Coronary artery	Area supplied	ECG representation
Left anterior descending artery (LAD)	Anterior, anteroseptal wall of LV	Lead V_1–V_6, I, and aVL
Left circumflex (LCx) artery	Anterolateral wall	Lead I, aVL, V_5, V_6
	Posterolateral wall	V_7–V_9
	Inferior wall (10–15%)	Leads II, III, aVF
Right coronary artery (RCA)	Inferior walls	Lead II, III, aVF
	Often posterolateral walls	V_7–V_9
	Right ventricular free walls	Special leads: V_3R–V_4R

ST Elevation Criteria

Recommendations[1]

- For men 40 years of age and older, the threshold value for abnormal J-point elevation is 0.2 mV (2 mm) in leads V_2 and V_3 and 0.1 mV (1 mm) in all other leads.
- For men <40 years of age, the threshold values for abnormal J-point elevation in leads V_2 and V_3 should be 0.25 mV (2.5 mV).
- For women, the threshold value for abnormal J-point elevation should be 0.15 mV (1.5) mm in-leads V_2 and V_3 and >0.1 mV (1 mm) in all other leads.
- For men and women, the threshold for abnormal J-point elevation in V_3R and V_4R should be 0.05 mV (0.5 mm) except for male <30 years, for whom 0.1 mV (1 mm) is more acceptable.
- For men and women of all ages, the threshold value for abnormal J-point elevation in V_7 through V_9 is 0.05 mm (0.5 mm).

Left Main Coronary Artery Occlusion

Left main coronary artery mostly supplies around 75% of the left ventricular (LV) myocardial mass. Hence, acute occlusion of the left main coronary artery (LMCA) has dreaded prognosis and usually presents with life-threatening hemodynamic instability and malignant arrythmias. A rapid diagnosis and followed by urgent revascularization is crucial and lifesaving in LMCA disease.

The ECG findings that are most commonly associated with LMCA occlusion are **(Fig. 3)**: (1) widespread ST-segment depression with maximal changes in lead V_4–V_6 with inverted T waves; (2) ST-segment elevation in lead aVR; and (3) anterior (anterolateral) ST-segment elevation.[5]

ST elevation in aVR is an important determinant for differentiating LMCA occlusion from left anterior descending (LAD) occlusion. ST elevation in Lead aVR greater than or equal to Lead V_1 differentiates LMCA lesion from an LAD lesion.[6] In case of LMCA occlusion, the transmural ischemia in the basal intraventricular septum due to impaired blood flow in fist septal branch (S1) leads to ST-segment elevation in lead aVR. On the other hand, counterbalance of injury current produced by transmural ischemia in both anterior and posterior walls leads to smaller ST elevation in V_1.

Nevertheless, electrocardiographic findings of acute LMCA occlusion is not consistent with one single uniform electrocardiographic pattern due to heterogeneity of the amount and localization of the ischemic jeopardized

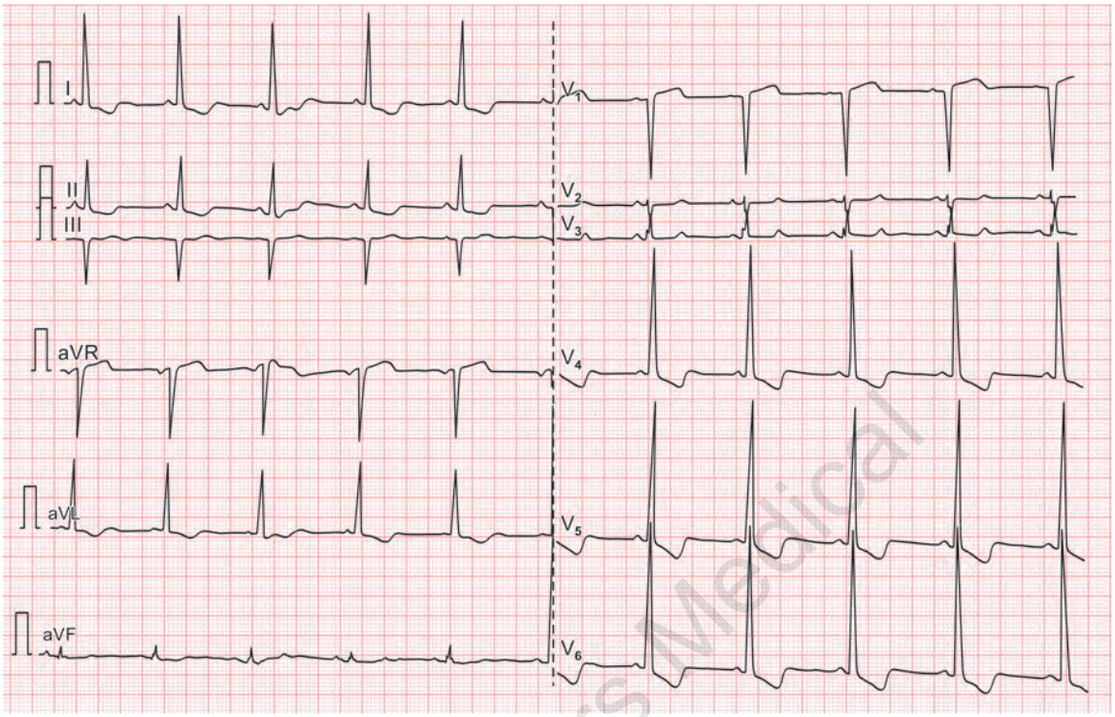

FIG. 3: ECG of a left main coronary artery occlusion. Global ST depression and T wave inversion with equal ST elevation in lead aVR and V_1.

myocardium.[7] The exact electrophysiological and pathophysiological background for different ECG manifestations of left main occlusion needs further validation.

LEFT ANTERIOR DESCENDING ARTERY OCCLUSION (TABLE 2 AND FIGS. 4 TO 6)

In a case of anterior wall myocardial infarction (AWMI), the site of occlusion in the course of LAD decides the amount of LV myocardium at risk of infarction. It is imperative to know the site of occlusion of LAD at first glance, by just looking at the ECG at the "first medical contact" and to guide the further therapeutic management. It has been suggested that[3,8] if there is failure in early detection of high-risk ECG patterns in patients with "acute myocardial infarction", quality care in the emergency room is greatly hampered. This highlights the need of a system change or new algorithm that improves the accuracy of ECG interpretation.

Depending on the location of occlusion, LAD occlusion may lead to a very extensive AWMI, or only septal, apical-anterior or mid-anterior MI.[3,9]

In patients with symptoms suggestive of acute coronary syndrome (ACS), who presents with ST elevation in precordial leads (V_1–V_6) indicates STEMI due to LAD occlusion[10] with a sensitivity around 99%.[11] This information alone is not sufficient enough to predict the extent of the jeopardized myocardium. LAD basically supplies three vectorially opposite areas, namely: (i) basal septal area perfused by proximal septal branch (S1); (ii) basolateral area perfused by first diagonal (D1), and (iii) inferoapical area, when distal LAD wraps around apex. Depending on the presence of ischemia in these areas, we get different manifestations on surface ECG. Knowing that the occlusion is proximal or distal to D1 or S1 may be pivotal for deciding on the best approach to treatment.[3]

Proximal Left Anterior Descending Occlusion

Proximal LAD occlusion is considered as an independent predictor of poor prognosis related to increased mortality and recurrent MI. On the contrary, distal LAD occlusion has been documented to have a favorable outcome.[12] In proximal LAD occlusion, the direction of ST-segment vector which is upward, toward leads V_1, aVL, and aVR, and away from the inferior leads.[3] This leads to ST-segment elevation in aVL or aVR, concomitant ST-segment depression in inferior leads. The most powerful predictors of proximal LAD occlusion include ST-segment elevation in aVL, V_1 or aVR, reciprocal ST-segment depression in inferior leads, ST-segment depression in V_5, and disappearance of preexistent septal Q waves in lateral leads.[3,13] New right bundle-branch block with a Q wave preceding the R wave (QRBBB) in lead V_1 is a specific marker of acute proximal LAD occlusion, but has low sensitivity **(Fig. 4)**.[13]

Distal Left Anterior Descending Occlusion

ST-segment elevation in leads V_1, V_2, and V_3 with absence of significant inferior ST-segment depression or presence of inferior ST elevation suggestive of LAD lesion distal to the origin of the first diagonal branch (D1),[13] indicating that the culprit vessel wraps around the apex to supply the inferoapical region of the left ventricle **(Fig. 6 and Table 2)**.

Algorithm for Left Anterior Descending Artery Occlusion[3,13]

Refer to **Flowchart 1**.

TABLE 2: ECG features for identifying culprit artery in left anterior descending (LAD) distribution.[3,14]

Location of occlusion	ECG findings	Sensitivity (%)	Specificity (%)
Occlusion proximal to S1	• ST elevation in V_1 > 2.5 mm	66	87
	• New RBBB	11.1	93.75
	• ST elevation in aVR	38.89	93.75
	• ST depression in V_5	11.1	100
	• ST depression in II, III, aVF > 1 mm	55	75
Occlusion proximal to D1	• ST depression in inferior leads (III > II)	50	60.7
	• Q wave in aVL	37	67
Occlusion distal to S1	• Absence of >1 mm ST depression in inferior leads	100	93.5
Occlusion distal to D1	• ST depression in aVL	85.75	100
	• Absence of ST depression/presence of ST elevation in inferior leads	85.7	44.7

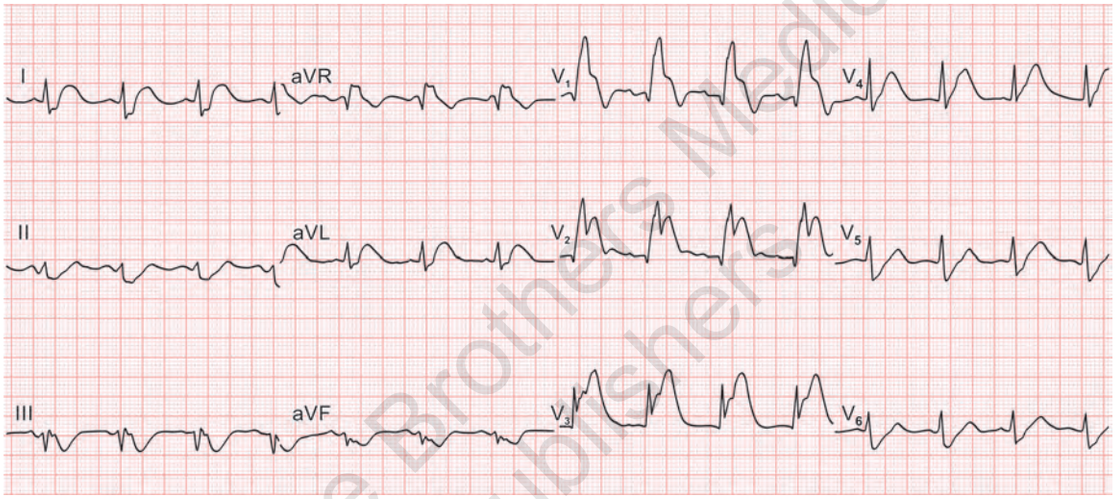

FIG. 4: Left anterior descending (LAD) occlusion proximal to first septal branch (S1), characterized by ST elevation in V_1 > 2.5 mm, ST elevation in aVL, new right bundle branch block (RBBB), ST depression in inferior leads, and V_5.

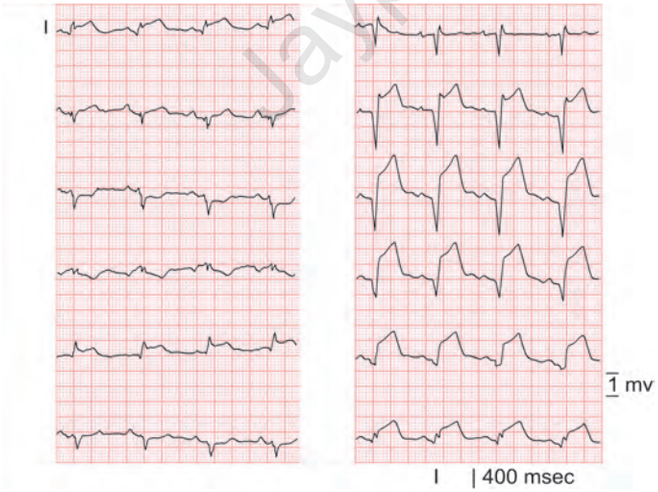

FIG. 5: ECG of a patient with acute myocardial infarction with a left anterior descending (LAD) occlusion distal to the first septal perforator and proximal to the first diagonal branch depicting characteristic abnormal Q-waves in V_4, V_5, V_6 and aVL, ST↓ > 0.1 mV in III and absence of ST↓ in II (and aVF).

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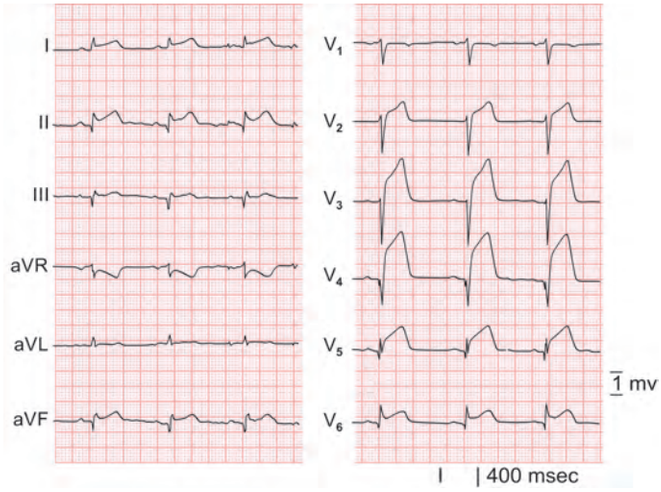

FIG. 6: ECG of a patient with an acute myocardial infarction due to left anterior descending (LAD) occlusion distal to both the first septal perforator and the first diagonal branch with characteristic abnormal Q-waves in V_4, V_5, and V_6 and absence of inferior ST↓ in all inferior leads.

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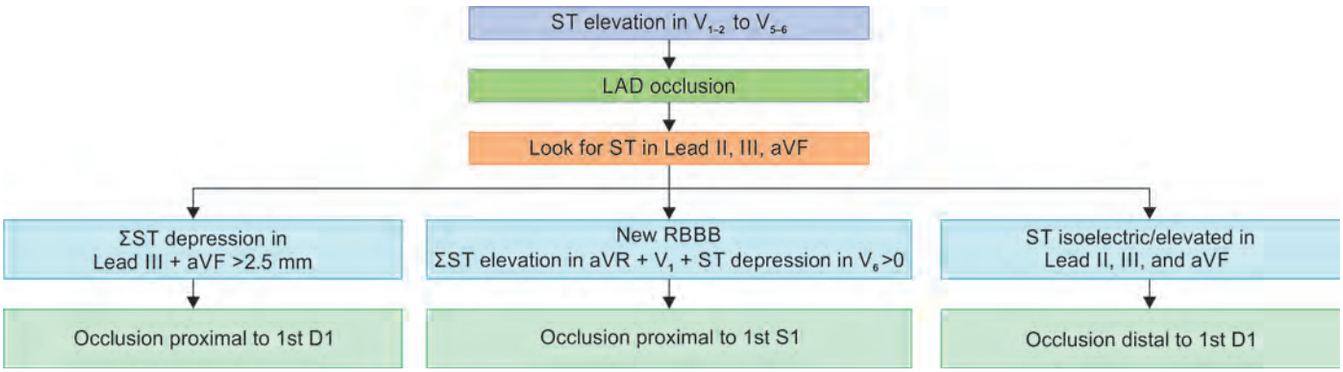


FLOWCHART 1: Algorithm for localization of left anterior descending coronary artery occlusion in the case of myocardial infarction with ST elevation in precordial leads.[3]

(D1: first diagonal branch; LAD: left anterior descending coronary artery; RBBB: right bundle branch block; S1: first septal branch; STD: ST segment depression; STE: ST-segment elevation; Σ = sum of)

INFERIOR WALL MYOCARDIAL INFARCTION

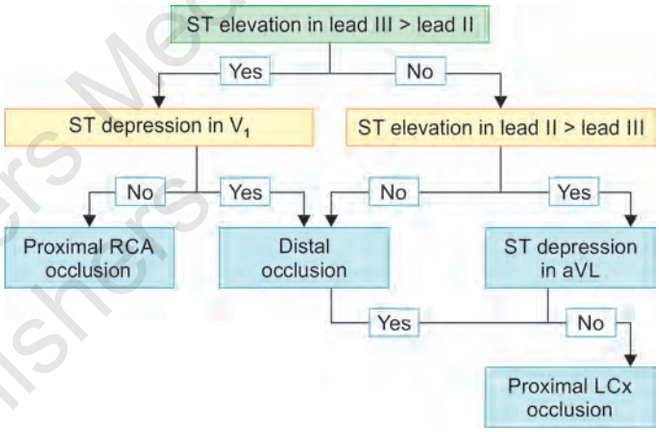
In majority of the situations, the inferior wall MI (IWMI) may be caused by occlusion in the course of the RCA (in 80% of the cases) and the LCx artery in the rest (20%). In cases of IWMI caused by RCA occlusion, the injury vector is directed toward right (lead III), leading to ST elevation in lead III > lead II along with reciprocal ST depression in lead I and aVL.[3,15] In cases of right ventricular infarction due to proximal RCA occlusion, there is the additional ST-segment elevation in lead V_1.[16]

Inferior wall myocardial infarction due to LCx occlusion, the injury vector is directed toward the left (lead II). This is due to the fact, ST-segment elevation in lead III is not greater than that in lead II, and there is an isoelectric or elevated ST segment in lead aVL.[3,17] Concomitant ST-segment depression in leads V_1 and V_2 in a case of IWMI suggests associated posterior wall involvement. This is usually caused by the occlusion in the LCx but also found often in dominant RCA occlusion.[18]

Sometimes, acute RCA occlusion and less extensive ST-segment deviation shows equal ST elevation in leads II and III, which might result in a "false-negative" ECG algorithm. In such situation, lead V_4R plays a crucial role identifying culprit artery.

Lead V_4R: Its Crucial Role in Culprit Artery Localization in Inferior Wall Myocardial Infarction

Due to its positioning on the right thorax, the injury currents at the right side of the heart are better monitored in V_4R when compared with extremity lead III. This may thereby reduce the amount of patients with a "false-negative" ECG algorithm due to similar STE in leads II and III.[19] Thus, lead V_4R plays a crucial role in differentiating proximal from distal RCA occlusion as well as LCx occlusion. The differentiation can be done by noting the presence of convex upward ST-segment elevation in V_4R and by T wave polarity in V_4R **(Flowchart 2 and Figs. 7 to 10)**.[20] Apart from this, a QS or QR pattern in leads V_3R and/or V_4R also



FLOWCHART 2: algorithm for culprit artery localization inferior wall myocardial infarction (MI).[22]

(LCx: left circumflex artery; RCA: right coronary artery; STD: ST-segment depression; STE: ST-segment elevation)

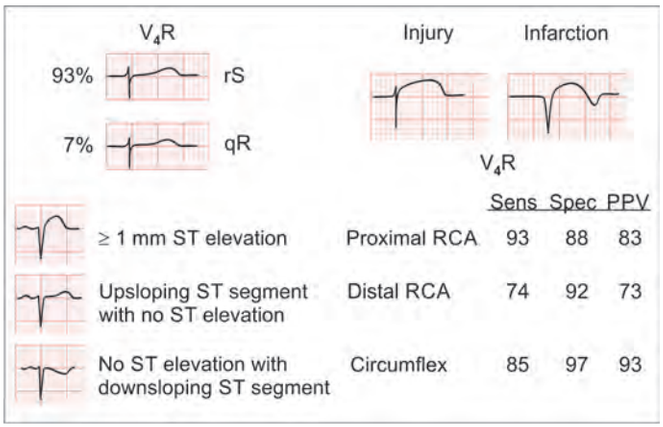


FIG. 7: Criteria for identification of culprit artery in inferior wall myocardial infarction (MI) on the basis of ST-T changes in V_4R.[21]

(RCA: right coronary artery)

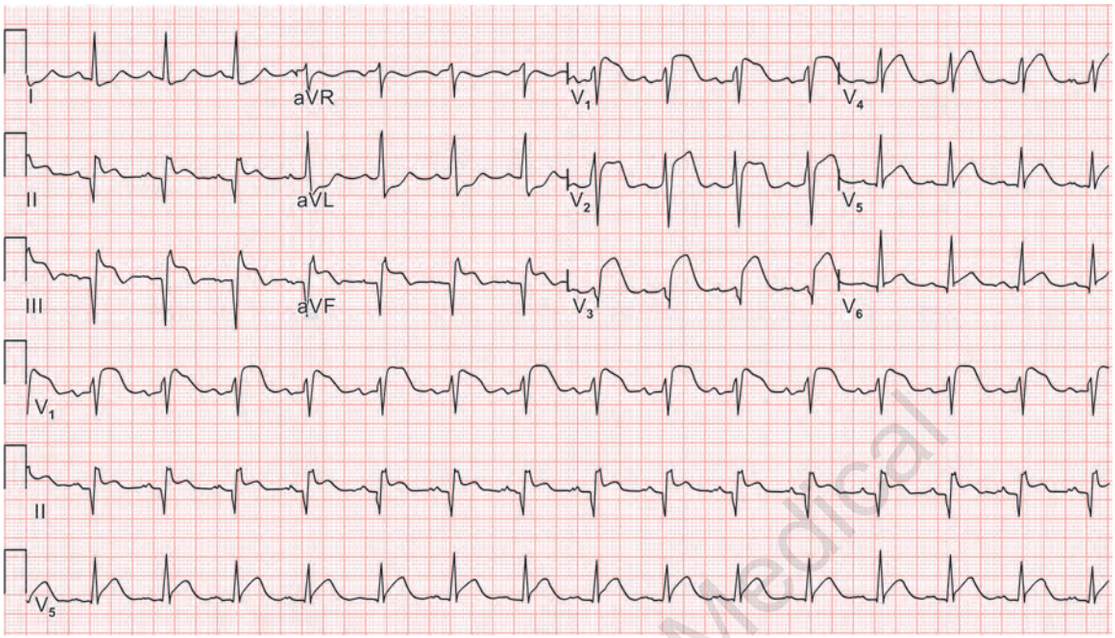


FIG. 8: Proximal right coronary artery (RCA) occlusion, ST elevation in lead III > lead II.

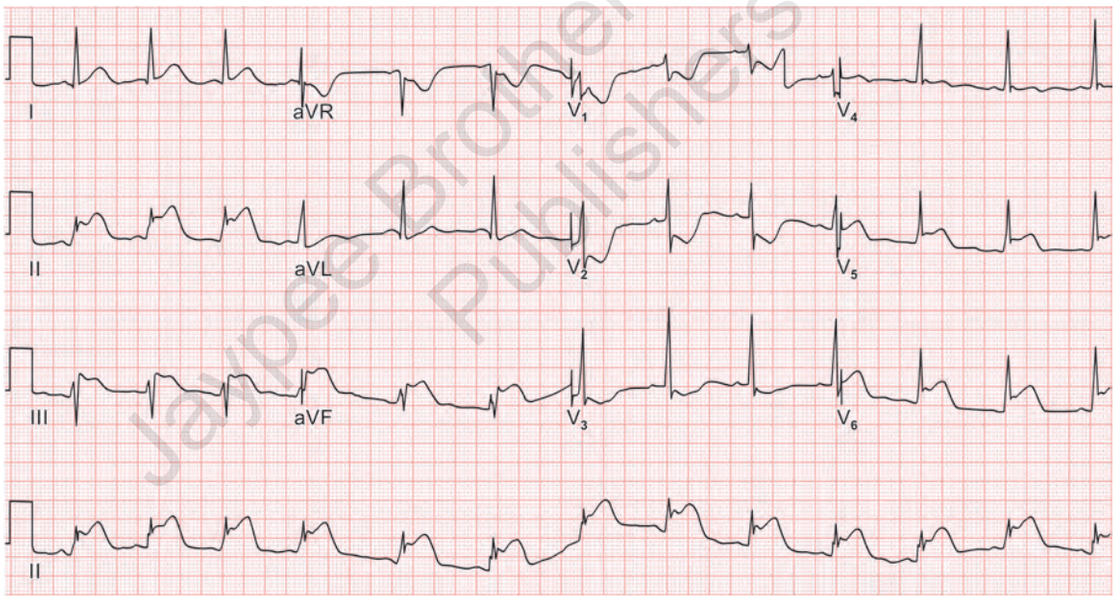


FIG. 9: Inferior wall myocardial infarction (MI) due to proximal LCx occlusion, ST elevation lead II > III, ST depression in lead aVL.

indicates right ventricular infraction but its predictive value is low as compared to the ST-segment elevation in these leads.[3]

POSTERIOR WALL INFARCTION

Posterior wall infarction can be caused by either occlusion of RCA or LCx and conventional 12 lead ECG has very low sensitivity for detection of posterior wall infarction.[3,20] ST elevation in posterior leads (V_7, V_8, and V_9), or reciprocal ST-segment depression in leads V_1–V_3[21] is consistent with acute posterior wall infarction. An abnormal R wave in V_1 (0.04 in duration and/or R/S ratio ≥ 1 in the absence of preexcitation or right ventricular hypertrophy), with inferior or lateral Q waves, indicates more toward an isolated occlusion of a dominant LCx without collateral circulation.

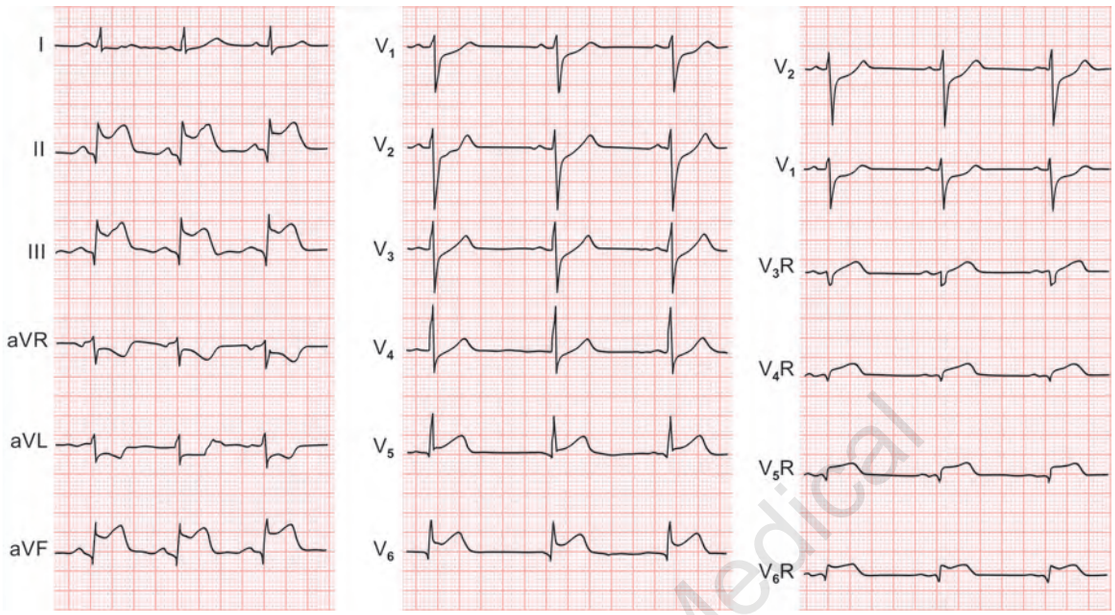


FIG. 10: The ECG of a patient with acute inferior myocardial infarction with the same amount of ST-segment elevation in leads II and III. Lead V_4R shows ST-segment elevation indicating a proximal RCA occlusion.[23]

CULPRIT ARTERY LOCALIZATION IN ACUTE NON-ST-ELEVATION MYOCARDIAL INFARCTION

Recently, various novel electrocardiographic changes have been described in ACS that may also take a pivotal role in localizing culprit coronary artery in patients with NSTEMI **(Fig. 11)**.[24] These novel ECG abnormalities include:

- *Delayed activation wave (N-wave)*: It defined by—(1) A notch or deflection in the terminal QRS complex; (2) the height of the notch or deflection of ≥2 mm, measured in reference to PQ-junction.
- *T-wave precordial instability*: Defined as upright T-wave in $V_1 > V_6$
- *De-Winter ST/T-wave complex*: Defined as ST-segment depression ≥ 1 mm at the J-point followed by upsloping ST-segments and peaked symmetrical T-waves.

In a recently conducted study[24] evaluated the predictive value of N-wave, T-wave precordial instability, de-Winter ST/T-wave complex, and inferolateral myocardial infarction in the identification of the culprit artery in patients with NSTEMI. T-wave precordial instability was the most common finding in patients with culprit LCx/obtuse marginal artery or RCA (28.3% and 13.5%, respectively). T-wave precordial instability and N-wave in leads II, III, or aVF were equally found (16.0%) in patients with LCx or obtuse marginal branch involvement. N-wave in lead aVL and T-wave precordial instability were found to be independent predictors of LCx/obtuse marginal occlusion.

LIMITATIONS OF ECG

The specificity and accuracy of the ECG in acute MI detecting culprit artery may be limited various factors. These include individual coronary anatomy variations, patients with a previous MI, collateral circulation, multivessel disease, preexistent bundle branch block, presence of preexcitation or

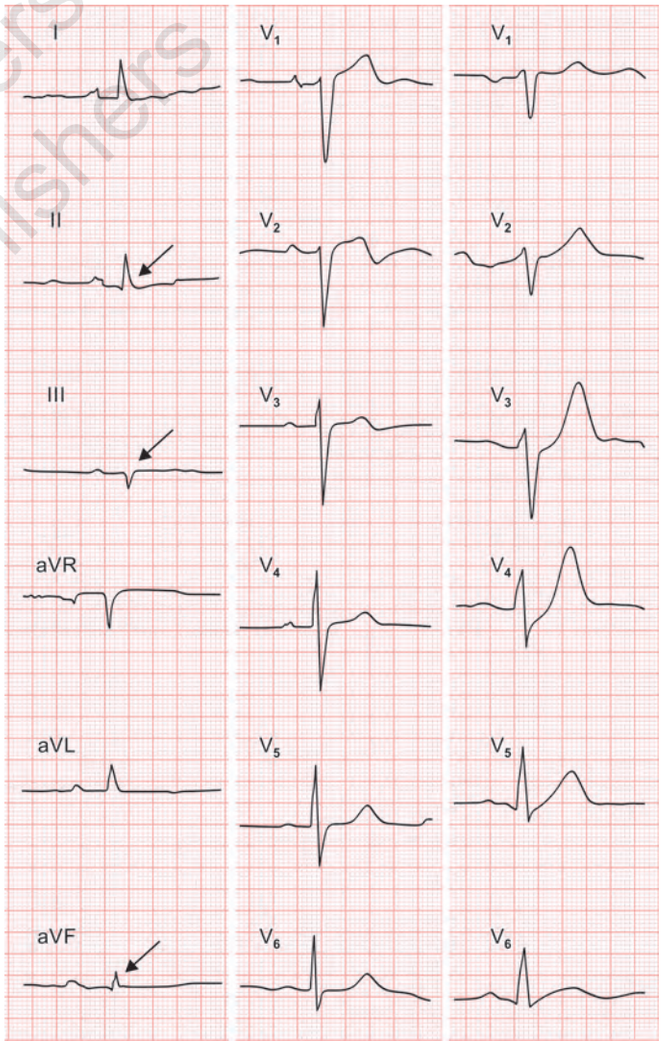


FIG. 11: Novel ECG changes in acute coronary syndrome.[24]

paced rhythm, and previous coronary artery bypass surgery.[3,14] The ECG also inadequately represents the posterior, lateral, and apical walls of the left ventricle. Due to the dynamic nature of the ECG changes, the ECG changes may not be reliable tool for culprit artery localization if the patient presents late after the window period. Moreover, the ST changes may not be depicted accurately if there is change in anteroposterior diameter of chest or presence of an extracardiac disease like COPD or plueral effusion.

CONCLUSION

Despite all limitations and pitfalls, ECG still remains as a primary preliminary diagnostic tool in acute myocardial infarction. An easy-to-use sequential ECG algorithm provides immense help identifying culprit artery, predict amount myocardium at risk, and thus takes crucial role deciding urgency of revascularization.

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CHAPTER 69

Management of Atrial Fibrillation after Acute Coronary Syndrome Intervention

Asok Kumar Kar, Ayan Kar

ABSTRACT

Acute coronary syndrome (ACS) is one of the most common life-threatening presentations in day-to-day cardiology practice. Percutaneous coronary intervention (PCI) is the standard treatment in most of these cases other than guideline-directed medical therapy. A significant percentage of these ACS cases also have atrial fibrillation (AF), and this is associated with increased risk of cardioembolic stroke. After PCI, these cases need triple or dual antithrombotic therapy using newer oral anticoagulants (NOACs) plus clopidogrel and/or aspirin for the shortest period of time. The radial route remains the preferred route of vascular access. However, tailoring of therapy to the individual patient should be made at the physician's discretion depending upon the balance between thrombotic and bleeding risks.

BACKGROUND

The diagnosis of atrial fibrillation (AF) is associated with an increased risk of cardioembolic stroke and mandates anticoagulation therapy. The additional presence of obstructive coronary artery disease requiring percutaneous coronary intervention (PCI) presents a unique clinical setting in modern interventional cardiology, where dual antiplatelet therapy (DAPT) is also required to curtail the increased thrombotic risk. Typically, such settings involve elderly patients and often entail an increased bleeding risk. It is important to emphasize that dual antiplatelet is inferior to oral anticoagulation for prophylaxis of thromboembolic events.[1] The clinical challenge lies in striking that perfect balance between increased thrombotic and bleeding risk. There have been trials on triple therapy with oral vitamin K antagonists (VKAs), which were associated with increased bleeding risk. However, with the advent of newer oral anticoagulants (NOACs), there seems to be a change in the modern standard of care favoring dual therapy along with mitigation of increased bleeding risk. This review intends to detail the currently available evidence.

INTRODUCTION

With a raging diabetic pandemic in India, one of the most common cardiovascular diseases to have is coronary artery disease (CAD). On the other hand, the most frequently diagnosed cardiac arrhythmia is AF which increases with age. Both happen to share common risk factors such as hypertension, diabetes, obesity, and obstructive sleep apnea and have inflammation as a common pathologic milieu. The incidence of CAD in patients with AF is anything between 17 and 46.5%.[2] In as many as 21% of such patients with stable CAD are likely to require PCI or coronary artery bypass surgery (CABG). It is also interesting to note that acute coronary syndromes (ACSs) are notorious for precipitating AF in as many as 21% of patients and are associated with a higher risk of in-hospital death, increased 30 day readmission rates, and a worse prognosis. This is evidenced in the Global Registry of Acute Coronary Events (GRACE), which showed a threefold increase in in-hospital death in patients who developed AF after an ACS compared to those who did not.[3] Patients with new-onset AF were twice as likely to have a hospital course complicated by heart failure and three times more likely to develop cardiogenic shock. Thus, the combination of ACS and AF presents the perfect case for initiating triple therapy [dual antiplatelet + anticoagulation—vitamin K antagonist (VKA/NOAC)] to mitigate the increased risk of thrombotic events. The obvious concern that remains is the increased bleeding risk.

This chapter intends to focus on the following pertinent issues from the perspective of an interventional cardiologist, which is important for the management of this group of patients in light of currently available evidence.

- Dual antithrombotic therapy versus triple therapy
- Role of aspirin

- Duration of either therapy
- Choice of concomitant P2Y12 inhibitors
- When to start triple therapy/dual antithrombotic therapy
- Definition of bleeding and thrombotic risk

DUAL ANTITHROMBOTIC VERSUS TRIPLE THERAPY

Over the past decade, there have been six major randomized controlled multicenter trials investigating this exact question and comparing warfarin/NOACs with dual/single antiplatelet agents, given to patients undergoing PCI in the background of AF. The oral anticoagulants investigated were warfarin, rivaroxaban, dabigatran, apixaban, and edoxaban. We will limit ourselves to the first four drugs as edoxaban remains unavailable to the Indian market. An overview of the trials is available in **Table 1**.

Acute coronary syndrome patients present in a state of profound "pan vascular" inflammation with an increased thrombotic risk which only gets worsened with new-onset AF/preexisting AF and an increase in rates of ischemic stroke. The risk of new-onset stroke at 1 year, in such cases, is equivalent to that of a patient having preexisting AF[4] and thereby warranting oral anticoagulation on top of standard DAPT.

In the warfarin era, the AFCAS (Atrial Fibrillation undergoing Coronary Artery Stenting) study established similar 1-year efficacy [stroke/transient ischemic attack (TIA)/peripheral embolization/repeat revascularization and stent thrombosis] and safety (minor and major bleedings) outcomes of dual antithrombotic therapy over triple therapy and was largely limited by low reporting of adverse events and only a small group using VKA + clopidogrel.[5]

This was followed by the much famed WOEST (What is the Optimal antiplatElet and Anticoagulation Therapy in Patients

TABLE 1: Major multicenter randomized controlled trials (RCTs) comparing dual/triple antithrombotic therapy.

Trial name	AFCAS	WOEST	PIONEER AF PCI	RE-DUAL PCI	AUGUSTUS
Objective	Three arms looking at TT versus DAPT versus VKA + P2Y12, prospective multicenter observational registry	VKA + DAPT versus VKA + P2Y12, international multicenter open label trial	Three groups: (1) 15 mg rivaroxaban + P2Y12 versus (2) 5 mg rivaroxaban twice daily + DAPT versus (3) VKA + DAPT (<15% on ticagrelor/prasugrel)	Three groups: (1) 110 mg dabigatran BD + clopidogrel/ticagrelor, (2) 150 mg dabigatran BD + clopidogrel + ticagrelor, (3) VKA aspirin + clopidogrel + ticagrelor	2 × 2 factorial design four groups, P2Y12 + apixaban + aspirin, P2Y12 + VKA + aspirin, P2Y12 + apixaban + placebo, P2Y12 + VKA + placebo
Population (*n*)	914	573	2,124	2,725	4,614
Year of publication	2013	2013	2016	2017	2019
Follow-up (month)	12	12	12	14	6
Age (years)	73 ± 8	70.3 ± 7.0	70.4 ± 9.1	71.5 ± 8.9	70.4 (64.1–77.2)
ACS (%)	57%	34%	51%	51.90%	60%
CHADSVASC	2.2 ± 1.2	88% > 2	90% > 2	3.7 ± 1.6	3.9 ± 1.6
HAS BLED	3.0 ± 0.7	NA	76% > 3	2.7 ± 0.7	2.9 ± 1.0
HF (%)	20	25	20.5	NA	42.3
H/o stroke (%)	17	18	NA	7.5	14.2
H/o GI bleeding (%)	NA	5	1	NA	NA
Chronic kidney disease (%)	NA	18	28.8	15–20	>90% of patients had a creatinine <1.5
Timing of randomization from PCI procedure	NA	4 hours	3 days	5 days	14 days
Clopidogrel usage (%)	100	100	93.1	86.4	93.4
Ticagrelor usage	0	0	5.2	12.6	5.4
Prasugrel usage	0	0	1.7	0	1.2
Primary outcome	MACCE including all-cause death, MI, repeat revascularization, stent thrombosis, TIA/stroke	Any bleeding episode	Clinically significant bleeding (composite of major bleeding or minor bleeding or bleeding) requiring medical attention	First major or nonmajor clinically relevant bleeding in a time-to-event analysis	Major or clinically relevant nonmajor bleeding

Continued

Continued

Trial name	AFCAS	WOEST	PIONEER AF PCI	RE-DUAL PCI	AUGUSTUS
Secondary outcome	Bleeding	MI, stroke, TVR, and stent thrombosis	MACE (cardiovascular death, MI, stroke) + stent thrombosis	Thromboembolic events (myocardial infarction, stroke, systemic embolization), death, unplanned revascularization	Composite of death or hospitalization or death and ischemic events
Treatment effect for intervention versus control	NA	HR 0.36 (95% CI 0.26–0.50); $p <$ 0.0001	HR 0.59 (95% CI 0.47–0.76); $p < 0.001$ for superiority	HR 0.72 (95% CI 0.58–0.88); $p < 0.001$ for noninferiority, $p = 0.002$ for superiority (dabigatran 150 mg bid); HR 0.52 (95% CI 0.42–0.63); $p < 0.001$ for noninferiority, $p < 0.001$ for superiority (dabigatran 110 mg bid)	HR 0.53 (95% CI 0.45–0.63); $p < 0.001$ for superiority

(ACS: acute coronary syndrome; AFCAS: Atrial Fibrillation Undergoing Coronary Artery Stenting; GI: gastrointestinal; HF: heart failure; HR: hazard ratio; DAPT: dual antiplatelet therapy; MACE: major adverse cardiac event; MACCE: major adverse cardiovascular and cerebrovascular event; MI: myocardial infarction; PCI: percutaneous coronary intervention; TIA: transient ischemic attack; TT: triple therapy; TVR: target vessel revascularization; VKA: vitamin K antagonist; WOEST: What is Optimal antiplatElet and Anticoagulation Therapy in Patients with Oral Anticoagulation and Coronary StenTing)

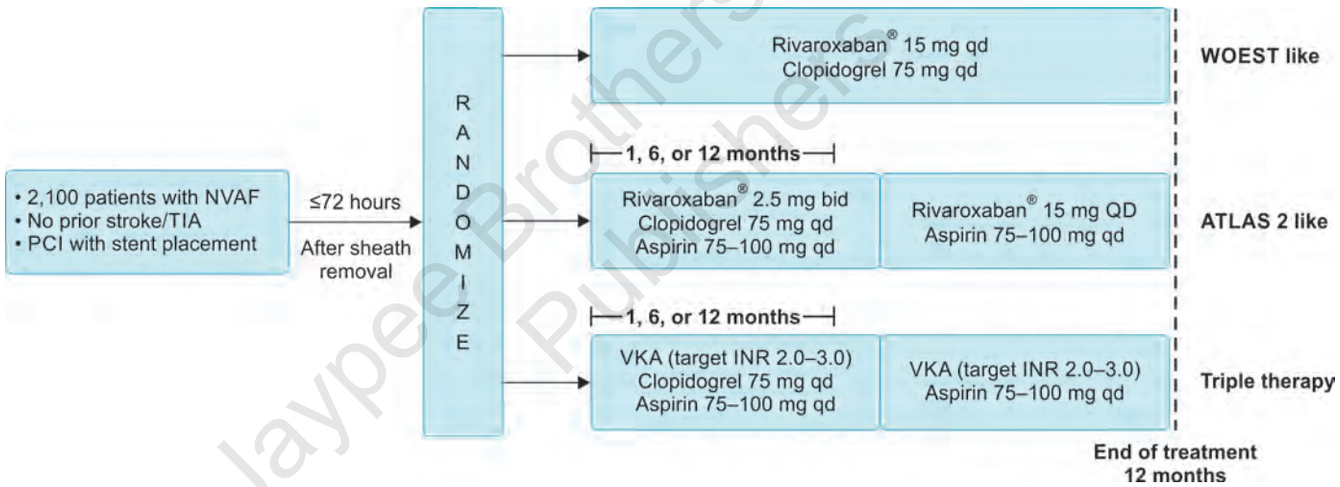

FIG. 1: Three arms of the PIONEER AF PCI study.

(INR: international normalized ratio; NVAF: nonvalvular atrial fibrillation; PCI: percutaneous coronary intervention; TIA: transient ischemic attack; VKA: vitamin K antagonist; WOEST: What is Optimal antiplatElet and Anticoagulation Therapy in Patients with Oral Anticoagulation and Coronary StenTing)

with Oral Anticoagulation and Coronary StenTing) trial, which showed that efficacy-wise dual antithrombotic therapy (VKA + clopidogrel) was as good as triple therapy with VKA + DAPT with overall lower levels of bleeding (minor + major). However, it was a small trial with 573 odd patients, and only 25–30% patients had a background of ACS. Two major highlights of this trial were that there were no increased major bleeds even in the triple therapy arm, and the secondary end point of mortality and cardiovascular death was significantly reduced by 40% [hazard ratio (HR) 0.60; 95% confidence interval (CI) 0.38–0.94; $p = 0.025$].[6] The problem with warfarin remains in its difficulty in the titration of dose to maintain therapeutic international normalized ratio (INR) and its significant interaction with food and drugs.

Subsequently, we had the PIONEER AF PCI trial evaluating rivaroxaban. It had three very unique arms looking at very contemporary real-word dosing strategy of rivaroxaban + P2Y12, rivaroxaban vascular dose with DAPT, and dose-adjusted VKA with DAPT **(Fig. 1)**.

The primary outcome of clinically relevant bleeding was significantly lower in the rivaroxaban group compared to the triple therapy group with VKA with no increase in thrombotic risks.[7]

The RE-DUAL PCI trial with dabigatran was another elegantly designed trial evaluating dabigatran versus VKA in the background of DAPT in patients of ACS with AF. Here too, both the dabigatran-based regimens showed a significant reduction in rates of major and minor bleeding with no increase in overall major adverse cardiovascular and

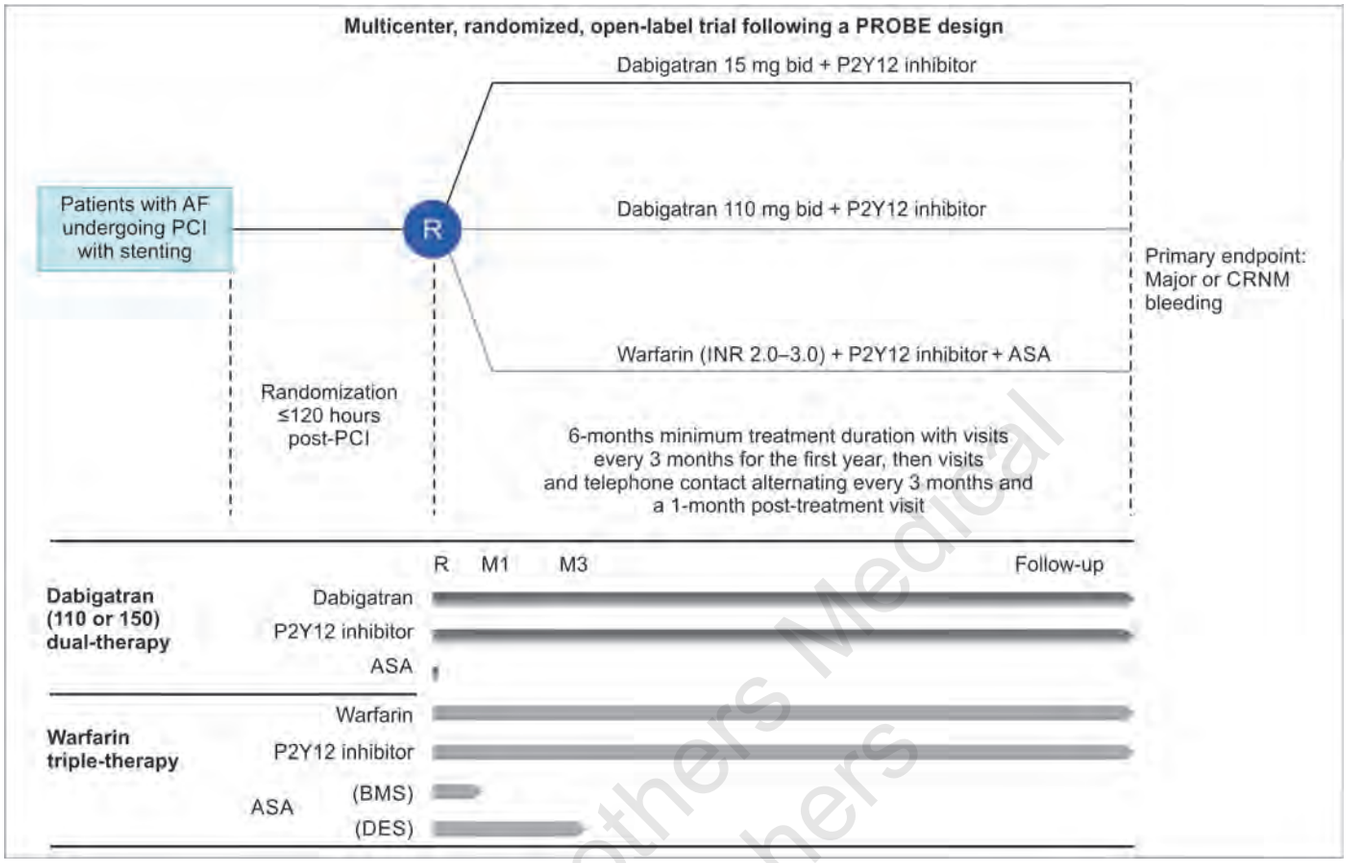

FIG. 2: Three arms of the RE-DUAL PCI trial.
(AF: atrial fibrillation; ASA: aspirin; BMS: Bare metal stent; CRNM: clinically relevant nonmajor; DES: drug-eluting stent; PCI: percutaneous coronary intervention)

cerebrovascular events (MACCE)/repeat revascularization or stent thrombosis **(Fig. 2)**.

Thus, both rivaroxaban and dabigatran significantly reduce major bleeds. However, it is nearly impossible to determine whether this outcome is because of NOAC or absence of aspirin.[8]

Last, apixaban was evaluated in a very contemporary trial—AUGUSTUS (largest of the three)—to evaluate the efficacy of using standard dose apixaban + P2Y12 or VKA + P2Y12, with and without aspirin **(Fig. 3)**. Unlike the previous trials, which used modified or lower than approved doses of NOACs, in the AUGUSTUS trial, standard approved doses of apixaban were used. Moreover, the previous two trials with rivaroxaban and dabigatran were not designed to assess whether the benefit obtained was from the NOAC or the absence of aspirin. Notably, this trial has shown that the incidence of reduced bleeding events was even greater when aspirin was avoided compared to the use of apixaban over VKA.[9]

To summarize, in patients with ACS undergoing PCI, after the initial procedure and medical stabilization, adopting a dual antithrombotic strategy with an approved dose of NOAC and P2Y12 seems like a reasonable strategy that is safer than using a VKA + P2Y12. However, the dosing of the chosen NOAC remains a spot of concern. Both the PIONEER AF PCI and RE-DUAL PCI studies used lower than approved doses of NOACs with no significant increase in stroke rates. Notably,

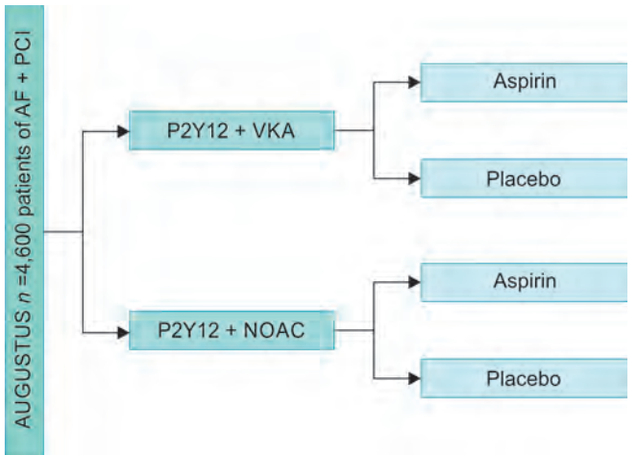

FIG. 3: Trial design of AUGUSTUS.
(AF: atrial fibrillation; NOAC: newer oral anticoagulant; PCI: percutaneous coronary intervention; VKA: vitamin K antagonist)

there was a nonsignificant increase in stent thrombosis rates in the 110 mg arm of the RE-DUAL PCI trial, thus raising a question over their efficacy in reducing thrombotic events. As far as apixaban is concerned, their dosing in this situation remains similar to its approved dose for AF.

ROLE OF ASPIRIN AND THE RISK OF STENT THROMBOSIS

Since, the beginning, aspirin has played a pivotal role as the first choice for antithrombotic therapy in patients undergoing PCI. But, in patients with concomitant AF, a network analysis of the PIONEER AF PCI, RE-DUAL PCI, and AUGUSTUS trials confirms the emerging role of dual antithrombotic therapy as the therapy of choice given its favorable safety profile. But it also shows a significantly higher risk of stent thrombosis, mostly driven by the 110 mg arm of the RE-DUAL PCI trial **(Table 2)**. Therefore, it would sound reasonable to give triple therapy for the initial few months followed by dual antithrombotic therapy, especially in patients undergoing complex stenting or with increased thrombotic risk.[10]

DURATION OF THERAPY

On this matter, there are two schools of thought on either side of the Atlantic. The North American Consensus on the Management of Antithrombotic Therapy in Patients with AF Undergoing PCI: Summary of the 2021 Focused Update categorically states that a patient of AF undergoing PCI should be treated with DAPT during the peri-PCI period with a rapid transition to dual antithrombotic therapy with a NOAC + P2Y12 predischarge. However, in patients deemed to have a high thrombotic risk, triple therapy may be contemplated at the physician's discretion.[11] The European guidelines seem more conservative where they recommend triple therapy albeit for as short a time period as possible in all such patients. The duration of triple therapy is decided depending on the acuity of the clinical presentation (ACS vs. non-ACS) and complexity of procedure or type of stent used (largely based on physician's discretion and his perception of thrombotic risk).[12]

CHOICE OF CONCOMITANT P2Y12 INHIBITOR

- Clopidogrel is the default choice for combination with either VKA or NOAC.
- However, ticagrelor may be considered a reasonable option, provided the perceived thrombotic risk is high.[11]
- Prasugrel is best avoided.

WHEN TO START DUAL ANTITHROMBOTIC THERAPY

There is no general consensus as to when the dual antithrombotic therapy or triple therapy should be started after the index PCI procedure. Going by timelines established in each of the above trials, it could be as early as 4 hours or immediately after securing vascular access to as long as 14 days from the index procedure. The North American consensus document draws up a simpler algorithm to follow and is shown in **Figure 4**.

Finally, to sum up, we have a beautiful pragmatic algorithm adapted from the North American Consensus document on treating patients undergoing PCI with concomitant AF, which should be used as a ready reckoner in our daily day-to-day practice **(Fig. 5)**.

DEFINITION OF BLEEDING AND THROMBOTIC RISK

At the crux of prescribing dual antithrombotic therapy lies a basic assessment of the patient's thrombotic and bleeding risk. To objectify this procedure, we have certain specific validated scoring systems like the CHADSVASC and the

TABLE 2: Outcomes based on the network analysis of the three trials: PIONEER AF PCI, RE-DUAL PCI, and AUGUSTUS.

	VKA + DAPT (reference)					
	VKA + P2Y12 inhibitor		DOAC + DAPT		DOAC + P2Y12 inhibitor	
Outcomes	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
TIMI major bleeding	0.58	0.31–1.08	0.70	0.38–1.23	0.49	0.30–0.82
TIMI major and minor bleeding	0.49	0.26–0.92	0.63	0.33–1.17	0.43	0.25–0.76
Primary safety outcome (trial defined)	0.45	0.21–0.92	0.64	0.31–1.31	0.47	0.25–0.85
ICH	1.44	0.40–5.22	0.54	0.15–1.92	0.26	0.08–0.79
All-cause death	0.84	0.40–1.56	1.04	0.54–1.98	1.02	0.59–1.74
Cardiovascular death	0.82	0.42–1.49	0.94	0.53–1.63	1.11	0.70–1.75
Primary MACE (trial defined)	0.96	0.60–1.46	0.94	0.60–1.15	1.02	0.71–1.97
MI	1.25	0.77–1.99	1.13	0.72–1.78	1.18	0.81–1.72
Stroke	1.02	0.36–2.65	0.91	0.35–2.32	0.77	0.34–1.67
Stent thrombosis	1.08	0.46–2.31	0.93	0.40–2.17	1.41	0.71–2.76
Hospitalization	0.86	0.57–1.23	0.80	0.55–1.13	0.80	0.59–1.08

Note: Odds ratio <1 favors nonreference strategy: odds ratio >1 favors reference strategy.

(DAPT: dual antiplatelet therapy; DOAC: direct oral anticoagulant; ICH: intracerebral hemorrhage; MACE: major adverse cardiac event; MI: myocardial infarction; TIMI: thrombolysis in myocardial infarction; VKA: vitamin K antagonist)

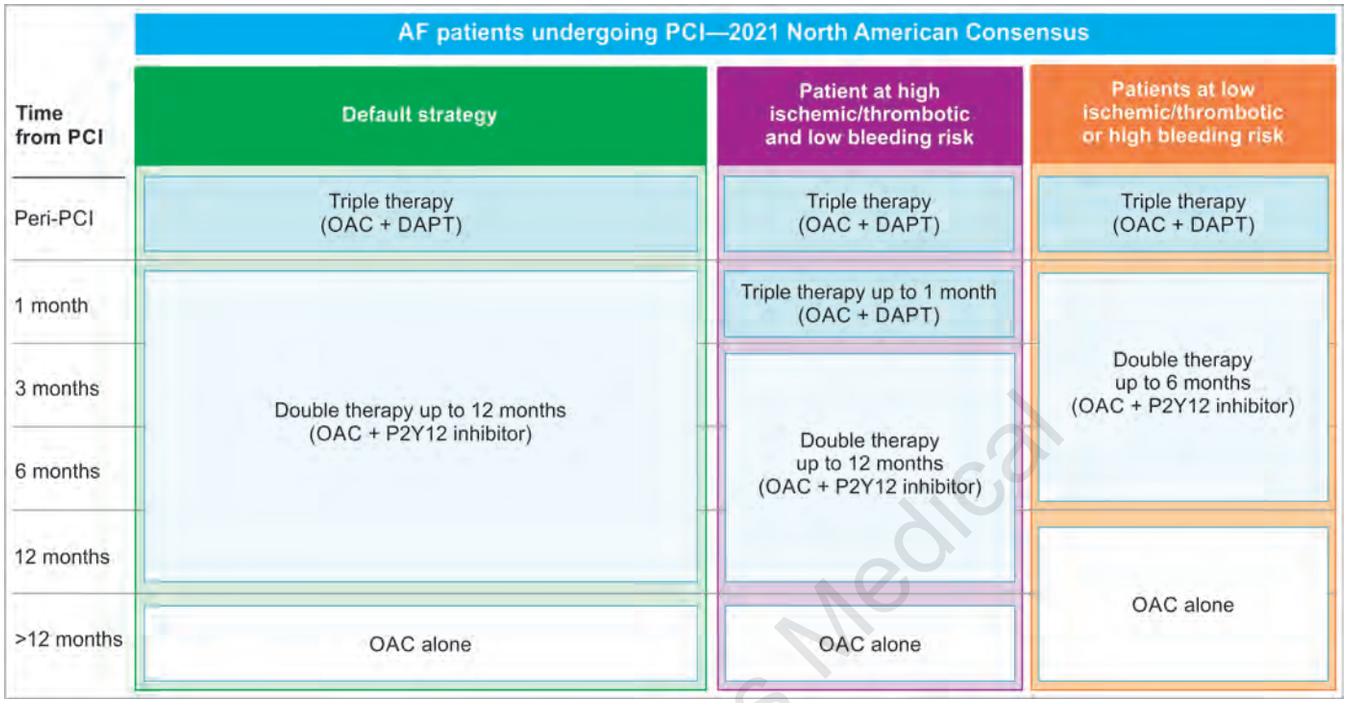

FIG. 4: Strategy for initiating triple therapy followed by dual antithrombotic therapy, followed by oral anticoagulant (OAC) in different patient subsets.

(AF: atrial fibrillation; DAPT: dual antiplatelet theory; PCI: percutaneous coronary intervention)

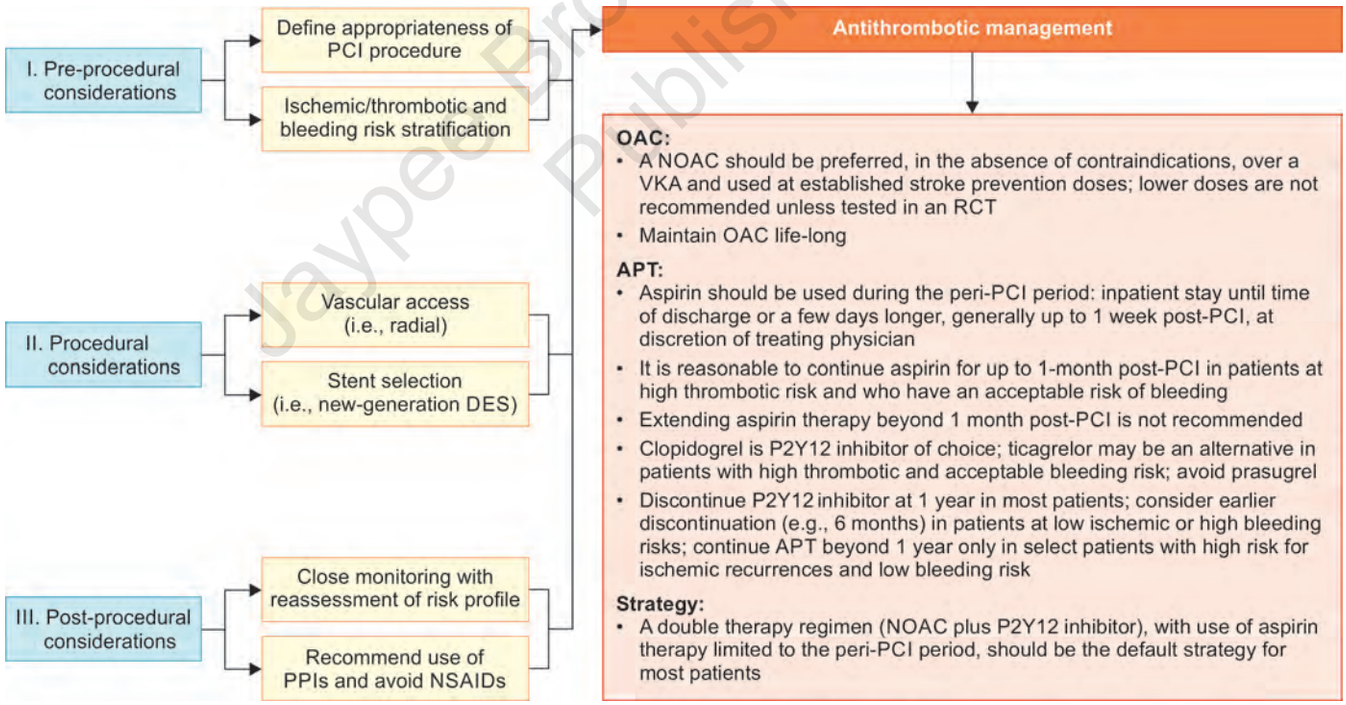

FIG. 5: Algorithm adapted from the North American Consensus document on treating patients undergoing percutaneous coronary intervention with concomitant atrial fibrillation.

(APT: antiplatelet therapy; DES: drug-eluting stent; NOAC: newer oral anticoagulant; NSAIDs: nonsteroidal anti-inflammatory drugs; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; PPIs: proton-pump inhibitors; RCT: randomized controlled trial; VKA: vitamin K antagonist)

PRECISE DAPT scores.[13,14] On the other hand, bleeding risk is assessed by the HASBLED[15] score. Interesting to note is that they have overlapping risk factors, and a higher HASBLED is only suggestive of reversible bleeding risk factors rather than a reason to preclude anticoagulants (as most of such patients also have a higher ischemic risk and are likely to benefit from anticoagulation). Thus, the ability of these scores to guide clinical decision-making is at best moderate, and it largely remains the clinicians' prerogative.

CONCLUSION

- In patients of ACS with concomitant AF who have undergone PCI, dual antithrombotic strategy using NOAC + clopidogrel seems safer to reduce bleeding complications without compromising on the thrombotic risk.
- However, in patients where the thrombotic risk is considered high, using triple therapy for the shortest period possible should be considered.
- Among the P2Y12 agents available, clopidogrel is the most widely used agent in dual antithrombotic therapy. Ticagrelor can be used in patients with high thrombotic risk. Prasugrel is best avoided.
- Dual antithrombotic therapy can be initiated as early as the procedure is completed and vascular access is secured (periprocedural). The radial route remains the preferred route of access.
- The use of VKA as a part of dual antithrombotic therapy remains restricted in patients undergoing PCI with metallic prosthetic valves or where NOACs are contraindicated [possibly dialysis dependent or estimated glomerular filtration rate (eGFR) <15 mL/min patients].

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CHAPTER 70

Coronary Ectasia and Aneurysm, Diagnosis and Management

Dharmesh Solanki, Jaydeep Desai, Dharmil Patel, Jay Vithlani

ABSTRACT

Coronary artery ectasia (CAE) and coronary artery aneurysm (CAA) are rare, and majority of the time, they are asymptomatic and accidentally detected during angiography. They are hypothetically considered as positive remodeling of advanced atherosclerosis to maintain luminal diameter. They can, however, also present as acute coronary syndromes (ACSs), stable angina, or rarely with compressive symptoms or rupture of the aneurysm. The natural progression of CAA is largely unknown; however, they have been associated with higher long-term mortality and major adverse cardiovascular events (MACEs). The goal of medical management is to prevent the progression of CAA, prevent in situ thrombus, and improve the flow at the site and distal to the pathology. Antiplatelets, statins, and oral anticoagulants are the mainstay of medical therapy—of course with variable outcomes. Percutaneous coronary interventions (PCIs) are challenging in view of the complex anatomy and morphology of the lesion. Stent-assisted coiling holds some promise to close the aneurysm in selected cases. Surgical management with coronary artery bypass graft (CABG) of CAA has been found more effective and safer and should be advocated to symptomatic cases with complex anatomy.

INTRODUCTION

Coronary artery ectasia (CAE) and coronary artery aneurysm (CAA) are rare, most of the time, they are asymptomatic and accidentally detected during angiography. The overall prevalence is 0.3–4.9% in patients undergoing coronary angiography (CAG).[1] CAA is defined as a focal coronary segment dilatation exceeding 1.5 times of normal adjacent segment, and CAE is defined as diffuse dilatation exceeding one-third of coronary artery length with a diameter >1.5 times.[2] Giant CAA is defined as focal dilatation of >20 mm. The most affected artery is right coronary artery (RCA): 40%, left anterior descending (LAD) artery: 32%, and left main coronary artery (LMCA): 3.5%, mainly involving proximal segments.[3] Etiological factors are atherosclerosis, vasculitis, congenital, autoimmune, drugs (cocaine), coronary intervention, and infection.[4]

CLINICAL PRESENTATION

Most of the patients detected are asymptomatic during CAG. Other common presentations in a chronologically descending order are acute coronary syndrome (ACS), stable angina, compression of adjacent structure with giant aneurysm or venous graft aneurysm, and rarely rupture of aneurysm resulting in pericardial effusion.[5-8]

DIAGNOSIS

- *Coronary angiography*: It remains a reliable and widely used modality of detection of CAA and CAE **(Fig. 1)**. Forceful and prolonged injection is required to delineate anatomy. Limitations are delayed antegrade filling, segmental backflow, contrast stasis, detection of thrombus, accurate measurement of the segment involved, and its diameter.[9,10]
- *Computed tomography* (*CT*) *coronary angiography*: It is a kind of noninvasive, outpatient base procedure, which gives better delineation of size, in situ thrombi, adjacent atherosclerosis, and calcification as compared to conventional angiography. It is the choice of investigation for anomalous coronary artery CAA, giant aneurysm, saphenous vein graft (SVG) aneurysm, and precise assessment of mechanical complications of CAA.[11]
- *Intravascular ultrasound* (*IVUS*): It is an excellent modality for differential diagnosis of true versus pseudoaneurysm, size of the aneurysm, and thrombus detection, including

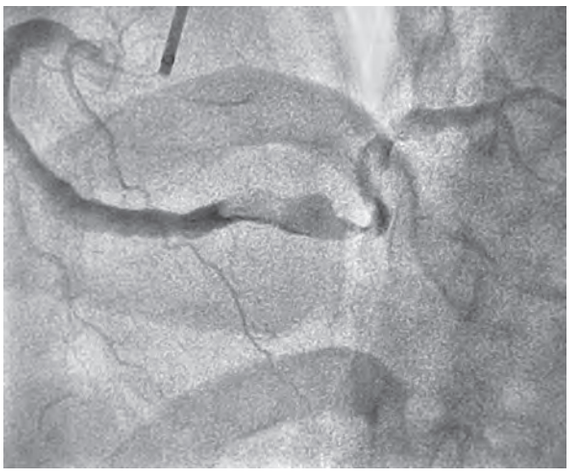


FIG. 1: Inferior wall infarction, diffuse ectasia with multiple thrombus, and tortuosity.

adjacent atherosclerosis and calcification. It gives better outcomes when such patients are treated with percutaneous coronary intervention (PCI).[10]

- *Coronary magnetic resonance angiography*: It is noninvasive. It gives a three-dimensional view of CAA without using contrast in a patient with proximal coronary involvement (including LMCA). Additionally, it gives information on myocardial viability and inflammation in special cases such as Kawasaki disease, granulomatous, and myocarditis. Limitations are cardiac arrhythmia, nonavailability, and learning curve.[12-15]
- *Echocardiography*: It is used as a simple bedside tool in diagnosing Kawasaki disease in children. Common findings observed are:
  - LAD or RCA *Z* score >2.5
  - In age, <5 years, coronary artery diameter >3 mm and >4 mm in age >5 years
  - Lumen diameter >1.5 times the adjacent segment
  - Luminal irregularity[16]

MANAGEMENT OF CORONARY ARTERY ANEURYSM AND CORONARY ARTERY ECTASIA

The natural history of CAA is largely unknown. CAA is associated with higher 5-year mortality; another study suggests a 54% major adverse cardiovascular event (MACE) rate at 4.5 years of follow-up. CAA, following cardiac intervention, has a 27% MACE rate at 3 years. CAE is associated with 3–5 times higher death and nonfatal myocardial infarction.[17-20]

Treatment will be individualized based upon phenotype, patient's risk factors, type of presentation, and whether CAA/CAE is the culprit or not. The goal of medical management is to prevent the progression of CAA, prevent situ thrombus, and improve the flow at the site and distal to the pathology.

Atherosclerosis is an important causative factor for CAA/CEA. Aggressive risk factor modification should be the cornerstone of management.[5]

Antiplatelet and antithrombotic agents comprise the mainstream therapy. Due to the lack of large, randomized trials and registry data, recommendations are based on small-scale studies and case reports. Statins are shown to inhibit the secretion of metalloproteinases-1, -2, -3, and -9 from macrophages and vascular smooth muscle cells and prevent the progression of CAA though there are no long-term randomized data available.

Some authors also suggest the role of angiotensin-converting enzyme (ACE) inhibitors in slowing the CAA/CAE by inhibiting transforming growth factor beta (TGF-β).[21,22]

ASYMPTOMATIC PATIENTS

Aspirin is suggested in all patients because of the coexistence of obstructive coronary artery disease, and many of the patients are at a higher risk of future myocardial infarction. The role of dual antiplatelet therapy (DAPT) is controversial, and no clinical data are available. Warfarin/Novel oral anticoagulant (NOAC) has been suggested to improve flow in the ecstatic segment; however, there are no prospectus data to support it. Anticoagulants are recommended in patients with multivessel ectasia and recurrent coronary events despite antiplatelet agents.[5] ACE inhibitors and statins are useful to prevent the progression of CAE.[4,23,24]

SYMPTOMATIC PATIENTS

In symptomatic patients with stable angina/ACS, there is evidence for the role of antiplatelet and anticoagulants in small-scale studies. Few scattered data on intravenous (IV) eptifibatide and heparin suggest clearance of thrombus.[25]

Case reports of NOACs along with aspirin provide better outcomes in LMCA or long length (>30 mm) CAE. Rivaroxaban 2.5 mg twice a day, along with antiplatelets, shows positive outcomes in case reports.

In special subsets, such as acute Kawasaki disease, IV immunoglobulin results in a higher rate of CAA regression and lower MACE. There is limited evidence of anticoagulant and antithrombotic therapy to reduce thrombotic events in Kawasaki disease. Currently, study with DAPT in children is underway.[26,27]

Vasodilators such as nitrates should be avoided as these increase myocardial ischemia.[28,29]

PERCUTANEOUS CORONARY INTERVENTION

Most of the data are from patients who present with ACS. Asymptomatic patients should be deferred from coronary interventions unless it is post drug-eluting stent (DES), post stent infection, and giant aneurysm where chances of rupture are very high.

Symptomatic patients' goal of therapy is to restore thrombolysis in myocardial infarction (TIMI)-III flow in infarct-related arteries with CAA.

A covered stent should be used to close an aneurysm, but short- and long-term outcomes are not promising **(Fig. 2)**. Case report of DES to treat CAA shows good short-term outcome in young patients with difficult anatomy including a double layer of stent. In case of CAE, stents are difficult due to the length and variable diameter of the involved segment.

Percutaneous coronary intervention should be aided by thrombectomy devices **(Figs. 3 and 4)** and glycoprotein (GP) receptors, fibrinolytic therapy, and intracoronary imaging. The challenges for PCI could be:[5,30-32]

- Large thrombus burden which is adherent and resistant to IV tirofiban or fibrinolytic therapy
- Distal embolization results in slow flow or no-reflow
- Major side branch arising at the site of the aneurysm

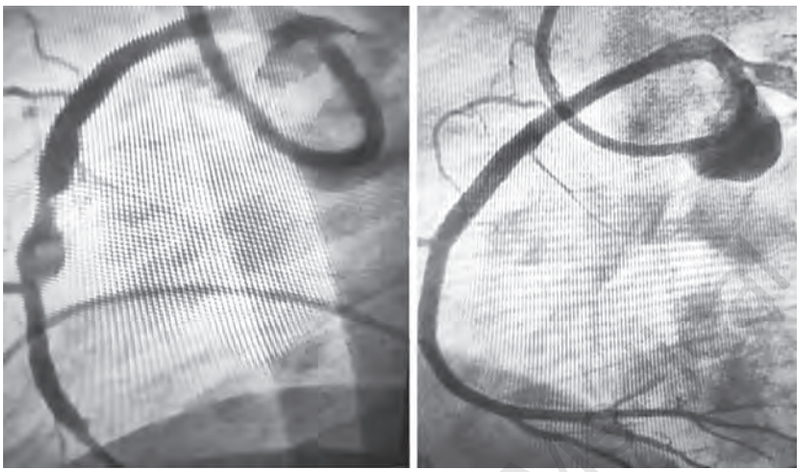


FIG. 2: Thrombus containing saccular aneurysm in a setting of inferior wall myocardial infarction treated with polytetrafluoroethylene (PTFE) covered stent graft with complete closure of aneurysm.

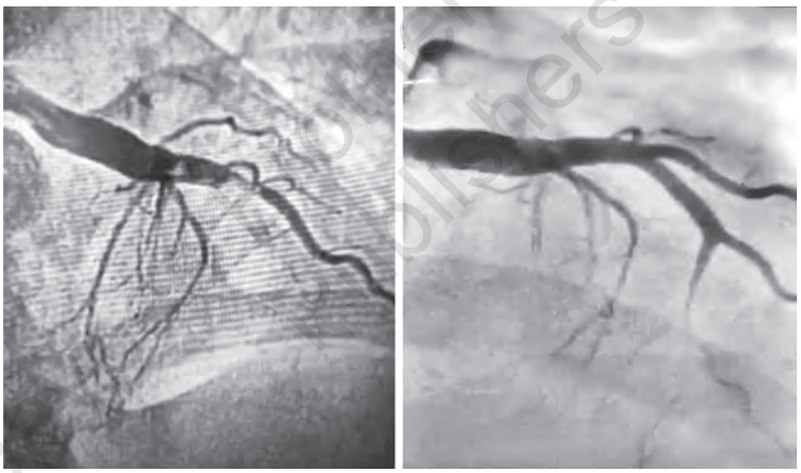
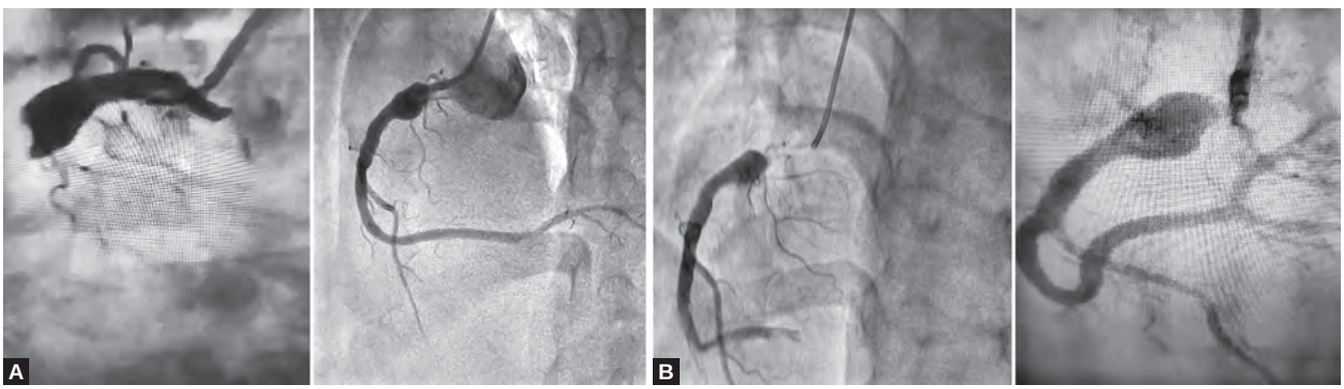


FIG. 3: Anterior wall myocardial infarction, proximal left anterior descending (LAD) coronary artery ectasia with side branch, and in situ thrombus treated with thrombosuction and glycoprotein (GP) IIb/IIIa receptor inhibitor.



FIGS. 4A AND B: (A) Giant aneurysm of right coronary artery (RCA) presented with inferior wall infarction with no-reflow in patent ductus arteriosus (PDA) following thrombosuction, intravenous (IV) glycoprotein (GP) IIb/IIIa inhibitor, and balloon angioplasty. (B) Same patient presented with reinfarction on dual antiplatelet therapy (DAPT), treated with thrombosuction and glycoprotein (GP) receptor inhibitor.

- LMCA and SVG aneurysms
- Type of cover stent and its apposition to vessel wall
- Sizing, landing zone, and delivery of the stiff polytetrafluoroethylene (PTFE)-covered stent
- Tortuous proximal anatomy
- Postdilatation at the aneurysm segment may result in rupture.
- Stent thrombosis and restenosis with cover stent
- Low success rate

In a retrospective study conducted by Szalat et al. comparing surgery versus PTFE, covered stents showed a higher rate of restenosis.[33]

Stent-assisted coil embolization can be used to close an aneurysm with conventional DES, particularly when a side branch is arising or unfavorable proximal anatomy to negotiate a stiff covered stent.[11]

A small series of pediatric and young adults with Kawasaki disease shows the need for repeated intervention due to high wall-bound thrombus and difficulty in assessing coronary diameter. In this subset, coronary artery bypass graft (CABG) was found to be superior as compared to PCI, and hence the current American Hospital Association (AHA) guidelines restrict PCI in a single vessel or focal multivessel in a patient with Kawasaki disease.[26]

SURGICAL MANAGEMENT

Surgical techniques to treat CAA: (1) aneurysm resection, (2) ligation, and (3) marsupialization with interposition graft. A majority of the cases were treated with proximal and distal ligation of CAA and bypass graft attached to the distal-most part. The surgical treatment is used as first-line therapy in patients with LMCA, giant aneurysms, and large side branches arising at the site of the aneurysm. Long-term data are still scanty of surgically treated CAA.[34,35]

A SUGGESTED ALGORITHM FOR MANAGEMENT OF PATIENTS WITH CORONARY ARTERY ANEURYSM[5]

A suggested algorithm for management of patients with CAA is shown in **Flowchart 1**.

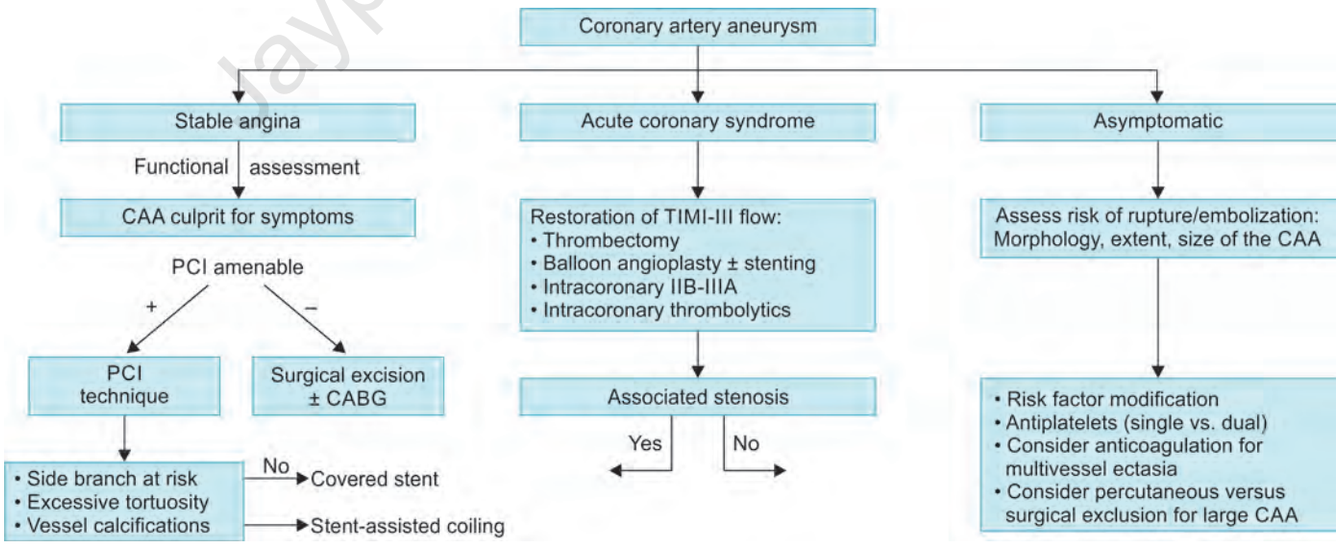
The only study which compares these three modalities is a retrospective study of 458 patients with CAA for a period of 68 months by Khubber et al. This study showed 39.6% in medical group, 26.1% in CABG group and 34.6% in PCI group ($p = 0.02$) had MACCE. Kaplan–Meier's survival analysis shows that CABG performs better as compared to medical management. Both Kaplan–Meier survival and regression analysis show that DAPT and anticoagulants were not associated with significant improvement in MACE rate.[36]

CONCLUSION AND FUTURE PERSPECTIVES

Coronary artery aneurysm and CAE are different phenotypes of the same disease. The majority are asymptomatic; most of them presented with ACS. Due to a lack of data on natural history and randomized trial, treatment is based on small-scale studies and case reports. Risk factor modification, aspirin, statin, and ACE inhibitor in asymptomatic patients, PCI for ACS along with antiplatelet and anticoagulant should be followed. Surgery is reserved for difficult anatomy and recurrent events following PCI and postintervention aneurysm.

Further investigation is required to answer the following questions:[5]

- What is the precise etiology of CAA and CAE?
- Are they different entities or different phenotypes of the same disease?



FLOWCHART 1: A suggested algorithm for management of patients with coronary artery aneurysm.
(CAA: coronary artery aneurysm; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction)

- What is the long-term outcome of symptomatic and asymptomatic patients?
- What is the long-term DAPT and anticoagulant in primary and secondary prevention?
- Which ideal method should be followed to treat CAA with bare-metal stents versus DES versus covered stent versus stent-assisted coiling versus surgical exclusion and so on
- What are the peri- and post-PCI medical regimens?

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CHAPTER 71

Approach to Non-ST-elevation Myocardial Infarction

Satish M Roplekar, Kedar S Roplekar, Kanchan S Roplekar

ABSTRACT

Non-ST-elevation myocardial infarction (NSTEMI) is one component of the spectrum of ischemic heart disease (IHD). Assessment of risk factors, clinical features, electrocardiogram (ECG), and laboratory investigations, especially cardiac enzymes and echocardiography (ECHO), will help in risk stratification and guide management according to the predefined pathways as per the guidelines. The role of invasive versus conservative and percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) medical treatment is described. Special considerations in specific groups/subsets are highlighted.

INTRODUCTION

Ischemic heart disease (IHD) is a spectrum **(Fig. 1)**. At one end, it is "silent" and at the other end it could present as "sudden cardiac death" (SCD). In between, one may come across chronic stable angina (CSA), acute coronary syndrome (ACS), unstable angina (UA), non-Q wave/non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI).[1]

Acute coronary syndrome is characterized by:

- Acute onset of symptoms, at rest or with minimum exertion, lasting for a minimum of 10 minutes if not treated
- Severe pain, pressure, discomfort, and heaviness in the chest
- Crescendo nature of angina, more intense, and lasting for more time

A 12-lead electrocardiogram (ECG) and biomarkers will differentiate between UA, NSTEMI, and STEMI.

FIG. 1: Spectrum of ischemic heart disease.

(ACS: acute coronary syndrome; NSTE: non-ST-elevation; SA: stable angina; SCD: sudden cardiac death; STEMI: ST-elevation myocardial infarction; UA: unstable angina)

Non-ST-elevation myocardial infarction definition: Typical symptoms, without persistent (>20 min) ST elevation in two contiguous leads, but with elevated biomarkers are defined as NSTEMI.

Unstable angina definition: Atypical symptoms and serial negative biomarkers are defined as UA.

CLINICAL ASSESSMENT

History

Non-ST-elevation (NSTE): ACS is relatively uncommon in men under the age of 40 years and in women under the age of 50 years.

Risk factors for coronary artery disease (CAD) are classified as modifiable (controllable) and nonmodifiable (uncontrollable).

Modifiable (Controllable) Risk Factors

- Obesity, syndrome X, metabolic syndrome, characterized by hyperglycemia, hypertension, hypertriglyceridemia, hyperinsulinemia, apple-shaped (central) obesity
- Smoking
- Hypertension
- Diabetes mellitus
- Sedentary lifestyle
- Hyperlipidemia
- Constant mental stress

- Indulgence in excess saturated fat and food items
- Hyperuricemia
- Hyperhomocysteinemia

Nonmodifiable (Uncontrollable) Risk Factors

- Heredity, familial hyperlipidemia
- Age
- Gender (women are protected from developing CAD till they attain menopause)

Clinical Features

Symptoms

Symptoms include retrosternal chest discomfort, heaviness, and pressure which are more frequent, more severe in nature, lasting for more than 10 minutes (compared to stable angina), and not relieved by rest or sublingual (SL) nitrates. The pain/discomfort might get radiated to the ulnar aspect of the left forearm, shoulder, lower jaw, back in the interscapular region, nape of the neck, throat, or epigastrium. The pain may be associated with sweating, nausea, dyspnea, giddiness, or frank syncope. At times, the patient may present with dyspeptic symptoms, "trapped gas," or burning sensation in the chest or feeling of indigestion. Such symptoms may be neglected by patients leading to under-recognition, underdiagnosis, undertreatment, and poor prognosis.

In an established patient of stable CAD, ACS may be precipitated by

- Severe anemia
- Infection/Inflammation
- Fever
- Metabolic/Endocrinological diseases

Physical Examination

Physical examination was usually unremarkable. On careful examination during pain, S4 may be heard. If the patient presents with complications such as left ventricular (LV) failure, cardiogenic shock, or precipitating factors, then related findings may be observed such as bilateral crepitations in the lungs, hypotension, etc.

Electrocardiogram

The most common abnormality is depression of ST segments and inversion of T wave, especially if the ECG is recorded during pain. If ECG recorded in the recent past is available for comparison, it helps to diagnose dynamic changes of ST depression. Even 1-mm ST-segment depression is sensitive but not specific. Greater degrees of ST-segment depression predict poor prognosis. T-wave inversion may not have much diagnostic importance. Transient elevation of ST segment lasting for <20 minutes may suggest UA or coronary vasospasm. More than 50% of the patients may have normal ECG findings; however, if the clinical suspicion is strong, then the patient should be labeled as "UA with normal ECG" and admitted for further observation/management. If ECG is recorded during an ischemic episode, ECG may pick up the changes, or else it may be normal. ECG for that matter should be repeated after every 20–30 minutes until symptoms resolve or the diagnosis is established or excluded. Patients with baseline conduction disturbances, especially bundle branch block and paced rhythm, pose difficulties in diagnosing ischemia. In such a scenario if the patient has older ECGs for comparison, it might be helpful. For final and complete evaluation, the gold standard investigation of coronary angiography (CAG) will detect the culprit lesion and vessel.

Role of Recording Extra Leads

To detect posterior wall ischemia [left circumflex artery (LCx)/obtuse marginal (OM) territory] V_7 to V_9 leads with doubling the gains (20 mm) should be considered. Similarly to detect right ventricular (RV) wall ischemia, [RV branch of right coronary artery (RCA)] leads V4R should be considered especially when inferior wall injury is seen on traditional 12-lead ECG.

Biomarkers (Enzymes)

Cardiac-specific troponin I (cTnI) and cardiac-specific troponin T (cTnT) are biomarkers of choice to diagnose myocardial injury, and after the injury the markers are elevated by >99th percentile of normal range **(Fig. 2)**.[2,3] In order to exclude other conditions of myocardial injury from CAD (ACS) and to avoid misdiagnosis, the elevated marker should be correlated with clinical presentation of the patient and ECG changes. The HEART (History, ECG, Age, Risk factors, and Troponin) approach is important to either diagnose or exclude ACS.

New high-sensitivity troponin (hsTn) assays can exclude acute myocardial infarction (MI) with single measurement in patients who are symptomatic for >3 hours or with two measurements performed at presentation and 1 hour later "*0/1*" approach in patients who present in <3 hours of symptoms. With serial measurements of hsTn at 0/1 hours MI could be ruled out with 100% sensitivity and negative predictive value; however, the specificity is 97% and positive predictive value is 84%. 0/1-hour approach is preferable than 0/3-hour approach. Prognosis can be assessed by applying multimarker approach, computed tomography (CT), and coronary or invasive CAG. Nowadays, measurement of creatine kinase-myocardial band (CK-MB) is not recommended when hsTn is measured. Several other biomarkers such as brain natriuretic peptide (BNP), N-terminal pro-BNP (NT-pro-BNP), high-sensitivity C-reactive protein (hsCRP), and growth differentiation factor (GDF) may be useful in judging the prognosis. Natriuretic peptides (NPs) rise in proportion to the degree of ventricular distention (strain) and correlate with complications such as heart failure (HF), MI, and death. Patients with elevated NP and hsCRP benefit more from more intense and aggressive treatment, such as anti-ischemic, lipid-lowering, and coronary revascularization **(Fig. 3)**.[4,5]

Imaging

Noninvasive testing plays several important roles in the management of NSTE-ACS.

- Establish the presence or absence of significant CAD.
- Correlate cTn elevation with CAD.

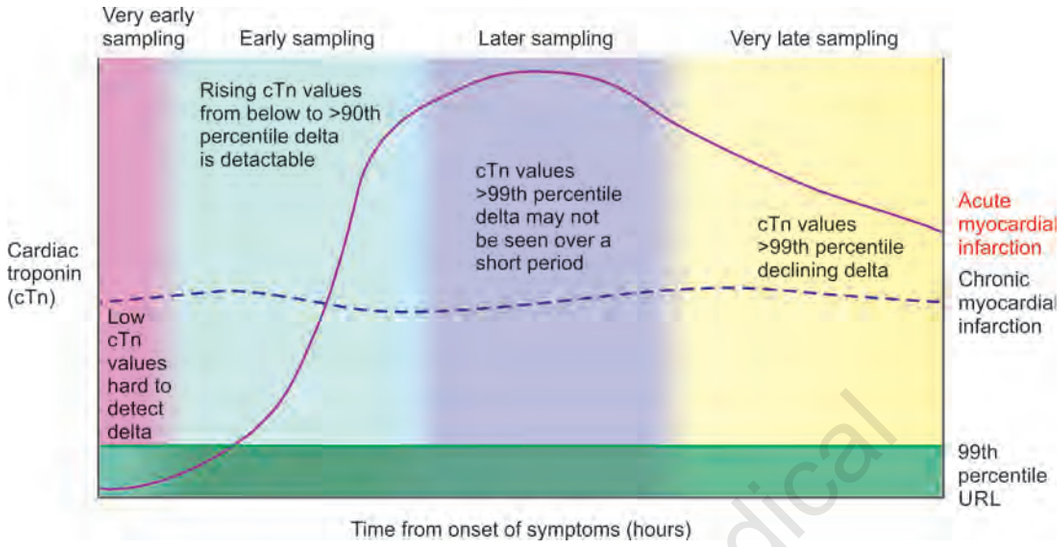


FIG. 2: Timing of biomarker release.
(URL: upper reference limit)

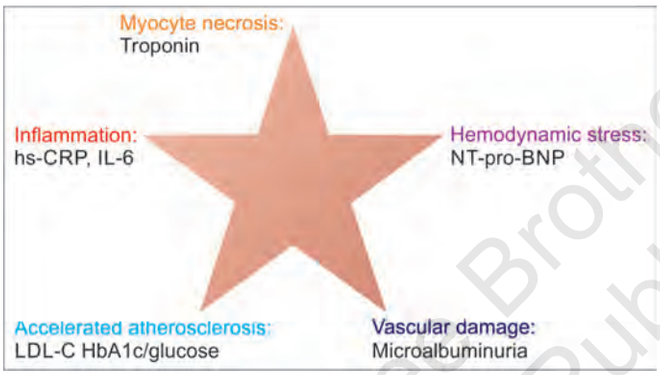


FIG. 3: Multimarker approach in ACS.
(HbA1c: glycated hemoglobin; hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin 6; LDL-C: low-density lipoprotein cholesterol; NT-pro-BNP: N-terminal pro-brain natriuretic peptide)

- Assess the extent of residual ischemia after initial medical therapy.
- Locate territory of ischemia (culprit lesion) for planning revascularization in multivessel disease (MVD).
- Assess LV function.

The role of treadmill or pharmacological stress testing (ECG stress test) is debated; however, it could be safely performed after 24 hours of stabilizing the patient both symptomatically and electrically. Treadmill stress testing (ECG stress test) could be done if resting ECG has no ST-T changes. However, if resting ECG shows ST-T changes, then stress perfusion or stress echocardiography (ECHO) should be done at rest and after exercise. For patients who are unable to exercise, pharmacological stress testing with imaging is recommended. Stress thallium (nuclear isotope studies) and stress ECHO with dobutamine have greater sensitivity than treadmill test (TMT; ECG stress test). High-risk findings on stress testing such as depression of ST segment by >0.2 mV at low workloads (<stage 3 of Bruce protocol), hypotension during exercise, ventricular arrhythmias, and signs of LV failure prompt us for early intervention.

ECHO is useful in

- Assessment of LV function
- Left atrial (LA) dilatation
- Functional mitral regurgitation (MR)
- Tricuspid annular plane systolic excursion (TAPSE)
- Ventricular dyssynchrony
- Ultrasound lung comets [extravascular lung fluid seen on ultrasonography (USG) of thorax]

All the findings suggest adverse prognosis in patients with NSTE-ACS.

Computed tomography coronary angiography helps to

- Recognize or exclude the presence of epicardial CAD
- Which vessels, at what location, and how significant?
- Assist in risk stratification and prognosis

Doing CT CAG directly without other studies expedites the diagnosis, thus shortening the hospital stay and cost; hence, it is a class I recommendation to perform CT CAG, especially in the emergency room (ER) in patients with chest pain and suspected to have NSTE-ACS.

Cardiac MRI using rapid scan protocol will:

- Provide precise measurements of ventricular volume and function
- Detect and assess ventricular wall edema
- Identify areas of infarcted versus viable hibernating myocardium
- Establish the presence of myocardial perfusion
- Quantify wall motion
- Identify myocardium at risk

At times, high-resolution late gadolinium-enhanced imaging may be required. Noninvasive cardiac imaging has a definite role to assess CAD in NSTE-ACS.

Invasive Imaging

Invasive CAG has been considered the gold standard technique to delineate coronary tree since the last six decades. The culprit vessel/lesion is usually eccentric, with scalloped or overhanging edges and narrow neck. If the plaque is disrupted with thrombus formation, then a space-occupying shadow/haziness/mass is seen in the lumen. Up to 90% of the patients with NSTE-ACS have significant (>50% stenosis) coronary obstruction in the culprit vessel. About 10% have left main with MVD. Out of the remaining 90% patients, one-third have triple-vessel disease, 25% have double-vessel disease, and 20% have single-vessel disease. No significant coronary obstruction (more common in women)[6,26] is seen in 10%, and is related to "microvascular coronary obstruction," endothelial dysfunction, or coronary artery spasm and carries favorable prognosis. The 1-month mortality or MI is 2.2% in nonobstructive CAD compared to 13.3% in obstructive CAD.[6]

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are invasive cross sectional imaging techniques useful in assessing plaque morphology and used during deployment of the stent.

RISK ASSESSMENT

Residual Risk

Lipoproteins, inflammation, obesity, glucose metabolism, platelet function, and coagulation process will determine the recurrent ischemic events in a patient either from culprit vessel/lesion or from blocks in other coronary vessels.[7] Aggressive medical management is necessary to prevent recurrent ischemic events.

Natural History

Patients with UA have lower mortality (<2% at 30 days) compared to patients with NSTEMI or STEMI. However, due to early diagnosis of UA the incidence and prevalence of NSTEMI are declining.[2,8] The early mortality in NSTEMI is related to the extent and amount of myocardial necrosis and resulting hemodynamic compromise and is lower than that in patients with STEMI which have larger infarcts. In TIMI (Thrombolysis in Myocardial Infarction) trials with NSTEMI, 85% deaths at 30 days were mostly related to cardiovascular (CV) events (recurrent MI and HF).[9] After 1 month, SCD was the most common cause (46%) of mortality. Factors such as advanced age, extent of CAD, history of MI, and comorbid conditions such as diabetes, chronic renal failure (CRF), and recurrent ischemic episodes, all point toward untoward events in patients with NSTE-ACS.

Risk Assessment Scores

Several risk scores have been developed on findings on the clinical scenario, changes on ECG, and biomarkers. The sum total of TIMI risk scores is directly proportional to death and recurrent ischemic events **(Fig. 4)**.[10-12] Risk assessment is important because patients who are at high-risk benefits immensely by early invasive strategy and more intense antithrombotic therapy. The Global Registry of Acute Coronary

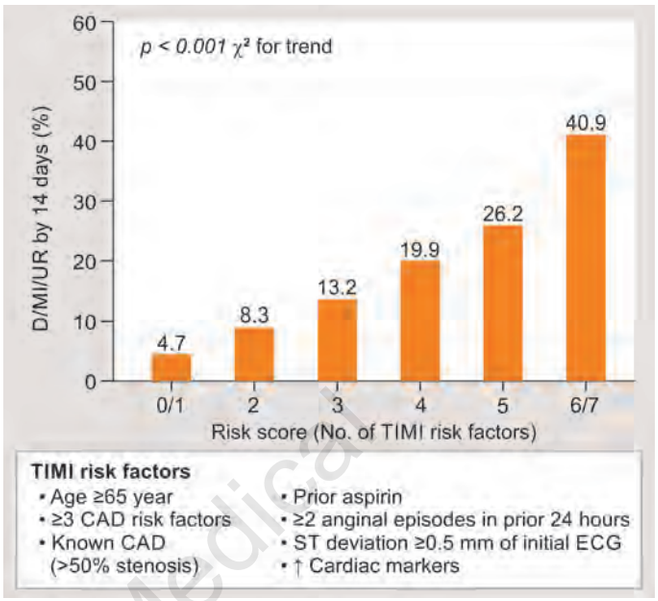


FIG. 4: TIMI risk score for NSTE-ACS.

(CAD: coronary artery disease; ECG: electrocardiogram; MI: myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction; UR: upper reference)

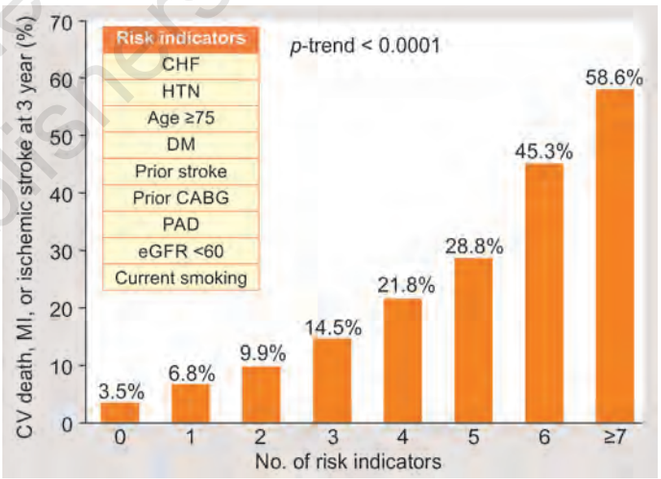


FIG. 5: TIMI risk score for secondary prevention, long-term risk stratification after MI.

(CABG: coronary artery bypass grafting; CHF: congestive heart failure; CV: cardiovascular; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HTN: hypertension; MI: myocardial infarction; PAD: peripheral artery disease)

Events (GRACE) risk score uses risk factors to predict mortality after NSTE-ACS; however, it is more complicated compared to the TIMI risk score. TIMI stable ischemic CAD risk score[13] **(Fig. 5)** is utilized for long-term prognostication in post-ACS patients using nine independent clinical predictors.

MANAGEMENT

Acute management includes relief of symptoms and hemodynamic stabilization. Long-term management is for rehabilitation and prevention of recurrent ischemic episodes.

TABLE 1: Anti Ischemic drugs in NSTE-ACS.

Class of the drug	Mechanism of action	Clinical effects
Traditional therapies		
Beta-blockers	Negative chronotropic and inotropic action plus reduction in BP	Decreased mortality[17]
Nitrates	Venodilator (preload reduction) and coronary dilator	No benefit on mortality
Calcium channel blockers	Non-DHP CCB: Reduce HR and contractility. DHP CCB: Vasodilatation	No clear benefit on mortality or reinfarction. With nifedipine reinfarction is increased
Newer and experimental therapies		
Ranolazine	Inhibits late inward sodium current	Recurrent ischemia and arrhythmias are reduced
Trimetazidine	Myocardial metabolism shifted from fatty acid to utilization of glucose	Reduction in short-term mortality
Nicorandil	Potassium channel opener, dilates arterioles, and ischemic preconditioning	Reduction in ischemia and arrhythmias

(BP: blood pressure; CCB: calcium channel blocker; DHP: dihydropyridine; HR: heart rate)

General Measures

Rapid transfer and hospitalization preferably in the ambulance is recommended. Since "time is muscle" quick decisions and reflexes on the part of medical team are expected. In the interest of time, initial history, evaluation, and ECG may be recorded in the ambulance, which should be recorded within 10 minutes. Blood sample should be sent for cTn or for hsTn and report should be available within an hour. Additional supportive laboratory tests may be carried out to rule out anemia, diabetes, renal dysfunction, and electrolyte imbalance. Patient should be admitted to the intensive care unit and observed continuously and very carefully for the likely occurrence of either electrical and/or mechanical complications such as arrhythmias and HF once the patient is diagnosed as NSTEMI-ACS.[14,15] The patient should be confined to bed, if SpO_2 is <90%, or if the patient has e/o pulmonary edema (LV failure) then inhalation of oxygen is recommended.[16]

Anti-ischemic Therapy

The aim of the therapy is to quickly restore the balance between oxygen supply and demand and thereby giving relief of symptoms, prevention of infarction, HF, arrhythmias, and death **(Table 1)**.[14,15]

Nitrates

Nitrates are the cornerstones in the therapy of ACS and could be administered through various routes such as, orally, sublingually, buccal spray, intravenously, or through skin (ointment or patches). Nitrates chiefly are venodilators thereby reducing preload; however; they reduce after load as well to a small extent. Thus they reduce the ventricular wall stress. Concomitant use of beta-blockers (BBs) will prevent the side effects of nitrates such as reflex tachycardia and positive inotropy. Nitrates though central in the ACS management, their use have not shown mortality benefit. If the patient is symptomatic and the systolic blood pressure (SBP) is >90 mm Hg, nitrates could be administered under careful monitoring. The intravenous (IV) nitroglycerine is indicated if the patient has uncontrolled hypertension, persistent or recurrent ischemic pain, and HF, and the recommended dose is 5–10 µg/min and could be increased up to 200 µg safely under careful monitoring. The IV nitroglycerine should not be abruptly stopped for the fear of rebound phenomenon; hence, it should be weaned over few hours. The patient may develop "nitrate tolerance" and to overcome "nitrate-free interval" may be considered. The contraindications for use of nitrates include hypotension SBP <90 mm Hg; consumption of sildenafil, tadalafil, and vardenafil within 24–48 hours (which through drug interaction may produce dangerous hypotension); left ventricular outflow tract (LVOT) obstruction; RV infarct; and acute pulmonary embolism.

Beta-blockers

Beta-blockers inhibit oxygen consumption through negative inotropic, chronotropic, and antihypertensive action. BB could be administered for rapid onset of action intravenously and subsequently continued orally. BB helps to prevent reinfarction, arrhythmias, and reduce the mortality. American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC) have recommended the use of metoprolol, bisoprolol, nebivolol, and carvedilol. Metoprolol (IV) may be given at a dose of 5 mg over a period of 2 minutes and could be repeated if ischemia and/or arrhythmias persist up to 15 mg over a period under careful monitoring. The contraindications for use of BB are atrioventricular (A-V) blocks, bronchial asthma, acute decompensated severe HF, hypotension, and coronary vasospasm especially in drug addicts (cocaine). The dose of BB should be stepped up slowly over days to weeks, watching the patients' hemodynamics carefully.

Morphine

This molecule has become of historical interest because it is not available easily in pharmacy. It acts as venodilator (preload reduction), anxiolytic, and analgesic and could be given subcutaneously or intravenously at a dose of 1–5 mg. The contraindications for morphine use are hypotension, allergy, and history of opiate addiction. Morphine is known to delay the absorption of clopidogrel from the intestines and the patient is exposed to increased short-term ischemic events. The side effects include hypotension and bradycardia and the overdose may produce respiratory and circulatory depression. The antidote for morphine overdose is naloxone 0.4–2.0 mg IV.

Calcium Channel Blockers

Nondihydropyridine derivatives such as verapamil and diltiazem are contraindicated in LV dysfunction, risk of impen-

ding cardiogenic shock, and A-V blocks including first degree. Dihydropyridine derivatives such as nifedipine, amlodipine, felodipine, and cilnidipine are vasodilators and produce hypotension. Older molecules through the action on A-V node may produce bradycardia, A-V blocks, and negative inotropism and thus reduce myocardial oxygen requirement. The calcium channel blocker (CCB) could be combined with nitrates and BB safely to reduce ischemia and angina.[14,15] Nifedipine should be combined with BB to control the tachycardia and heart rate (HR). Amlodipine and felodipine can be safely used for long term in presence of LV dysfunction and CAD.

Antiplatelet Therapy

See **Box 1 and Figure 6**.

Oral Antiplatelet Drugs

Aspirin (ASA): Cornerstone in All Acute Coronary Syndrome Patients!

Aspirin acetylates platelet cyclooxygenase-1 (COX-1), thereby blocking the synthesis and release of thromboxane A2 (TxA2), which is a platelet activator thus reducing platelet aggregation and arterial thrombus formation. Inhibition of COX-1 by ASA is irreversible; hence, the antiplatelet effects last for a week to 10 days (life span of platelets). Several trials have shown mortality and other benefits [major adverse cardiovascular events (MACEs), ischemic events] with aspirin in patients with NSTE-ACS;[18] thus, it is useful for primary as well as secondary prevention. The dose of ASA ranges from 50 to 1,300 mg/day. The risk of gastrointestinal (GI) bleeding is more with higher doses.[18] The CURRENT OASIS-7 trial[19] randomized patients with ACS to high dose 300–325 mg/day or low dose 75–100 mg/day for 30 days. No differences in the risk of CV death, MI, and stroke were observed between the two groups, but GI bleeding was more in high-dose group. The guidelines recommend that the initial loading dose should be 162–325 mg of soluble (not enteric coated) ASA followed by a maintenance dose of 75–100 mg daily.[20] Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided along with ASA because they produce prothrombotic effects. ASA resistance may occur in 2–8% of the patients during chronic therapy exposing them to recurring cardiac events. The causes of ASA resistance are poor compliance, use of enteric-coated formulation, reduced absorption, interaction with NSAIDs, and overexpression of COX-2 mRNA. Contraindications for the use of ASA include allergy, allergic asthma, nasal polyps, active bleeding, and known platelet disorder. In such a situation, clopidogrel, prasugrel, or ticagrelor may be substituted.[14]

BOX 1 Anti-thrombotic therapy for NSTE-ACS.[18,19]

- *Aspirin*: All patients must receive the loading dose (soluble aspirin 150–300 mg)
- *Parenteral anticoagulation before percutaneous coronary intervention (PCI)*:
  - Unfractionated heparin (UFH), or enoxaparin or bivalirudin. Avoid fondaparinux
  - Patients on vitamin K antagonist (VKA): Continue, do not interrupt
  - Patients on novel oral anticoagulants (NOACs): Stop NOAC and start parenteral anticoagulation with UFH, or low-molecular-weight heparin (LMWH) regardless of the timing of last NOAC dose.
- *Anticoagulation during PCI*:
  - If immediate (<2 hours of symptoms) use low-dose IV coagulation regardless of the last dose of oral anticoagulation. Options are UFH 60 U/kg body weight or enoxaparin 0.5 mg/kg IV.
  - If >2 hours of symptoms and if the patient is on vitamin K injection (VKI), perform PCI without stopping VKA, if the international normalized ratio (INR) >2.5 without additional parenteral anticoagulation. In case INR is between 2.0 and 2.5, low-dose UFH or enoxaparin is used. In case INR is <2.0, standard dose is used.
  - Patients on NOAC: Use additional intraprocedural low-dose parenteral anticoagulation, irrespective of the timing of the last dose of NOAC
  - *P2Y12 inhibitors*: To minimize bleeding risk, consider postponing administration of P2Y12 inhibitors until coronary anatomy is known and PCI is planned. Use less potent agents such as clopidogrel.
  - Glycoprotein (Gp) IIb/IIIa inhibitors are only to be used during bailout situations
  - *Stent selection*: Bioabsorbable stents should be avoided due to the high thrombotic risk.

P2Y12 Inhibitors

Management of ACS includes dual antiplatelet therapy (DAPT) consisting of ASA and a P2Y12 inhibitor such as clopidogrel and prasugrel (thienopyridines). P2Y12 receptor is blocked by these molecules and these molecules also block adenosine diphosphate (ADP) binding to the surface of platelets. The action is irreversible. However, the action of ticagrelor is reversible. Thienopyridines also reduce fibrinogen, blood viscosity, and red blood cell (RBC) deformity and aggregability.

Clopidogrel

Clopidogrel is the first thienopyridine, widely used for more than a decade in patients suffering from CAD and NSTE-ACS, and in patients undergoing PCI. Clopidogrel used with ASA (DAPT) is the most preferred combination in multiple guidelines. In CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events) trial, patients with NSTE-ACS who were treated with ASA were randomized to either clopidogrel or placebo.[21] Addition of clopidogrel reduced CV death, MI, and stroke by 20% in low-risk as well as high-risk patients irrespective of whether they were managed medically, PCI, or coronary artery bypass grafting (CABG) surgery. Benefit was observed as early as 24 hours and was the same before and after the interventions.[22] A small increase (nonsignificant) in bleeding risk was observed. The current guidelines recommend a loading dose of 600 mg of clopidogrel followed by 75 mg once a day in addition to ASA in patients of NSTE-ACS. Loading dose ensures a steady state of platelet inhibition after 2 hours of consumption. Some cardiologists prefer not to load the patients with clopidogrel until CAG is performed because they are not sure whether the patient will require CABG surgery or PCI.[15] Once you commit to load and use clopidogrel and

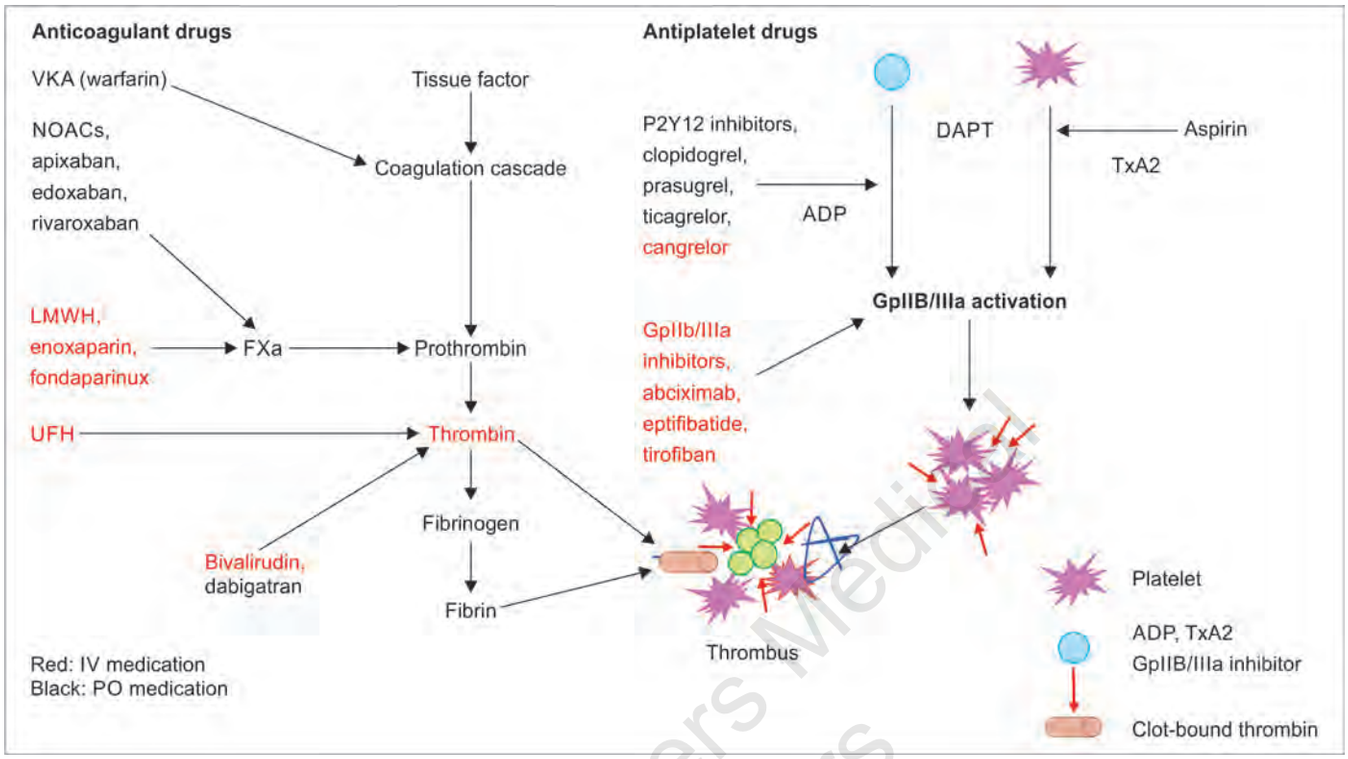


FIG. 6: Mechanism of action of anti-thrombotic treatment.
(ADP: adenosine diphosphate; DAPT: dual antiplatelet therapy; FXa: factor Xa; IV: intravenous; LMWH: low-molecular-weight heparin; NOAC: novel oral anticoagulant; TxA2: thromboxane A2; UFH: unfractionated heparin; VKA: vitamin K antagonist)

if the patient has to undergo CABG surgery, then clopidogrel needs to be stopped at least 5 days before the surgery in order to minimize the risk of bleeding. Although DAPT reduces recurrent ischemic events, up to 10% patients treated with DAPT (ASA and clopidogrel) have MACE including stent thrombosis in 2% patients at 1 year.[23] Hyporesponders to clopidogrel (?clopidogrel resistance) have been observed in 5–30% patients resulting in recurrent cardiac events, stent thrombosis, MI, and death. Resistance occurs due to failure of conversion of prodrug to active drug and is more often seen in patients with diabetes, elderly individuals, obesity, and certain genetic polymorphisms, especially Asians.[24] Proton-pump inhibitors except omeprazole reduce the antiplatelet effect of clopidogrel.[25]

Prasugrel

Prasugrel is a prodrug and requires oxidation in the liver to form an active metabolite and irreversibly binds to P2Y12 receptor on platelets. However, the mechanism of action is quick and within 30 minutes of ingestion the action starts. Prasugrel is 10 times more potent than clopidogrel. The loading dose of prasugrel is 60 mg and the maintenance dose is 10 mg OD. The maintenance dose should be reduced to 5 mg OD if the patient is more than 75 years and/or the weight is less than 60 kg in order to reduce the risk of bleeding. Prasugrel has been compared with clopidogrel in TRITON-TIMI 38 trial.

- The primary composite endpoint of CV death, MI, or stroke was reduced significantly by 19% in patients randomized to prasugrel and the effect was consistent till 15 months of follow-up **(Figs. 7 and 8)**.[17]
- There was significant 24% reduction in MI and particularly in diabetic patients (30% reduction).[26]
- There was significant reduction in the rate of definite or probable stent thrombosis by 52%, especially in patients in whom drug-eluting stent (DES) was deployed (64%).[27]

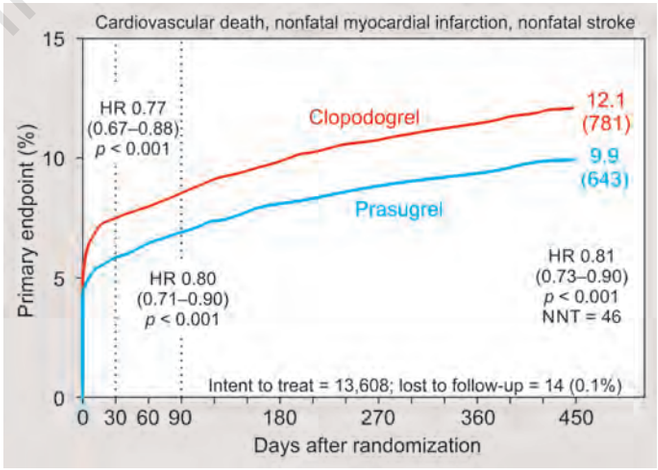


FIG. 7: Long-term comparison between clopidogrel and prasugrel in TRITON TIMI 38 trial 17.
(HR: hazard ratio; NNT: number needed to treat)

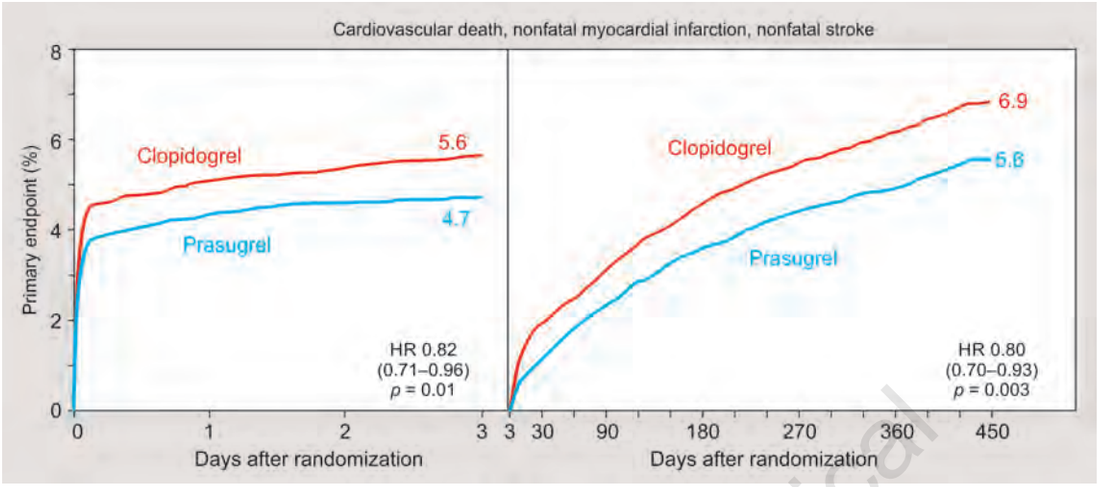


FIG. 8: Short-term and Long-term comparison between clopidogrel and prasugrel in TRITON TIMI 38 trial 17.
(HR: hazard ratio; NNT: number needed to treat)

However, severe bleeding complications were more common with prasugrel than clopidogrel including non-CABG major, spontaneous, and fatal bleeding. Prasugrel should be contraindicated in patients with a history of stroke or transient ischemic attack (TIA). Prasugrel needs to be stopped at least a week before cardiac surgery.[28]

Prasugrel 10 mg was compared with clopidogrel 75 mg in patients with NSTE-ACS in TRILOGY ACS randomized trial.[29]

- There was no benefit of treatment with prasugrel over clopidogrel and the bleeding risks were similar.

The ACCOAST trial of high-risk patients with NSTE-ACS who were managed with an early invasive approach were randomized to prasugrel or clopidogrel prior to angiography.[30]

- There was no significant difference in composite primary efficacy endpoint; however, prasugrel did increase bleeding compared with clopidogrel.

Thus it could be concluded that between clopidogrel and prasugrel, prasugrel in addition to ASA is most suitable in patients with NSTE-ACS who are <75 years and weighing >60 kg without a past history of stroke or TIA, in whom PCI is planned. Prasugrel is not recommended for use in NSTE-ACS patients before the coronary anatomy is known.[20]

Ticagrelor

Ticagrelor is the first approved nonthienopyridine ADP blocker and unlike thienopyridines such as clopidogrel and prasugrel, it is a reversible inhibitor with a short half-life of 12 hours.[31] Parent drug, as well as its metabolite, is active and is a potent inhibitor of P2Y12 receptor on platelets.

Phase III PLATO trial **(Fig. 9)**[23] compared ticagrelor 180 mg loading dose followed by 90 mg BD maintenance dose with clopidogrel 300 or 600 mg loading followed by 75 mg OD maintenance dose with ASA.

- Ticagrelor significantly reduced the primary endpoint (CV death, MI, or stroke) by 16%.
- Ticagrelor reduced stent thrombosis by 33%.
- Ticagrelor reduced CV death by 21%.
- Ticagrelor reduced total mortality by 22%.

The benefit with ticagrelor was consistent even in patients >75 years, weight <60 kg, with a past history of stroke or TIA and those patients who were managed with noninvasive strategy.

The dose of ASA should be 75 mg OD whenever ticagrelor is used. Between ticagrelor and clopidogrel non-CABG-related major bleeding, dyspnea, and sinus pauses lasting for >3 seconds, especially in the first week, were more common with ticagrelor. Though ticagrelor is reversible unlike clopidogrel or prasugrel, it needs to be stopped at least 5 days before any major surgery.[28]

The PEGASUS-TIMI 54 trial was done to assess the long-term use of ticagrelor with ASA in patients who have suffered MI 1–3 years earlier.[32]

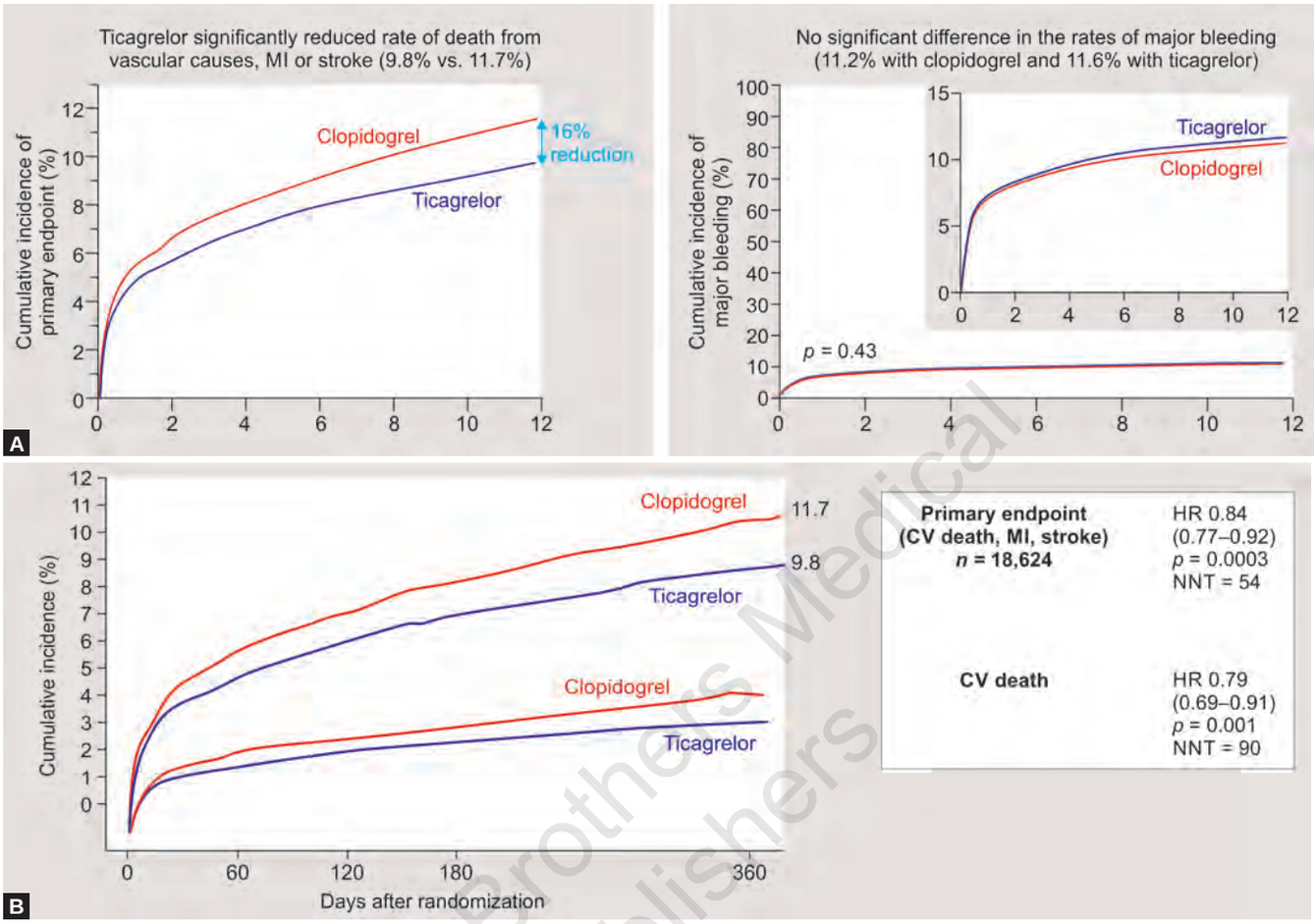
- Compared with placebo, both the standard maintenance dose of ticagrelor 90 mg BD and 60 mg BD reduced the rate of primary composite endpoint of CV death, MI, or stroke by 15% and 16%, respectively.
- TIMI major bleeding was high with ticagrelor, but rates of intracranial and fatal bleeding were not increased.

Ticagrelor versus Prasugrel

The ISAR-REACT 5 trial[33] was an open-label, multicentric, randomized trial that compared ticagrelor versus prasugrel in patients with ACS and in whom invasive evaluation was planned. There was 40% relative risk reduction in patients with NSTE-ACS randomized to prasugrel versus ticagrelor in primary composite endpoint of CV death, MI, or stroke at 1 year. Bleeding risks were similar in both the groups.

SELECTION AND DURATION OF DUAL ANTIPLATELET THERAPY IN NSTE-ACS

Patients with NSTE-ACS are managed with (1) PCI 50–70%, (2) only medically 30–50%, and (3) with CABG surgery



FIGS. 9A AND B: (A) Comparison of efficacy and safety of clopidogrel and ticagrelor in PLATO trial; (B) Cumulative incidence of CV death, MI, stroke combined and CV death alone in clopidogrel and ticagrelor treated patients in PLATO trial.[23]

(CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction; NNT: number needed to treat)

Source: Wallentin L, Becker, RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045-57.

5–15%.[34] Selection of DAPT regimen and its duration post ACS is a complex decision due to many factors and needs to be individualized. However, in majority of patients, a duration of 6–12 months of DAPT is reasonable. Shorter duration of DAPT is recommended for individuals who are at low risk of ischemic events, or at high risk of bleeding or who are receiving concomitant oral anticoagulants. The TWILIGHT trial randomized high-risk patients with NSTE-ACS, post PCI who had received 3 months of ASA + ticagrelor to either continue DAPT or ticagrelor alone in double-blind study. The primary endpoint of bleeding at 1 year was reduced from 7.6 to 3.6% with ticagrelor monotherapy and there was no statistical difference in other efficacy composites (4.3% vs. 4.4%).[35] Thus nowadays, there is a trend toward shorter duration of DAPT post PCI. However, if the patient is exposed to high risk for ischemic events such as diabetes mellitus (DM), elderly, recurrent MI, multivessel CAD, and chronic kidney disease (CKD), then longer (>12 months)[15,32,36] duration of DAPT is recommended. The reduced dose of ticagrelor 60 mg BD has been shown to be equally effective.[20]

Switching between oral P2Y12 inhibitors

Patients with the following scenarios need change of P2Y12 inhibitors:

- Recurrent ischemic events, who are receiving clopidogrel and ASA
- Intolerance or side effects such as bleeding with existing molecule
- Cost issue

Based on PLATO trial, an international expert consensus has provided details of how to switch between P2Y12 inhibitors.[37]

Intravenous Antiplatelet Agents

Cangrelor is an IV direct-acting P2Y12 inhibitor that blocks activation of platelets and aggregation with immediate (instant) onset of action and a very short half-life of 3–6 minutes and overcomes the drawback of oral P2Y12 inhibitors of slower onset of action, gut absorption issues, and on cangrelor patient could be subjected for CABG surgery (if need arises) immediately without stopping it. In a meta-analysis of more

than 25,000 patients who have undergone PCI (NSTE-ACS scenario), cangrelor significantly reduced the risk of primary endpoint of death, MI, ischemia-driven revascularization, and stent thrombosis at 48 hours by 18%.

Glycoprotein IIb/IIIa Inhibitors

Glycoprotein IIb/IIIa inhibitors were frequently used in the past when potent oral P2Y12 inhibitors such as ticagrelor or cangrelor were not available. Abciximab (monoclonal antibody and long acting), eptifibatide, and tirofiban (reversible small-molecule inhibitors with short duration of action) have been approved for use in patients with NSTE-ACS and who are undergoing PCI. Several trials (Gp IIb/IIIa inhibitors and DAPT) have shown small but significant 9% reduction in MI or death at 1 month in NSTE-ACS patients, especially in high-risk subsets such as ST-segment changes, elevated troponin levels, and DM. However, the bleeding risk was more 2.4 versus 1.4% (placebo) secondary to thrombocytopenia. Based on the available evidence routine use of Gp IIb/IIIa inhibitors apart from DAPT, in patients with NSTE-ACS, is not recommended and should be reserved for patients with low risk of bleeding, undergoing PCI who are at high risk of thrombus formation (DM) or with angiographic evidence of thrombus.

Anticoagulant Therapy

Parenteral anticoagulants in addition to DAPT should be started immediately (if there is no contraindication) after diagnosis of NSTE-ACS.

Heparin

Unfractionated heparin prevents clotting by blocking thrombin [factors IIa and Xa (FXa)]. UFH also binds to circulating plasma proteins, acute phase reactants, and endothelial cells. The anticoagulant effect is short and unpredictable. Continuous IV infusion needs to be given to ensure a stable anticoagulant effect. A meta-analysis has shown 33% reduction in death or MI with UFH plus ASA versus ASA alone.[38] The dose of UFH is 60 units/kg bolus followed by 12 units, kg/h infusion. Activated partial thromboplastin time (APTT) needs to be monitored and should be maintained between 50 and 70 seconds or 1.5–2.5 times control.[14,15] Prolonged infusion of UFH increases the risk of heparin-induced thrombocytopenia (HIT) which is an infrequent but a serious fatal complication leading to thrombosis and bleeding.

Heparin reversal is done with protamine sulfate, and 1 mg neutralizes approximately 100 units of UFH. The side effect of protamine is hypotension and bradycardia. Protamine reverses approximately 60% of enoxaparin and will not reverse FXa inhibitor such as fondaparinux. Heparin reversal should never be done in patients who have been stented recently for fear of stent getting thrombosed and occluded.

Low-molecular-weight Heparin

Low-molecular-weight heparin has more predictable anticoagulant effects compared with UFH. The advantages are as follows:

- Inhibits thrombin generation more effectively through greater anti-FXa activity
- Induces greater release of tissue factor pathway inhibitor than UFH and is not neutralized by platelet factor
- Less frequent occurrence of HIT compared to UFH
- High and consistent bioavailability, and hence could be administered subcutaneously
- Monitoring of anticoagulation levels not required
- More consistent anticoagulation effect compared to UFH

Enoxaparin in patients with ACS is recommended amongst all LMWH.[14,15] The standard dose is 1 mg/kg body weight subcutaneously (SC) every 12 hours and could be given safely for a week to 10 days. If the creatinine clearance is <30 mL/min, the injection is given OD. In meta-analysis of 21,945 patients with NSTE-ACS enoxaparin was compared with UFH, new or recurrent MI occurred significantly less frequently with enoxaparin whereas risk of bleeding was similar. LMWH is contraindicated in patients with a history of HIT.

Direct Thrombin Inhibitors

Bivalirudin is a direct thrombin inhibitor and would inhibit clot-bound thrombin. Stable level is maintained once it is administered IV and does not cause thrombocytopenia; hence, it is safe in patients with a history of HIT. The half-life is approximately 25 minutes. In trials of patients with ACS undergoing PCI, patients randomized to bivalirudin without Gp IIb/IIIa inhibitors experienced less bleeding compared with a combination of Gp IIb/IIIa inhibitor with either UFH or enoxaparin. However, there was no difference in major bleeding between heparin and bivalirudin in patients taking Gp IIb/IIIa inhibitors and no difference in ischemic events as well.[39] A meta-analysis showed that heparin-based regimens reduced MACEs slightly compared with bivalirudin-based regimens.[40] The current European guidelines recommend the use of bivalirudin with DAPT an acceptable second-line alternative to heparin-based regimens in patients with NSTE-ACS managed with early invasive strategy.[28] The dose of bivalirudin is as follows:

- *Before angiography*: 0.1 mg/kg IV bolus followed by infusion of 0.25 mg/kg/h.
- *During angiography*: 0.75 mg/kg bolus followed by infusion of 1.75 mg/kg/h during PCI. The arterial sheath could be removed safely after discontinuing the infusion.

Factor Xa Inhibitors: Oral and Intravenous

Fondaparinux indirectly inhibits FXa and requires the presence of antithrombin for its action. The OASIS-5 trial compared daily SC fondaparinux (2.5 mg) with standard dose of enoxaparin in high-risk patients of NSTE-ACS.[41] No difference was found in primary ischemic composite through 9 days although fondaparinux reduced major bleeding by one half and mortality at 30 days tended to be lower. However, there was three-fold increased incidence of catheter-related thrombi with fondaparinux. Fondaparinux is an alternative for patients with NSTE-ACS who are managed medically, particularly in patients with high risk of bleeding.

Oral Factor Xa Inhibitors

Rivaroxaban and apixaban have been studied in phase III trials of patients with ACS. *ATLAS ACS 2-TIMI 51 trial*: Low-dose

rivaroxaban 5 mg BD and very low-dose 2.5 mg BD reduced the primary composite (death, MI, or stroke) significantly by 16% compared with placebo on a background of DAPT.[42] Bleeding complications including intracranial were significantly high with the addition of rivaroxaban to DAPT.

CONDITIONS REQUIRING BOTH ORAL ANTICOAGULANT AND ANTIPLATELET THERAPY

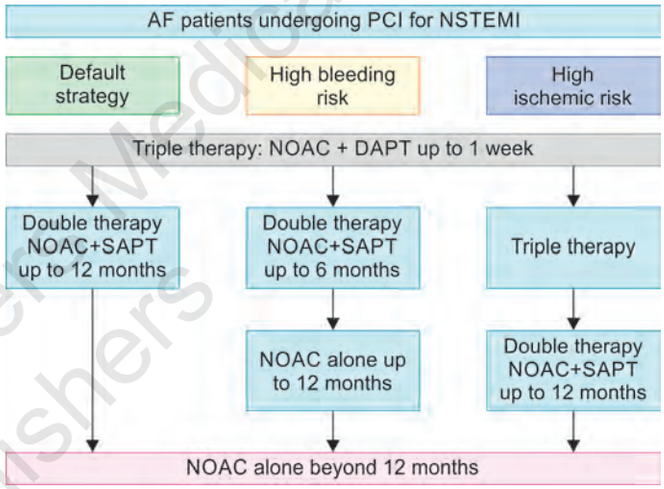
Approximately 10% of the patients presenting with NSTE-ACS have indications for anticoagulants. Atrial fibrillation (AF), mechanical heart valve, and recent venous thromboembolism are some of the indications for simultaneous administration of oral anticoagulants apart from antiplatelet agents. In AF, the combination of oral anticoagulants with DAPT is associated with an incidence of major bleeding of 10% per year, and in patients more than 90 years of age, history of prior major bleeding or when CHADS-VASc (C: Congestive heart Failure, H: Hypertension, A: Age, D: Diabetes, S: Stroke/TIA/thromboembolism, Va: vascular disease, Sc: sex category) is 6 or higher the incidence is 17–23%.[43] NOACs approved for prevention of stroke and systemic embolism in patients with AF have been compared with warfarin (VKA). A meta-analysis of patients with AF undergoing PCI for ACS demonstrated 38% reduction in major or clinically relevant nonmajor bleeding favoring NOAC+ P2Y12 inhibitor compared with VKA+ DAPT; however, there was an increased risk of stent thrombosis and MI.[44] There was no difference in all-cause mortality, stroke, or MACEs. Current consensus statements in patients with AF and ACS who undergo PCI recommend NOACs instead of VKA due to lower risk of bleeding and ease of use.[45,46] The treating cardiologist needs to assess bleeding risk versus thrombotic risk in the patient and should tailor the treatment according to the need.

Situation 1: Acute antithrombotic therapy for NSTE-ACS in patients on chronic anticoagulation treatment–

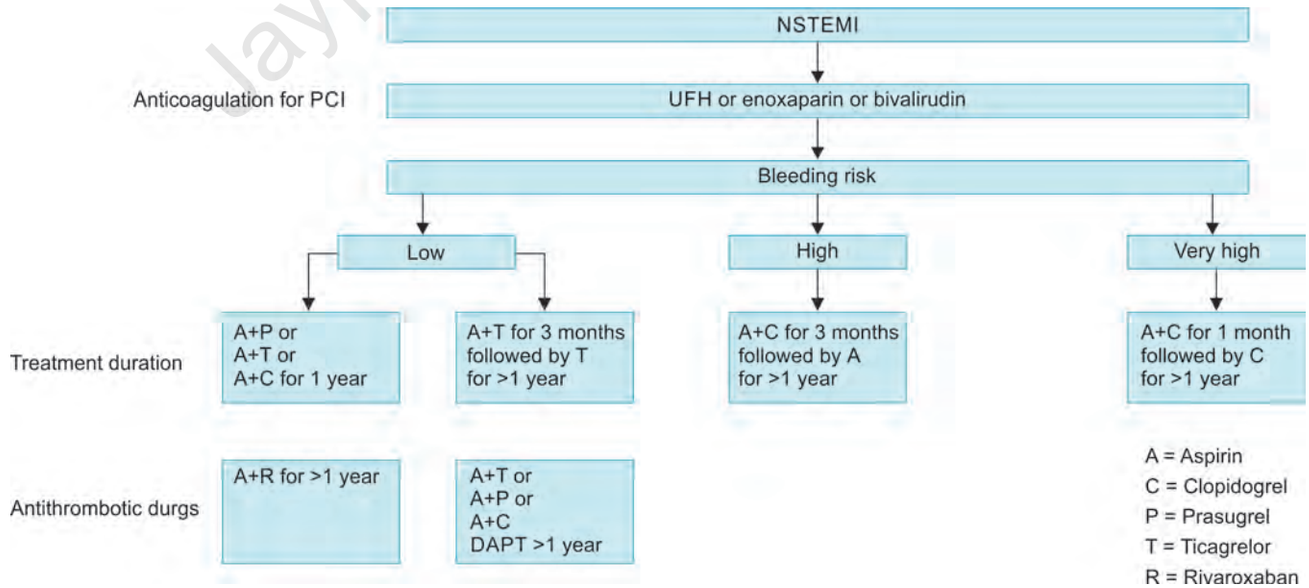
Limited data and no randomized trials available to guide.

Situation 2: Recent NSTE-ACS with an indication for oral anticoagulation–

Some patients with a recent <6–12 months NSTE-ACS receiving DAPT may develop a condition requiring administration of anticoagulants. Here, the risk of bleeding with the addition of anticoagulant needs to be carefully balanced with the risk of stent thrombosis and recurrent MI. NOAC should be started in such patients along with one antiplatelet agent, preferably P2Y12 inhibitor **(Flowcharts 1 and 2)**.[46]



FLOWCHART 2: Algorithm for antithrombotic therapy with AF.[45,46]
(AF: atrial fibrillation; DAPT: dual antiplatelet therapy; NOAC: novel oral anticoagulant; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; SAPT: single antiplatelet therapy)



FLOWCHART 1: Algorithm for antithrombotic therapy without AF.[15]
(DAPT: dual antiplatelet therapy; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; UFH: unfractionated heparin)

Bleeding: Risk Assessment, Prevention, and Treatment

Severe bleeding is the most common complication of antithrombotic therapy and the risk of bleeding needs to be carefully balanced with the risk of stent thrombosis and recurrent MI. Risk score (CHADS) should be studied. Patient's age, body weight, renal function, gender, and concomitant use of other drugs which may increase the risk of bleeding such as verapamil, dronedarone (through drug interaction), and NSAIDs should be assessed and accordingly select the most appropriate antithrombotic treatment regimen and duration. Radial route with small-sized sheath should be preferred over femoral artery for performing intervention. Bear-metal stents requiring a shorter duration (1 month) of DAPT wherever possible should be used. Prophylactic administration of PPI should be considered. New recommendations from 2020 ESC guidelines may be followed.[14]

- Perform PCI without stopping oral anticoagulant.
- Do not administer UFH in patients receiving VKA, if INR > 2.5.
- In patients on NOAC, the addition of enoxaparin or UFH should be critically assessed.
- Avoid routine pretreatment with P2Y12 inhibitors and should be reserved for bailout procedures.

In case of bleeding:

- Stop both anticoagulant and antiplatelet drugs
- Neutralize anticoagulant therapy
- Platelet transfusion (not blood transfusion)
- Blood transfusion indicated only when hemoglobin (Hb) drops below 7 g%

Anti-inflammatory Therapy

Oral colchicine has been studied in double-blind COLCOT trial. The patients were randomized within 30 days of MI to either low-dose colchicine (0.5 mg OD) or placebo. After 23 months, colchicine significantly reduced broad CV composite compared with placebo.[47] The CANTOS trial of monoclonal antibody targeting interleukin 1β (canakinumab) versus placebo with a past history of MI showed significant reduction in recurrent CV events.[48]

INVASIVE VERSUS CONSERVATIVE MANAGEMENT

- *Early invasive strategy*: Within 48 hours of initial evaluation cardiac catheterization followed by PCI, CABG, or continuing active medical management depending on coronary anatomy
- *Delayed invasive approach*: CAG after 2 days of presentation
- *Ischemia-guided approach (selective invasive)*: Active medical management initially and CAG reserved for patients with hemodynamic instability, and recurrent ischemic episodes followed by revascularization

A meta-analysis of seven trials confirmed a significant 25% reduction in mortality and 17% reduction in nonfatal MI after 2 years of follow-up in patients managed with an early invasive strategy compared with a more conservative approach. An early invasive approach should be advocated in elderly, women, recurrent ischemic episodes, congestive HF, cardiogenic shock, NSTE-ACS with a past history of CABG surgery or PCI, and patients with CKD. Thus in the absence of contraindications, an early invasive strategy should be recommended.

Indications for initial conservative strategy include patients with life-threatening comorbid conditions or in low-risk patients without recurrent symptoms and in whom the risk of procedure outweighs the potential benefits.

Timing of Invasive Procedure

- Immediate invasive <2 hours of presentation in very high-risk patients
- Early invasive <24 hours in high-risk patients
- Delayed invasive approach >48 hours in intermediate-risk patients **(Flowchart 3)**

A meta-analysis of 13 randomized controlled trials in 11,972 patients demonstrated a significant 15% reduction in MI in long-term follow-up after an early invasive approach.[49] No difference in mortality was observed. Patients with >140 GRACE risk score (high risk) who underwent an early invasive approach had a significant 12% reduction in MACE.

Risk Stratification on Discharge

Stable patients managed with ischemia-guided strategy should be evaluated noninvasively on discharge. This could be done by either exercise stress testing (no ST-T changes on ECG), exercise stress testing with imaging (ST-T changes on ECG), e.g., stress echo, or pharmacological stress testing in those who are unable to exercise.

Percutaneous Coronary Intervention

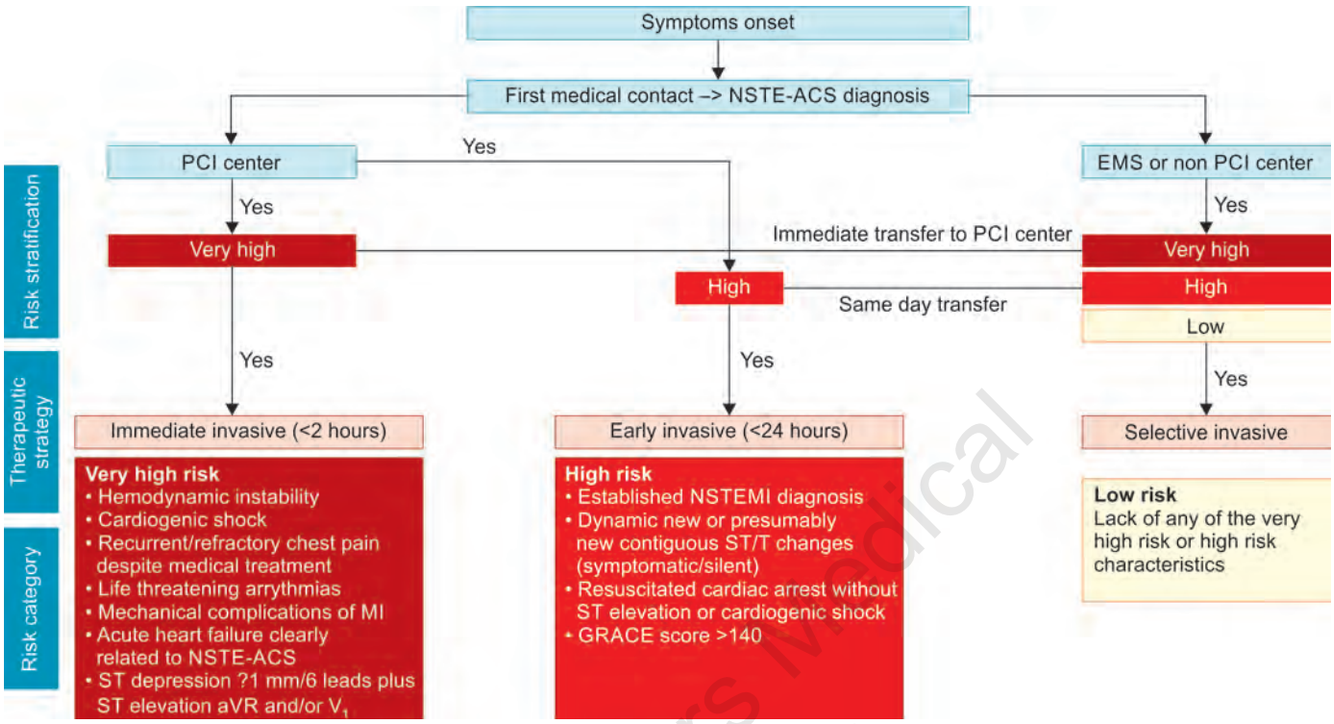
Thrombolysis in Myocardial Infarction II or III flow in coronary arteries (successful intervention) could be achieved in 95% patients with NSTE-ACS who undergo PCI, even in high-risk patients. Within 30 days of PCI, the risk of death or MI can occur if complications such as side branch occlusion, no-reflow phenomenon, abrupt closure of the vessel and distal embolization occur.[50] Stent thrombosis, late luminal loss, and in-stent stenosis have been observed even when DES are used and when DAPT is stopped early. DAPT should be continued for >12 months after stenting. New-generation DES (third generation) nowadays require shorter duration of DAPT.

Complete Revascularization or Culprit-only Lesion?

Data from 21,857 patients with NSTEMI and MVD treated demonstrated 10% reduction in mortality favoring complete revascularization.[51]

Percutaneous Coronary Intervention versus Coronary Artery Bypass Grafting Surgery

Coronary artery bypass grafting should be preferred for revascularization in patients with disease of LM, diffuse MVD



FLOWCHART 3: Treatment strategies and timings according to risk stratification.[15]
(ACS: acute coronary syndrome; EMS: emergency medical service; GRACE: Global Registry of Acute Coronary Events; MI: myocardial infarction; NSTE: non-ST-elevation; PCI: percutaneous coronary intervention)

with calcified vessels, reduced left ventricular ejection fraction (LVEF) <35–40%, and diabetic subsets, when the Syntax score is high, there is contraindication to DAPT, and when other surgeries such as valve replacement are also needed. EXCEL trial has suggested that for LM disease, even PCI could be a viable option.[52] PCI is less traumatic for the patient, risk involved is much less compared to CABG surgery (less morbidity and mortality), lower rates of stroke, and the recovery is very fast; however, the patient may need repeat revascularization in future and the revascularization may not occur completely compared to CABG surgery and the patient may persist to have angina. The best way to decide the mode of revascularization is "heart team approach" wherein interventional cardiologist, a cardiac surgeon, and cardiac anesthetist will guide the decision.

LIPID-LOWERING THERAPY

In PROVE IT-TIMI 22 trial, atorvastatin 80 mg (high intensity) was used and there was significant reduction in composite of CV death, MACE, or stroke by 20% over 2 years.[53] Atorvastatin reduced low-density lipoprotein cholesterol (LDL-C) and hsCRP very significantly. In a meta-analysis of 13 randomized controlled trials involving 17,963 patients with ACS, an early intensive statin therapy compared with placebo decreased the rate of death and CV events over 2 years of follow-up significantly by 19%.[54,55] US, European, and Indian guidelines support the use of maximally tolerated statin which would reduce the LDL-C levels by >50% in patients with NSTE-ACS.

- For secondary prevention in very-high-risk patients, LDL-C goals of <50 mg/dL are recommended (Lipid Association of India).
- A target of <70 mg/dL is recommended by the US guidelines.[56]
- A target of <55 mg/dL is recommended for high-risk patients by the European guidelines and even lower goal of <40 mg/dL for very high-risk patients.[57]

The IMROVE-IT trial demonstrated added clinical benefit of adding ezetimibe (cholesterol absorption inhibitor) to statin therapy in ACS patients. Ezetimibe significantly reduced the risk of CV death, MACE, or stroke by 6.4% at 7 years. The incidence of MI and stroke was reduced by 13% and 21%, respectively.[58] The results of the trial prompted the US and European guidelines to recommend ezetimibe in patients with NSTE-ACS who are at very high risk and in whom LDL-C remains >70 mg/dL (United States) and >55 mg/dL (ESC) in spite of intense statin therapy. PCSK9 inhibitors (evolocumab, alirocumab) have shown to reduce LDL-C by 40–60% regardless of background statin therapy. FOURIER trial conducted in 5,711 patients with a history of MI <12 months showed that evolocumab significantly reduced the risk of MACE by 19% and the secondary endpoint of CV death, MI, or stroke by 25% compared with placebo after a follow-up of 2.2 years.[59] The ODYSSEY OUTCOMES trial, the largest trial for alirocumab versus placebo, conducted on more than 18,000 patients showed that the primary endpoint was reduced significantly by 15% with the drug after a median of 2.8 years.[60] An adverse event with PCSK9 inhibitors that may occur is a minor local

injection site reaction. PCSK9 inhibitors should be introduced in the therapy only after high-intensity statins and ezetimibe have failed to achieve the LDL-C target, because the cost is prohibitive. The lipid-lowering therapy should be continued indefinitely, without dose reduction, if the patient is tolerating the dose.

SPECIAL GROUPS AND SUBSETS

Elderly Patients

Patients More Than 75 Years of Age

- Likely to have more adverse outcomes in NSTE-ACS
- Likely to have more comorbid conditions and disease-related changes in hemodynamics
- Are usually on polypharmacy exposing them to the risk of drug–drug interactions
- Present more often with atypical symptoms, and ECG changes are less diagnostic
- However, these patients derive similar or greater benefits from (1) guideline-directed therapy (DAPT), (2) early invasive approach, (3) DES instead of bare metal stent (BMS), and (4) intense lipid-lowering therapy.
- Paradoxically, these patients are less likely to receive such proven therapies (under treatment) due to apprehensions in the minds of both relatives and treating physicians.
- Several suggestions to reduce the risk of bleeding are: (1) low-dose ASA 75–100 mg; (2) clopidogrel instead of potent P2Y12 inhibitors such as prasugrel or ticagrelor; (3) avoid concomitant medications, which are likely to increase the risk of bleeding, such as NSAIDs, and (4) avoid using Gp IIb/IIIa inhibitors as far as possible.
- The doses should be adjusted looking at the body weight and renal functions. Renal functions should be assessed not only at admission but also periodically after every 3 months.
- Advanced age should not be deprived of evidence-based treatment including revascularization procedures just because of imaginary fear of complications such as bleeding.

Women

- Heart disease is the leading cause of death in women.
- Women are understudied, underdiagnosed, and even undertreated, especially in countries such as India.
- Presentation is with atypical symptoms and more often they are found to have nonobstructive CAD (microvascular/nonatherosclerotic) on CAG.[61]
- However, they should receive the same pharmacological therapy for acute condition and for secondary prevention as in men including early invasive therapy.
- Secondary preventive measures should be of the same magnitude and intensity in nonobstructive CAD as in obstructive CAD.
- Women are likely to have renal dysfunction more often than men.
- Evidence- and guidelines-based therapy should be practiced in women.

Diabetes Mellitus

- India is declared as the world capital of DM.
- CAD is responsible for 75% of deaths in DM.
- More than 30% patients with NSTE-ACS have DM.
- Higher rates of adverse CV outcomes are found in DM.
- All patients presenting with NSTE-ACS should be screened for the presence of DM including estimation of glycated hemoglobin (HbA1c) and periodic evaluation during hospitalization should be done.
- Uncontrolled DM should be controlled with insulin and blood sugar level (BSL) should be maintained between 140 and 180 mg% and should never fall below 90 mg%.
- Metformin has interaction with contrast material and is responsible for metabolic acidosis and deterioration in renal functions; hence, it is better to avoid metformin.
- Proper hydration should be maintained and hemoconcentration should be avoided by infusing half normal saline, especially in ketoacidosis or hyperosmolar nonketotic states.
- Blunted response to antiplatelets is observed in DM; hence, potent P2Y12 inhibitors, including Gp IIb/IIIa inhibitors such as prasugrel or ticagrelor, should be preferred.
- Early invasive strategy should be adopted for revascularization.
- CABG is preferred over PCI, especially in LM and diffuse MVD.
- If PCI is selected as a mode of revascularization, newer generation DES (everolimus) should be used.
- Renal functions should be closely monitored for 2–3 days after CAG and/or PCI, especially if the patient is receiving metformin.
- DM is associated with a significantly higher risk of mortality at 30 days and 1 year.[62]

Chronic Kidney Disease

A meta-analysis of five trials of 1,453 patients with NSTE-ACS and CKD with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 demonstrated favorable trends in all-cause mortality, the composite of death, or nonfatal MI, and rehospitalization with an early invasive strategy compared with conservative management.[63] All patients admitted with NSTE-ACS should have GFR estimated on admission, to decide proper dosing of medicines such as antithrombotic.

- Patients are usually older and more likely to have additional comorbidities, such as DM, peripheral artery disease (PAD), and HF exposing them to increased risk for recurrent ischemic events, including stent thrombosis, post-PCI ischemic events, and treatment complications.
- As the renal function worsens, the use of PCI steadily decreases.
- Randomized data on patients with advanced CKD and ACS are limited as most trials excluded patients with eGFR <30 mL/min/1.73 m^2.
- CAG should be considered, and benefits of prompt revascularization should be weighed against the risks of bleeding and contrast-induced nephropathy.
- Newer generation DES are preferred over BMS.

- When the life expectancy is >1 year, in a patient with MVD with an acceptable surgical risk, CABG is preferred over PCI; however, if life expectancy is shorter and surgical risk is higher, PCI is recommended.
- Impaired platelet function is responsible for a greater risk of bleeding; hence, doses of medicines such as Gp IIb/IIIa inhibitors, enoxaparin, and bivalirudin need adjustment.
- Contrast-induced nephropathy could be prevented by adequate hydration, by infusing isotonic or 0.45% saline from 12 to 24 hours before the procedure.
- Minimum contrast volume should be used. Ratio of contrast volume to eGFR should not exceed 3.7.[28]

Heart Failure

- AHA, ACC, and ESC recommend an early invasive approach because these patients are at an increased risk of major morbidity and death, and revascularization particularly CABG surgery improves the outcome.
- Revascularization strategy CABG versus PCI is decided by coronary anatomy, underlying LV function and the presence of valvular abnormalities. LV support may be required in cases where LV systolic function is severely depressed.
- Cardiogenic shock as such is uncommon in NSTE-ACS; however, if present, immediate revascularization with PCI should be performed. If coronary anatomy is not suitable, then CABG may be considered. Mechanical circulatory support [Impella, left ventricular assist device (LVAD)] is invariably required. Use of intra-aortic balloon pump (IABP) has not shown any benefit in such patients.[64,65]

Vasospastic Angina (Prinzmetal's Variant Angina)

Spasm of one or more proximal coronary arteries with resultant transmural ischemia, chest pain at rest, accompanied by ST-segment elevation, and abnormalities in LV function are the hallmarks of vasospastic angina (VA). Patients may develop acute MI, ventricular tachycardia (VT) or ventricular fibrillation (VF), and SCD.[66] At times, patients may have syncope due to A-V blocks. Prevalence is more common in Japan and South Korea and between midnight and 8 AM.

The patients are younger, and heavy cigarette smoking is the risk factor seen frequently in them. One-third of VA patients have severe fixed coronary obstruction and have a combination of exertional angina with depression of ST segments and angina at rest with elevation of ST segments. COVADIS (Coronary Vasomotor Disorders International Study Group) have developed diagnostic criteria: (1) Nitrate-responsive angina during spontaneous episodes, (2) transient ECG changes of ischemia (ST-segment elevation or depression), and (3) transient coronary artery occlusion with angina and ECG changes either spontaneously or following the provocative stimulus. Three provocative tests could be performed during CAG to establish the diagnosis: (1) Hyperventilation, (2) intracoronary acetylcholine, and (3) intracoronary ergonovine.[66,67] VA may be associated with generalized vasospastic disorders such as migraine and Raynaud phenomenon. VA could be precipitated because of certain drugs such as aspirin, ergot derivatives, cyclophosphamide, and serotonin antagonists.

The key to diagnosis of VA is documenting elevation of ST segment during severe chest pain at rest. Patients with de novo coronary spasm (without obstruction of coronary artery) usually have a good prognosis and benign course.

Management

- Abstinence from smoking
- Calcium antagonists (dihydropyridine derivatives) are the mainstay either alone or in combination with nitrates.
- *Nitrates*: SL nitrate may abolish the acute attack of VA. Long-acting nitrates may prevent the episodes of VA.
- BB show variable response and are useful in patients with fixed obstructions, but may prove deleterious in de novo spasm.
- Statins are useful and reduce risk of MACE.[68]
- Revascularization may be required in patients with discrete proximal, fixed obstructive lesions, but is contraindicated in de novo VA.
- Implantable cardioverter defibrillator (ICD) may be implanted in patients in whom VF has been documented secondary to myocardial ischemia.
- Remissions and relapses in natural history of VA have been described.

CONCLUSION

The NSTE-ACS may present as unstable angina or NSTEMI. Early, prompt diagnosis and risk stratification is essential for which clinical presentation, cardiac biomarkers, and other diagnostic imaging modalities are useful. Proper and aggressive management of the condition choosing right strategy: drugs and/or early invasive management (PCI), depending on the timing of presentation would certainly prevent major catastrophe like STEMI/SCD, and help to preserve the LV function and ultimately effort tolerance by minimizing the necrosis of myocardium.

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CHAPTER 72

Acute Myocardial Infarction: Primary Angioplasty in Myocardial Infarction versus Lytics

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ABSTRACT

Management of ST-elevation myocardial infarction (STEMI) involves prompt restoration of quality, sustained, antegrade flow in the infarct-related artery (IRA), which can be achieved by primary percutaneous coronary intervention (PPCI). The twin limitations of the availability of PPCI-capable hospitals and the time delays involved in transfer of patients to such facilities demand the more practically feasible approach of pharmacoinvasive strategy, implemented promptly in the PPCI-non-capable hospitals. The strength of pharmacoinvasive strategy lies in the early transfer of all successfully thrombolysed STEMI patients to cardiac catheterization laboratories for swift implementation of the invasive step within 2–24 hours of thrombolytic therapy (TLT) to achieve recanalization of the IRA and accrue full benefits of the pharmacoinvasive strategy. Pharmacoinvasive strategy should not be confused with the need for emergency transfer and rescue percutaneous coronary intervention (PCI) for failed thrombolysis. The strength of STEMI management at the societal level lies in a good "Hub and Spoke" model of PPCI-capable and non-capable centers.

INTRODUCTION

Acute coronary syndromes (ACS) are one of the most common medical emergencies. They share a common pathophysiology of plaque rupture with associated thrombosis causing interruption of coronary blood flow. ACS are classified into ST-elevation ACS (STEACS) [ST-elevation myocardial infarction (STEMI)] and non-ST-elevation ACS (NSTEACS) [non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (USAP)] based on the electrocardiogram (ECG) changes. The usual inference is that total occlusion of epicardial coronary artery results in STEMI, whereas a nonocclusive acute plaque rupture thrombosis results in NSTEACS. This has some exceptions but is a helpful categorization of ACS to direct our therapies in the right direction.

Management of STEMI revolves around the central pivot of prompt restoration of blood flow in the infarct-related artery (IRA), aptly called reperfusion. Successful reperfusion and prevention of reinfarction in STEMI help in minimizing myocardial damage and morbidity and mortality reduction. The management of NSTEACS involves similar strategies except for the expediency of reperfusion that a STEMI demands.

REPERFUSION STRATEGIES: MORE DIFFERENT THAN SIMILAR

There are two types of reperfusion strategies in STEMI: Primary angioplasty and stenting of the IRA (PPCI) and thrombolytic therapy (TLT) or fibrinolytic therapy. While traditionally these two strategies have been compared and debated against, in reality, they are more different than similar. The fundamental difference can be explained in two terms: Reperfusion and recanalization. Reperfusion involves establishment of antegrade flow in the occluded epicardial coronary artery, which a thrombolytic drug can achieve in 70–80% of cases (successful reperfusion). This is achieved in a significantly higher number of PPCI cases. Recanalization, on the other hand, refers to the epicardial coronary artery: Normalization of the arterial lumen with removal of the stenotic lesion using, usually, a drug-eluting stent (DES). This is achieved in a very high percentage of PPCI cases. TLT very rarely achieves recanalization; in fact, a majority of cases of successful reperfusion with thrombolysis will have severe residual stenosis in the IRA, which needs to be treated by percutaneous coronary intervention (PCI) to minimize the chances of reinfarction.

Successful management of STEMI requires both reperfusion and recanalization. PPCI is a single-step strategy with achievement of reperfusion and recanalization, while thrombolysis, even if successful, would only result in reperfusion of IRA with incomplete recanalization in the majority of such cases. Thus, thrombolysis can be considered a two-step strategy with pharmacological reperfusion as the first step of therapy, and follow-through coronary angiography and PCI where needed, completing the second step of recanalization. This strategy has been aptly called the "pharmacoinvasive strategy." Ideally, the second step in pharmacoinvasive strategy needs to be implemented between 2 and 24 hours after institution of TLT to tackle the residual stenosis to achieve good outcomes.

Failed thrombolysis is a totally different scenario wherein the thrombolytic drug could not achieve any reperfusion. This demands an emergency approach of PCI, sometimes called rescue PCI.

PRACTICAL CONSIDERATIONS OF REPERFUSION STRATEGIES

While PPCI is the evidence-based gold-standard approach to treat STEMI, there are two practical limitations in its implementation. First, the availability of 24/7/365 equipped cardiac catheterization laboratories with well-trained personnel (primarily interventional cardiologists) who can carry out these procedures with safety and success. Hospitals with such facilities have been aptly called "STEMI receiving hospitals or PPCI-capable hospitals" in distinction to the hospitals that can only treat them with thrombolysis but not PPCI, again aptly called "STEMI referring hospitals or PPCI-non-capable hospitals." The ground reality is that the number of PPCI-capable centers in our country is very less. The second limitation is that of time delays. Since, myocardial damage is proportional to the total ischemic time (TIT), the aim is to minimize it wherever possible. Any delay in achieving good reperfusion–recanalization with PPCI, beyond 120 minutes of the patient presenting to a hospital, would nullify the benefits of PPCI. In reality, <10% of people in our country can reach or be transferred to a PPCI-capable hospital within 120 minutes of the first medical contact (FMC). The common scenario would then entail STEMI patients reaching to PPCI-non-capable hospitals, wherein initial TLT as part of pharmacoinvasive strategy would take precedence to transfer the patient to a far-off PPCI center. It is also ideal to strengthen the second step of the pharmacoinvasive strategy by establishing "Hub and Spoke" model of care with each PPCI-capable center catering to a number of PPCI-non-capable centers. This would be the practical strategy for our country **(Fig. 1)**.

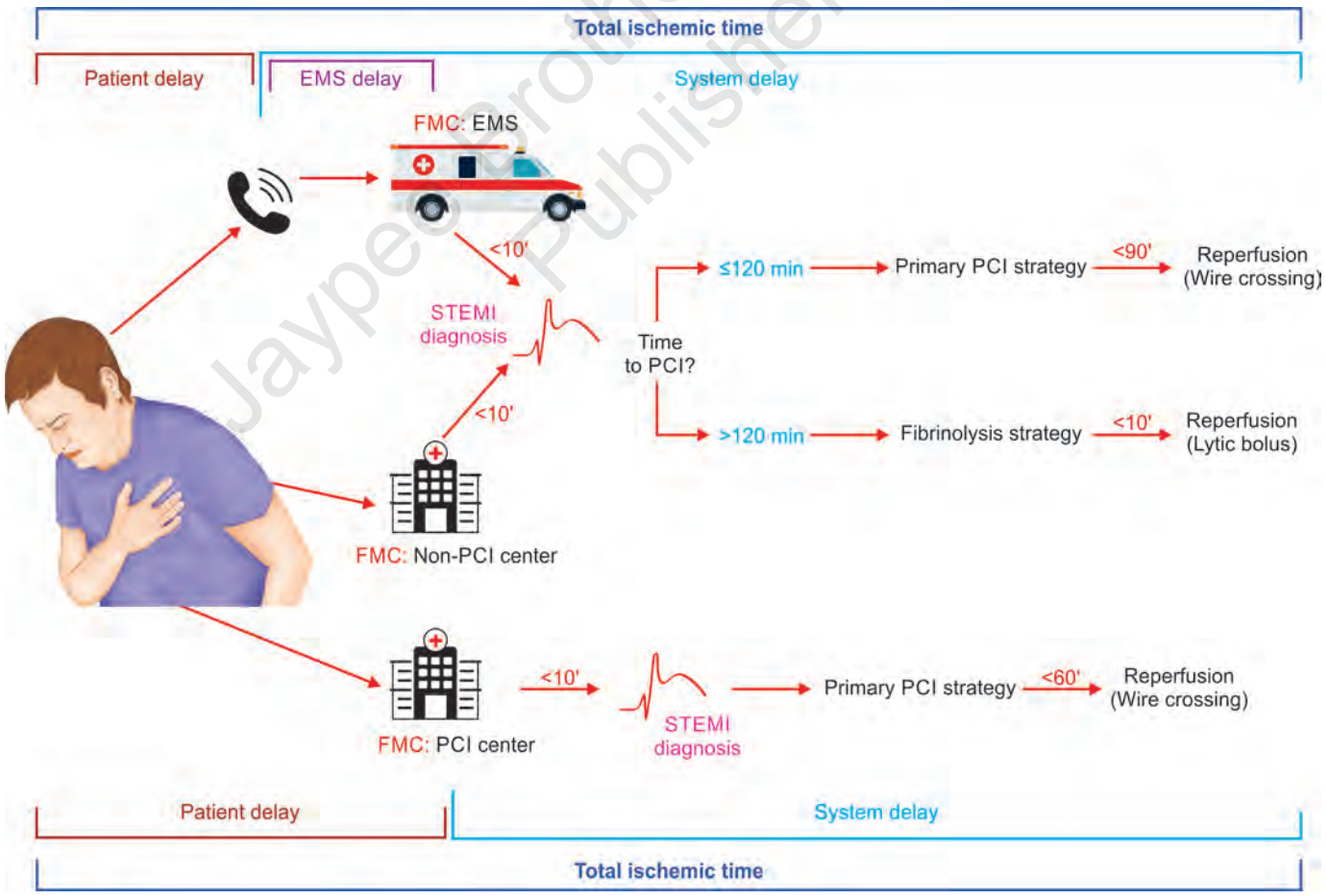


FIG. 1: The European Society of Cardiology (ESC) guideline 2017 for ST-elevation myocardial infarction (STEMI) for reperfusion strategy selection.
(EMS: emergency medical services; FMC: first medical contact; PCI: percutaneous coronary intervention)

A DETAILED DISCUSSION OF THE TWO STRATEGIES

Thrombolytic Therapy

Improving cardiovascular outcomes requires restoring myocardial blood flow. The benefit of TLT declines rapidly as the time from the onset of symptoms to therapy increases beyond 3 hours. After 12 hours, the risk may exceed the benefit. TLT is recommended only in cases in which PPCI is not immediately available and the delay from hospital presentation to PCI is anticipated to be more than 120 minutes.[1] Because approximately 35% of patients treated with thrombolytics do not achieve reperfusion,[2] and an additional 10% have ineffective reperfusion [thrombolysis in myocardial infarction (TIMI) flow grade less than 3].[3] For patients with STEMI in whom thrombolysis is chosen as the reperfusion strategy (i.e., when PPCI is not available), treatment should be given as soon as possible after the diagnosis. In many countries, administering TLT prior to hospital arrival (e.g., in an ambulance) is the standard practice. The rationale, training, treatment protocols, and quality assurance programs are needed to ensure safe and effective prehospital thrombolysis. A mortality benefit is less likely with TLT at 13–18 hours. A meta-analysis from the Fibrinolytic Therapy Trialists' Collaborative Group found that the absolute mortality benefit from fibrinolytic therapy at 5 weeks was 3% for those presenting within 6 hours from symptom onset, 2% for those presenting within 7–12 hours, and a nonsignificant 1% for those presenting within 13–18 hours.[4] However, there may be a benefit in patients presenting 12 hours after symptom onset and possibly up to 24 hours if the patient has ongoing or stuttering chest pain.[5] Bleeding (severe bleeding 1.8%)[6] is the primary complication of TLT, and hemorrhagic stroke is the greatest concern. Clinically important bleeding modestly reduces the total benefit associated with TLT. The risks of stroke and intracranial hemorrhage (ICH) were 1.2% and 0.7%, respectively, in a nontrial community registry of 12,739 patients.[7]

A total of 40–45% of patients who receive fibrinolytic therapy will develop primary failure, and it is widely recommended that all patients who present to non-PCI-capable hospitals be transferred to a PPCI-capable hospital as soon as possible after the thrombolytic agent is administered. In patients with failed thrombolysis, early randomized trials comparing rescue PCI (most patients had balloon angioplasty rather than stenting) with conservative therapy indicated a trend toward decreased mortality and lower risks of heart failure and reinfarction with rescue PCI.[8] Stenting was later proven to be superior to balloon angioplasty.[9] In the REACT trial, 427 patients with STEMI who had failed thrombolysis were randomly randomized to receive conservative medical treatment, repeat fibrinolysis with a fibrin-specific drug, or rescue PCI (69% with stenting). Failed thrombolysis was defined as less than 50% ST-segment elevation resolution within 90 minutes after therapy.[10,11] A higher rate of event-free survival (primary endpoint of death, reinfarction, stroke, or severe heart failure) was observed at 6 months [85% vs. 69% and 70% compared with repeat fibrinolysis or conservative therapy, adjusted hazard ratio (HR) 0.43 (95% confidence interval (CI) 0.26–0.72) and 0.47 (95% CI 0.28–0.79), respectively] and at 1 year [82% vs. 64% and 68%, adjusted HR 0.44; (95% CI 0.28–0.71) and 0.51 (95% CI 0.32–0.83), respectively]. At a median follow-up of 4.4 years, there was a decreased rate of all-cause mortality (6.2% vs. 12.7% and 12.8% compared with repeat fibrinolysis or conservative therapy). At 1 year, there was a greater rate of independence from revascularization (85% vs. 67% compared with repeat fibrinolysis or conservative therapy).

Primary Percutaneous Coronary Intervention

If conducted in a timely manner, coronary reperfusion with PPCI improves outcomes in patients with acute STEMI, myocardial infarction (MI) with a new or probably new left bundle branch block, or a real posterior MI. The majority of PCI now use DES, which have a lower risk of restenosis than bare metal stents. When compared to fibrinolysis, PPCI is the reperfusion therapy of choice because it achieves a higher rate of TIMI grade 3 flow (>90%), does not entail the danger of cerebral bleeding, and is associated with improved results. Revascularization after 12 hours with PCI, in contrast to fibrinolysis, may be useful in the 9–31% of patients with STEMI who present more than 12 hours after the onset of symptoms.[12,13]

Initial evidence to support the preference for PPCI comes from randomized trials of fibrinolysis compared with balloon angioplasty.[14-17] The famous meta-analysis by Keeley et al. of 23 clinical trials of PPCI showed that the TIMI grade 3 flow could be achieved in 95% of patients. There was a 2% absolute survival advantage for PPCI compared to TLT with lesser occlusion and virtually eliminated the 1% risk of ICH seen with TLT.[3] Studies have shown that PCI with stenting reduces the risk of death, nonfatal reinfarction, and stroke when compared to balloon angioplasty.[18] Finally, many randomized trials (DANAMI-2, PRAGUE-2, AIR PAMI, STAT, STOPAMI-1, and STOPAMI-2) directly compared PPCI with stenting to fibrinolysis.[19-27] In these studies, PCI was associated with a lower risk of death and a lower risk of recurrent MI than fibrinolysis. A major meta-analysis of randomized controlled trials (RCT) and observational studies (OS) comparing PPCI (with balloon angioplasty or stenting) to fibrinolysis was published in 2009 which showed that PPCI was linked with significant relative risk reductions in short-term (6 weeks) mortality of 34% in the RCT and 23% in the OS, as well as significant reductions in long-term (>1 year) mortality of 24% and reinfarction of 51% in the RCT.[28]

PHARMACOINVASIVE PERCUTANEOUS CORONARY INTERVENTION

The rationale for performing PCI after fibrinolysis is that many patients have a persistent reduction in flow in the IRA and are at risk for reinfarction. Although fibrinolysis restores patency (TIMI grade 2 or 3) in 80% of IRA, only 50–60% of arteries have normalized blood flow (TIMI grade 3). The clinical benefits of fibrinolytic therapy are seen only with the restoration of normal flow **(Fig. 2)**.

The STREAM trial is a well-powered multicenter open-labeled randomized clinical trial.[2] This was designed to test whether fibrinolytic therapy—administered before arrival to hospital or early after admission—coupled with early coronary

angiography provides outcomes similar to PPCI in patients presenting with acute STEMI. Ultimately, 1,892 patients underwent randomization to either receive tenecteplase along with antiplatelet and anticoagulant therapy, followed by coronary angiography within 6–24 hours (pharmacoinvasive group), or PPCI group. At 30 days, the primary outcome was a composite of mortality from any cause, shock, congestive heart failure, or reinfarction. Ischemic stroke and intracranial and nonintracranial hemorrhagic bleeding were among the safety endpoints. At 30 days, the primary endpoint occurred in 116 patients (12.4%) in the pharmacoinvasive group and 135 patients (14.3%) in the PPCI group (relative risk in the pharmacoinvasive group, 0.86; 95% CI 0.68–1.09; $p = 0.21$), which was not significant. Up to 36% of patients in the pharmacoinvasive group required "rescue" PCI. Significantly more open vessels were found during coronary angiography (before PCI) in the pharmacoinvasive group compared to the PPCI group (TIMI flow grade 0 in 16% vs. 59.3%; $p < 0.001$). This trial showed that the total stroke was, however, higher in the pharmacoinvasive arm 15/939 (1.6%) versus 5/946 (0.53%) in the PPCI arm ($p < 0.03$). Hemorrhagic strokes were higher in pharmacoinvasive arm 7/936 (0.96%) versus 2/946 (0.21%). Fatal stroke and fatal hemorrhagic stroke were not different. At 1-year follow-up, the all-cause mortality was 6.7% in pharmacoinvasive versus 5.9% in PPCI, and cardiac mortality was 4.0% in pharmacoinvasive versus 4.1% in PPCI.

The Canadian Vital Heart Response STEMI Registry comparing two contemporary reperfusion strategies, namely pharmacoinvasive treatment (adopting half-dose tenecteplase in the elderly) versus PPCI, demonstrated improved reperfusion, as measured by the ECG (core-laboratory), accompanied by enhanced clinical outcome within 1-year follow-up for those receiving pharmacoinvasive therapy.[29]

The primary composite was significantly lower with a pharmacoinvasive approach [16.3% vs. 23.1%, inverse probability (IP)-weighted HR 0.84; (95% CI 0.72–0.99); $p = 0.033$]. Major bleeding and ICH were similar between the pharmacoinvasive strategy and PPCI (7.6% vs. 7.5%; $p = 0.867$; 0.6% vs. 0.6%; $p = 0.841$, respectively). In STEMI, their findings suggest a selective pharmacoinvasive reperfusion strategy, especially when first PCI is delayed **(Flowchart 1)**.

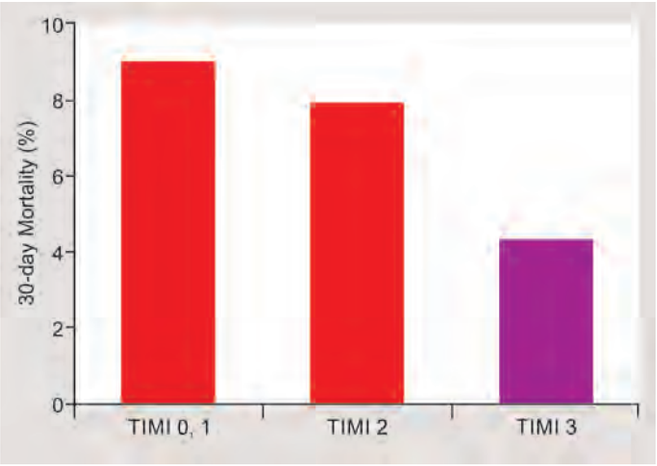
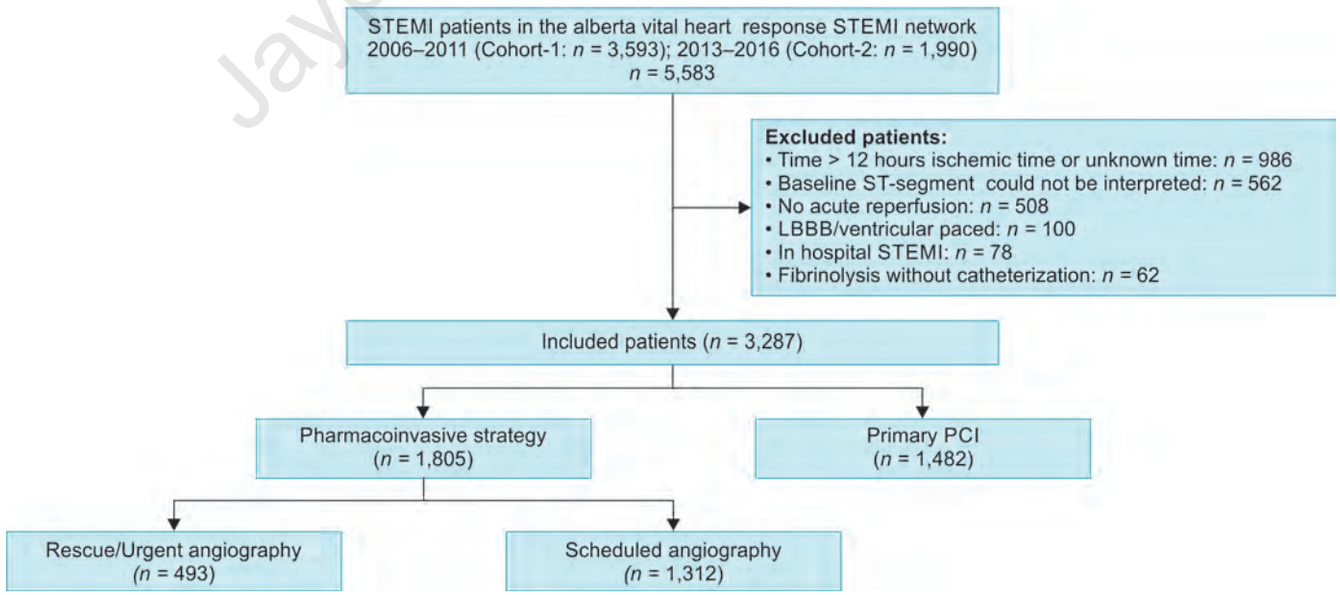


FIG. 2: Thrombolysis in myocardial infarction (TIMI) grade 3 coronary flow is associated with improved survival after thrombolysis.

Source: Data from the GUSTO Investigators. N Engl J Med. 1993;329:673.

Note: In the Global Utilization of t-PA and Streptokinase for Occluded Coronary Arteries (GUSTO-I) trial, the 30-day mortality rate after thrombolysis for acute ST-elevation myocardial infarction varied with the degree of vessel patency achieved. The mortality was lowest (4.3 percent) in patients with TIMI grade 3 (normal) flow in the infarct-related artery at 90 minutes. Partial restoration of flow (TIMI grade 2) did not improve outcomes compared with no or faint flow (TIMI grade 0 and 1).



FLOWCHART 1: Study Cohort.

(LBBB: left bundle branch block; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction)

FIBRINOLYSIS VERSUS PRIMARY PERCUTANEOUS CORONARY INTERVENTION IN STEMI CARDIOGENIC SHOCK

There are limited contemporary data on the use of initial fibrinolysis in STEMI cardiogenic shock (STEMI-CS). Coronary reperfusion is the mainstay of therapy for patients with STEMI-CS, with PPCI being preferred.[30] The current societal guidelines recommend PPCI for revascularization in patients with STEMI-CS irrespective of time delay from STEMI onset (Grade of Recommendation Class I, Level of Evidence B).[30,31] When PPCI is not available, a pharmacoinvasive strategy is recommended for patients with STEMI and hemodynamic instability (Grade of Recommendation Class I, Level of Evidence C) and urgent revascularization by either PCI or coronary artery bypass grafting (CABG) (Grade of Recommendation Class I, Level of Evidence B).[31,32] Despite robust evidence for PPCI, only 39% of hospitals have catheterization facilities even in the developed countries such as United States, and as a consequence, fibrinolysis with subsequent early coronary angiography with PCI continues to be used as first-line therapy in >25% of STEMI patients.[32] These numbers are even higher in resource-poor countries, where fibrinolysis continues to be the first choice of therapy.[33]

An observational study by Vallabhajosyula et al. sought to compare the outcomes of STEMI-CS receiving initial fibrinolysis versus PPCI.[34] In this study, the fibrinolysis group had higher rates of hemorrhagic complications (13.5% vs. 9.9%; $p < 0.001$). The fibrinolysis group had comparable all-cause in-hospital mortality [logistic regression analysis: 28.8% vs. 28.5%; propensity-matched analysis: 30.8% vs. 30.3%; adjusted odds ratio 0.97; (95% CI 0.90–1.05); $p = 0.50$]. The fibrinolysis group had comparable rates of acute organ failure, hospital length of stay, rates of palliative care referrals, do-not-resuscitate status use, and lesser hospitalization costs.

In the DANAMI-2 (Danish Multicenter Randomized Study of Fibrinolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction) trial, 103 patients developed in-hospital cardiogenic shock (CS). Angioplasty did not protect against development of in-hospital CS compared with fibrinolysis. Interestingly, there was no difference seen with regard to 3-year mortality in CS patients treated with angioplasty versus fibrinolysis [HR 1.05; (95% CI 0.67–1.64); $p = 0.25$] **(Fig. 3)**.[21]

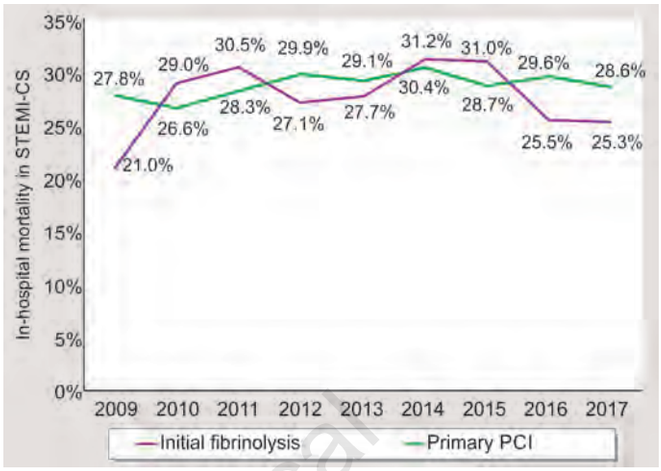


FIG. 3: Trends in inhospital mortality in admissions receiving fibrinolytics versus primary percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction cardiogenic shock (STEMI-CS).
(PCI: percutaneous coronary intervention; STEMI-CS: ST-segment elevation myocardial infarction cardiogenic shock)

Source: Data from Vallabhajosyula S, Verghese D, Bell MR, Murphree DH, Cheungpasitporn W, Miller PE, et al. ESC Heart Failure. 2021;8:2025-35.

THE INDIAN SCENARIO

The CREATE, a major clinical registry of ACS patients from 89 prominent hospitals in 10 regions and cities across India, provides the most comprehensive data on current trends in STEMI patients.[35] Among the more than 20,000 patients enrolled in CREATE, over 60% had STEMI, a proportion that is substantially higher than in North American and European registries. When compared to non-STEMI patients, STEMI patients were also younger and had a poorer socioeconomic status. In STEMI patients, the median time from onset of symptoms to hospital arrival was 300 minutes, more than double the duration observed in industrialized countries. Finally, during their hospitalization, around 60% received fibrinolytic therapy and just 8% underwent PCI.[36] The recent STREAM data[2] and the Indian data from the STEP PAMI study[37] showed that the pharmacoinvasive strategy compared well with PPCI in reducing overall morbidity and mortality. Based on this information, STEMI India created a plan that combines PPCI with a pharmacoinvasive reperfusion strategy to provide a coherent framework for building a STEMI system of care that is appropriate for India.[38,39]

- PPCI is recommended for patients who are close to catheterization laboratories—typically patients in urban regions with short travel times to hospitals that offer PPCI 24 hours a day, 7 days a week.
- Patients in remote locations with extensive travel times to PCI-capable institutions will use the pharmacoinvasive technique of thrombolysis followed by catheterization and, if necessary, PCI within 3–24 hours of thrombolysis.

The pilot Kovai Erode study[36] and the subsequent pilot Tamil Nadu STEMI program[40] have shown the feasibility of combining the two strategies of PPCI and the pharmacoinvasive strategy.

CONCLUSION

Management of STEMI involves prompt restoration of quality, sustained, and antegrade flow in the IRA, which can be achieved by PPCI. The twin limitations of the availability of PPCI-capable hospitals and the time delays involved in transfer of patients to such facilities demand the more practically feasible approach of pharmacoinvasive strategy, implemented promptly in the PPCI-non-capable hospitals. The strength of pharmacoinvasive strategy lies in the early transfer of all successfully thrombolysed STEMI patients to cardiac catheterization laboratories for swift implementation of the invasive step within 2–24 hours of TLT

to achieve recanalization of the IRA and accrue full benefits of the pharmacoinvasive strategy. Pharmacoinvasive strategy should not be confused with the need for emergency transfer and rescue PCI for failed thrombolysis. The strength of STEMI management at the societal level lies in a good "Hub and Spoke" model of PPCI-capable and non-capable centers.

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CHAPTER 73

Left Ventricular Thrombus Following Acute Myocardial Infarction

Saumitra Ray, Supratip Kundu

ABSTRACT

Left ventricular (LV) thrombus following acute myocardial infarction (AMI) is a poorly explored but potentially life-threatening entity. With advent of the use of antiplatelets, anticoagulants, and thrombolytic therapy, the incidence has decreased dramatically, which was even more reduced after primary percutaneous angioplasty. Certain features of the infarct and the patient predispose to more thrombus formation, such as anteroapical location, large infarct, aneurysm formation, and hypercoagulable state in the patient. Detection depends on the modality of imaging and timing of imaging, with cardiac magnetic resonance (CMR) done in the second week giving the highest yield. In high-risk cases, prophylactic anticoagulation is recommended along with the optimal antiplatelet regimen. Warfarin is still the drug of choice, but the novel oral anticoagulants (NOAC) show promising results in such a scenario. Once detected, triple antithrombotic therapy should be instituted for at least 3 months. The best regimen and the optimum duration of therapy are still elusive.

INTRODUCTION

Left ventricular (LV) thrombus after acute myocardial infarction (AMI) is a potentially life-threatening complication due to its propensity to cause stroke and systemic thromboembolism.[1] Formation of LV thrombus is mainly favored by endothelial damage due to ischemic insult, blood stasis due to severe LV systolic dysfunction, and hypercoagulable state due to clotting factor activation.[2] In the pre-percutaneous coronary intervention (PCI) and pre-thrombolytic era, the incidence of LV thrombus was around 30%. However, with the advent of thrombolysis it came down to 8–17%.[3] Another important thing is the choice of an optimal anticoagulation regimen for the prevention of stroke and systemic embolism. Till now, as per the American College of Cardiology (ACC) criteria, only vitamin K antagonists (VKA) are used along with dual antiplatelets.[4] However, there are few case reports with novel oral anticoagulants (NOAC) along with dual antiplatelets.[5] Bleeding risk has increased in these cases due to triple therapy. So whether a single antiplatelet along with one anticoagulant can be used or not is a matter of debate in this case. In this chapter, we would like to discuss about epidemiology, diagnosis, and management of this condition.

EPIDEMIOLOGY

The incidence of LV thrombus in the pre-thrombolytic era was quite high. In one series, it was as high as 60% after anterior myocardial infarction (MI). However, with the advent of dual antiplatelet therapy (DAPT) and thrombolysis, the incidence has been reduced significantly to around 30%. Apical wall motion abnormality, large area of infarction, LV dimension change, and higher aspartate level were some of the predictors of thrombus formation.[6,7] The incidence has been further reduced with the introduction of primary PCI.[8] However, the incidence varies widely in different case series. Probably this reflects the variation in patient character and the extent of myocardial injury, timing of PCI, recovery of systolic function post-PCI,[9] and last but not the least, the imaging modality used. Cardiac magnetic resonance (CMR) imaging has increased the sensitivity and specificity of detection of LV thrombus, especially of small mural thrombus, which is often missed by echocardiography. The timing of imaging also influences the detection of LV thrombus. Majority of LV thrombus appears after 48 hours.

Around 20% cases of LV thrombus show evidence of systemic thromboembolism and stroke. Two important

factors which determine the incidence of thromboembolic phenomenon are large size of the clot and protruding and labile nature.[10]

Anticoagulant therapy after AMI causes clot stabilization and decrease in size of the clot. LV dysfunction may worsen or remain same in most of the cases even after clot stabilization.

Post-treatment, rate of all-cause mortality is 19%, major adverse cardiac event (MACE) 37%, embolic complications 22.2%, and bleeding 13%. Clot regression reduces the rate of all-cause death but does not change the incidence of thromboembolism.[2]

PATHOPHYSIOLOGY

Pathophysiology of LV thrombus can be explained by the Virchow triad.[11] Endothelial injury is initiated by ischemic insult. Infarct expansion leads to tissue thinning and dilation of localized region of myocardium. It gives rise to regional wall motion abnormality such as akinesia or dyskinesia, which leads to stasis of blood. Localized myocardial injury exposes subendothelial collagen, which leads to activation of tissue factors and coagulation system. Cross-linked fibrin polymers are formed, which trap platelets and lead to thrombus formation. Hypercoagulable state after AMI persists for about 6 months. Baseline C-reactive protein (CRP), neutrophil lymphocyte ratio, and higher fibrinogen level are predictors of early thrombus.[12] Early thrombus generally incites myocardial inflammation and it binds more platelets from blood and expands its size. Chronic thrombus becomes endothelized in the wall, becomes less protruding and mural. It also helps in stabilization of LV wall resulting in limitation of infarct extension, prevention of aneurysm expansion, improvement of global myocardial performance, and restoration of partial thickness of the wall. Generally, 50% of thrombus resolution occurs within 6 months.[13] So, the consequences of the thrombus depend upon the physical characteristics of the thrombus such as size, shape, and duration as well as on the patient's characteristics.

DIAGNOSIS

Cardiac magnetic resonance is the optimum modality for detection of LV thrombus. It has around 90% sensitivity and 100% specificity. CMR, when performed with late gadolinium enhancement, becomes the better modality for detection. Due to the avascular nature of the clot, it does not take up gadolinium and appears as sharp contrast against the infarcted myocardium. However, the usefulness of gadolinium is limited by its cost and prohibition to use in renal failure patients. Besides the detection of LV thrombus, gadolinium-enhanced CMR also identifies patients at risk of LV thrombus by identifying scar burden. As the scar burden is higher in ischemic cardiomyopathy, the chance of thrombus formation is also higher.[14]

Echocardiography

Transthoracic echocardiography (TTE) is a cheap and easily available modality of detecting LV clot. Its specificity is excellent, but sensitivity is quite low. It is mainly due to poor echo windows, inadequate visualization of LV apex, and a small thrombus. Sensitivity can be improved by contrast agents.[9]

Left ventricular thrombus can be divided into two morphological types, protruding thrombus in acute phase and laminar thrombus in chronic stage.[10]

Transthoracic echocardiography can also be used as a good screening test before CMR imaging. Weinsaft et al. showed that a higher apical wall motion score (>7 with contrast and >5 without contrast) is associated with 100% sensitivity and 100% negative predictive value for detecting LV thrombus. Transesophageal echocardiography (TEE) has limited added advantage because in dilated ventricle and with apical dyskinesia, LV apex is typically foreshortened.[14]

Computed Tomography

Computed tomography (CT) has not been validated as an investigation modality to detect LV clot. Left atrial appendage thrombus can be detected with CT. Contrast-enhanced coronary CT angiography can be used to detect LV apical thrombus due to its very high spatial resolution.[15]

Molecular Imaging

Positron emission tomography (PET) study can demonstrate active thrombus in LV as well as in cerebral circulation. ^{131}F glycoprotein 1 (GP1) radiotracer can bind to activated platelet GPIIb/IIIa receptor and can identify active thrombus and thus helps to understand the development of LV thrombus and its complications.[16]

Timing of Imaging

The rate of detection of LV thrombus varies as per the timing of doing imaging. Majority of patients with detection of LV thrombus in TEE occurs within 2 weeks, specifically within day 8–15. The ideal timing for performing CMR is in between 9 and 12 days. Hence, those patients with absent thrombus on initial imaging but with high-risk features should be reimaged after 2 weeks. This fact also highlights the importance of surveillance even after hospital discharge.[17-19]

PROPHYLAXIS

The 2013 ACC/American Heart Association (AHA) guidelines have issued class IIb recommendations for VKA like warfarin along with DAPT for the prevention of LV thrombus and stroke. The 2014 ACC/American Stroke Association (ASA) guidelines advised prophylactic anticoagulation with VKA along with DAPT for 3 months. The American College of Chest Physicians suggests prophylactic anticoagulation with VKA for 3–6 months after index events in anterior AMI patients with high-risk features such as LV ejection fraction (EF) <40% and anterior wall akinesia.[4,20] In the pre-PCI era, anticoagulants decreased the rate of LV thrombus formation at the expense of increased bleeding. However, in this primary PCI era, there are no randomized controlled trials. The role of NOACs is rather controversial. RE-DEEM (RandomizEd Dabigatran Etexilate Dose Finding Study in Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel) study examined the role of dabigatran[21] and APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events 2) study examines the role of apixaban.[22] In both the studies, the MACE rates are not

altered but the bleeding risk has been increased. ATLAS ACS-2 TIMI-51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome 2 Thrombolysis In Myocardial Infarction 51) trial evaluated rivaroxaban 2.5 mg twice daily, 5.0 mg twice daily or placebo in 1:1:1 randomization in addition to standard DAPT in patients within 1 week of admission for ACS. Rivaroxaban treated patients had reduced the risk of the composite endpoint of death from cardiovascular causes, myocardial infarction, or stroke with increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding. There is no difference among the rates of strokes in the three groups.[23]

TREATMENT

Observational studies comparing VKA versus NOAC yields conflicting results. Some studies show around 80% resolution of LV clot in 264 days with NOACs, whereas some studies show an increased rate of strokes and systemic thromboembolism with NOACs as compared to VKA. However, NOACs are more commonly used due to ease of use and because monitoring is not needed.[24-31] There is one randomized controlled trial for comparison of rivaroxaban versus warfarin. In No-LVT (Left Ventricular Thrombi) trial, rivaroxaban is used at a dose of 20 mg once daily. Only 50% patients received DAPT. The target international normalized ratio (INR) in warfarin group was 2–3. Patients in the warfarin group were within therapeutic range for 82% of the time. Thrombus resolution was 72%, 77%, and 87% in the rivaroxaban group versus 48%, 68%, and 80% in the warfarin group. Stroke event is nil in the rivaroxaban group versus four in the warfarin group. Major bleeding is slightly more common with rivaroxaban. This was a small trial, and results should be interpreted with caution.[5]

As per guidelines 2013 ACC/AHA, 3 months of oral anticoagulant (OAC) is recommended in patients of ST-elevation myocardial infarction (STEMI) and asymptomatic LV thrombus (level of recommendations 2a). The 2014 ASA guidelines recommend 3 months' VKA in ischemic stroke or transient ischemic attack (TIA) patients along with anterior MI with LV thrombus. The American College of Chest Physicians has recommended 3–6 months of VKA in anterior wall MI with definite LV thrombus. The European Society of Cardiology (ESC) guidelines also recommend use of VKA in STEMI after repeated TTE and considering bleeding risk. But the important thing which is unclear from these guidelines is whether long-term risk of thrombus persists in the patients with LV aneurysm or long-term anticoagulation is needed in these patients.[4,20]

ALGORITHMIC APPROACH

There is no definite guidelines approach to patients presenting with ACS and noted to have LV thrombus before discharge. An approach akin to atrial fibrillation with ACS with or without percutaneous intervention may be extended to such patients. An intital Triple therapy (DAPT + Oral anticoagulant,either warfarin or NOACS, followed by Clopidogrel plus oral anticoagulation therapy seems logical.The duration of triple therapy may be decided based on PCI status post-ACS. All patients with AMI should be screened with TTE within 24 hours. If thrombus is detected, a dual pathway inhibitor with one P2Y12 inhibitor and VKA along with heparin bridging with target INR 2–3 should be started. Triple therapy can also be given considering the ischemic risk of these patients. Target INR in this case is 2–2.5. The duration of triple therapy is decided on a case-to-case basis. Repeat imaging needs to be done every 3 months. If thrombus resolution occurs, anticoagulation can be stopped. Repeat TTE should be performed after 3 months of resolution. In a patient with larger infarct, anteroapical hypokinesia and low EF, repeat TTE is to be done after 72 hours post-PCI and if clot is not detected, then 2 weeks post-PCI. In a patient who is intolerant to VKA, NOACs, specifically rivaroxaban 20 mg daily, should be started. Another strategy is to use low-dose rivaroxaban in high-risk patients along with DAPT. However, this strategy carries increased bleeding risk. This approach is most valuable where access to routine imaging is not present.[32,33]

CONCLUSION

Left ventricular thrombus after MI is still a poorly understood entity. Early detection is the key for successful management. Optimal timing window for detection is important. VKA is the preferred mode of therapy. However, in a patient intolerant to VKA, NOACs can be used. The optimal strategy of management is to be determined on a case-to-case basis by considering the ischemic and bleeding risks.

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CHAPTER 74

Postmyocardial Infarction Ventricular Septal Rupture: Challenges in Diagnosis and Management

Smit Shrivastava

ABSTRACT

Post-myocardial infarction ventricular septal rupture (PMVSR) remains an important life-threatening mechanical complication of acute myocardial infarction. It leads to sudden hemodynamic decompensation, arrhythmia and majority die within 24 hours. Those who survive initial insult, percutaneous closure or surgical closure may be offered depending on the competence of the center.

INTRODUCTION

Postmyocardial infarction ventricular septal rupture (PMVSR) is a rare yet fatal mechanical complication of acute myocardial infarction. The *incidence* of PMVSR decreased with percutaneous coronary intervention (0.23–0.7%) and thrombolytics (0.3%) than in prethrombolytic era (1–3%), however, with an earlier onset.[1] The following discussion reflects on our present understanding of the challenges (*inscribed in italics*) and their possible management for PMVSR.

HISTORY

- *1847*: First PMVSR at autopsy by Latham
- *1923*: First antemortem diagnosis by Brunn
- *1934*: Clinical criteria for diagnosis and association with coronary artery disease by Sager
- *1957*: First surgical repair by Cooky
- *1988*: First transcutaneous closure (TCC) by Lock[2]

PATHOPHYSIOLOGY

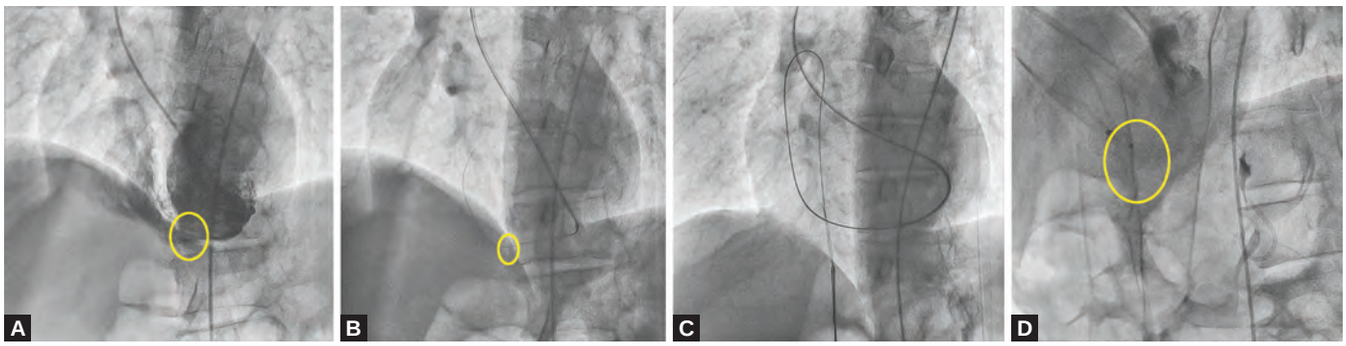
The risk factors associated with occurrence of PMVSR are:[3]

- Advanced age–median
- Female sex
- Anterior wall
- Complete occlusion of a single coronary artery
- First episode of myocardial infarction
- ST-elevation myocardial infarction
- High GRACE (Global Registry of Acute Coronary Events) risk score
- Chronic kidney disease
- Prior hypertension
- Delayed thrombolysis

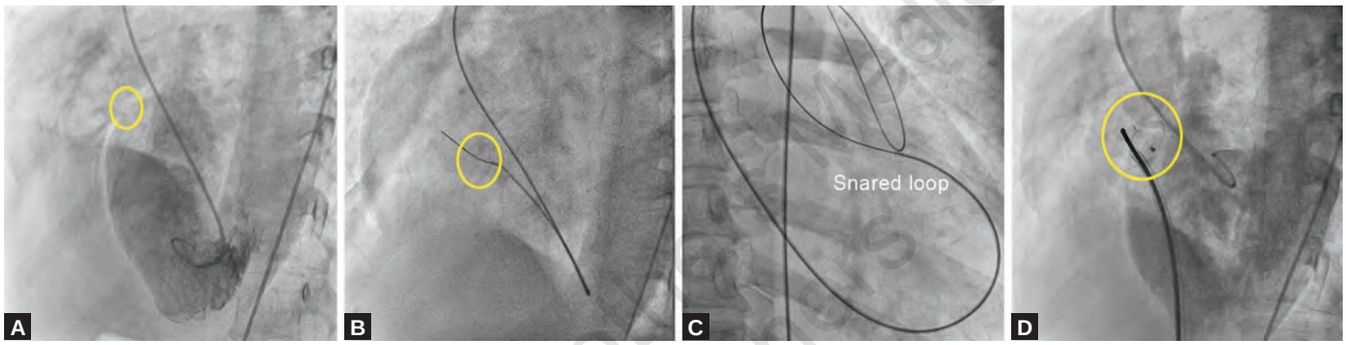
The two-thirds of PMVSR occur in anterior **(Figs. 1A to D)** *and rest in inferior or posterior interventricular septum* **(Figs. 2A to D)**. The most common cause of PMVSR is transmural myocardial infarction in one of the following coronary arteries:

- Left anterior descending artery supplying most of the anterior part of interventricular septum causing apical PMVSR
- Dominant right coronary artery supplying inferior and basal ventricular septum
- Dominant left circumflex artery supplying posterior ventricular septum and is rarest.

The incidence of PMVSR is higher with ST elevation (0.9%) than with non-ST-elevation myocardial infarction (0.17%) and unstable angina (0.25%).[4] *The PMVSR tends to occur in the first week after myocardial infarction mostly presenting with cardiogenic shock.* The PMVSR that occurs *within 24 hours* is suspected to be the result of intramural hematoma into the diseased septum. Total occlusion of usually single coronary artery causes hypoxic coagulation necrosis of infarcted septum while exerting excessive traction from the preserved myocardial contractility from the areas supplied by other coronary arteries leading to a septal rupture in the *next 3–5 days*.



FIGS. 1A TO D: The transcutaneous device closure of apical-anterior postmyocardial infarction ventricular septal rupture (PMVSR). (A) Apical-anterior postmyocardial infarction ventricular septal rupture; (B) Guidewire tracking across the apical-anterior PMVSR; (C) Guidewire snared to form loop across the apical-anterior PMVSR; (D) Apical-anterior rupture closed by ventricular septal device.



FIGS. 2A TO D: The transcutaneous device closure of posterior postmyocardial infarction ventricular septal rupture (PMVSR). (A) Posterior postmyocardial infarction ventricular septal rupture; (B) Guidewire tracking across the posterior PMVSR; (C) Guidewire snared to form loop across the posterior PMVSR; (D) Posterior rupture closed by ventricular septal device.

Becker and Mantgem classification for free wall rupture can also be utilized for *classifying PMVSR*:[5]

- *Type I*: Sudden in onset, slit in septum in first 24 hours
- *Type II*: Subacute with erosion of infarcted myocardium
- *Type III*: Delayed with rupture and aneurysm formation

The pathological anatomy classifies PMVSR:

- Simple PMVSR has entry and exit points at the same level, usually seen in anterior septum.
- Complex PMVSR has a serpiginous tract, only 20% of anterior septum, all of basal PMVSR, associated with other mechanical complications of pseudoaneurysm, free wall rupture, papillary muscle rupture (PPMR), and aneurysm.

The PMVSR causes *sudden left-to-right shunt* that increases the right ventricular volume and pulmonary blood flow causing pulmonary congestion. The *compensatory peripheral vasoconstriction* increases the left-to-right shunt causing progressive cardiac failure added with decreased preload from right ventricular dysfunction. *Right ventricular indices* are a more powerful determinant of cardiogenic shock.

CLINICAL PRESENTATION

Over 70% patients experience an abrupt low cardiac output state with tachycardia within minutes to hours of appearance of pansystolic murmur. Pulmonary edema is less fulminant than PPMR **(Table 1)**. *Excessive efforts* such as agitation, vomiting, or coughing prior to rupture were noted in 18% PMVSR.[6] Hypotension and tachycardia are common in nonsurvivors [mean systolic blood pressure (BP) 93 ± 19 mm Hg vs. 110 ± 20, $p < 0.01$ and heart rate 104 ± 24 vs. 87 ± 18, $p < 0.05$].[7] The third heart sound commonly arises from high right ventricular and pulmonary flow and pressure and rarely from left ventricular (LV) failure.

DIAGNOSIS

The clinical diagnosis, especially from papillary muscle dysfunction, is foremost **(Table 1)**.

Electrocardiogram

The utility is restricted to diagnosis of myocardial infarction, persistent ST elevation in pseudoaneurysm, and heart block in 30%.

Chest X-ray

Florid pulmonary edema is less common than papillary muscle dysfunction. LV enlargement is seen in 82%, pulmonary edema in 78%, and pleural effusion in 64%.

TABLE 1: Differential diagnosis: PMVSR versus PPMR.

	PMVSR	PPMR
Mean age (years)	63	65
Days after myocardial infarction	3–5	3–5
Anterior myocardial infarction	66%	25%
Murmur	Pansystolic at left lower sternal border in 90%	Variable systolic
Thrill	Common (48%)	Rare
V wave	Yes	Yes
Step-up	At right ventricle	–
Echocardiography		
2D	Defect documented	Flail/Prolapsing leaflet
Doppler	Shunt documented	Regurgitation in left atrium
Mortality		
Medical	90%	90%
Surgical	50%	40–90%

(PMVSR: postmyocardial infarction ventricular septal rupture; PPMR: papillary muscle rupture)

Source: Jeremias A, Brown DL. Cardiac Intensive Care, 2nd edition. Philadelphia: Saunders; 2010.

Echocardiography

2D Echocardiography

It may demonstrate the number, site, and size of PMVSR in 50%, ventricular dilatation and functions, regional wall motion abnormalities, and other mechanical complications. Negative contrast in the right ventricle by agitated saline increases the sensitivity of detection to 80%.

M-mode Echocardiography

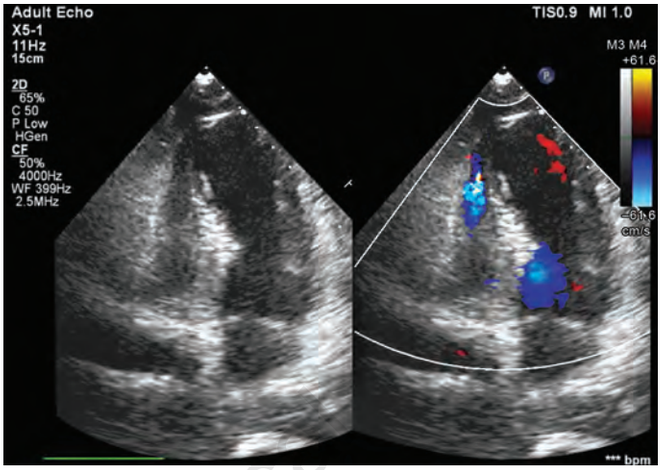
M-mode echocardiography can ascertain the chamber and vessel diameters and their functions.

Transesophageal Echocardiography

It is utilized in patients on mechanical ventilation and large body mass.

Color Doppler Flow Imaging

The sensitivity of 58% by 2D echocardiography increases to 96% with color flow Doppler to visualize the defect. The posterior septal defects are most difficult to localize as they have serpiginous track and are not perpendicular to the standard echocardiography views. The useful views for inferior-basal ventricular septal defect (VSD) are basal short-axis view, apical four-chamber view, and subcostal long-axis view; and for antero-apical defects, the low parasternal long-axis view, apical four-chamber view **(Fig. 3)**, and a subcostal view can be utilized. The complex paths of these ventricular defects necessitate off-axing imaging.



Note: Color flow mapping is more sensitive than 2D echocardiography to pick up the septal defects.

FIG. 3: Color flow mapping on echocardiography demonstrating apical-anterior postmyocardial infarction ventricular septal rupture.
(BPM: beats per minute)

Spectral Wave Doppler

This yields a direct estimation of shunt gradient, right ventricular systolic pressure, and pulmonary artery pressure.

Gated Multidetector Cardiac Computed Tomography

It offers better delineation of the tract and other associated complications such as a pseudoaneurysm; however, the flow is not detected, and contrast use is high.

Left Heart Catheterization

The coronary angiography can be utilized for planning revascularization. It may be unsafe in a sick patient with deranged renal functions. The contrast ventriculography poorly portrays the complex shunts and complications such as pseudoaneurysms. The left and right ventricular pressures can help differentiate acute mitral regurgitation and determine the biventricular failure. About a third of ventricular septal rupture will have some degree of mitral regurgitation associated with LV dysfunction.

Right Heart Catheterization

It is not often required but when used it can be utilized for the shunt calculation and oxygen step-up at the right ventricle to differentiate from other mechanical complications. The right heart balloon flotation catheter can be used to determine increased right atrial pressure from right ventricular failure and tricuspid regurgitation, elevated pulmonary artery pressures from high pulmonary venous return and LV diastolic failure and increased right-sided cardiac output. The oximetry step-up from right atrium to right ventricle gives false results in 5% cases when fluoroscopy-guided samples are used and in 10% cases if nonfluoroscopic samples are used. The inflation of a 7 French balloon catheter in the main pulmonary artery has shown to successfully resuscitate the BP in a postmyocardial ventricular septal rupture.

DIFFERENTIAL DIAGNOSIS

The clinical conditions of acute mitral regurgitation due to papillary muscle dysfunction, shock in free wall rupture/pseudoaneurysm, tricuspid regurgitation, congenital VSD in an acute myocardial infarction patient, and acute flash pulmonary edema need to be clinically differentiated from PMVSR.

TREATMENT

Surgery versus Transcutaneous Closure

With over 94% in-hospital mortality with medical management, the current guidelines recommend surgical repair; however, recent advances in TCC **(Fig. 4)** are fast emerging as a viable alternative in selected cases.[8] The paucity of large studies prevents triaging patients benefiting from early or delayed surgery or TCC. The evidence favoring surgical closure hails from large observational series from the past, while TCC is from the small recent series.

The ideal time for the procedure is debated; however, waiting for scar maturation is not a feasible option in most of the patients. The surgical techniques use:

- *Infarct exclusion technique*: David procedure with sutures in left ventricles
- *Infarct inclusion technique*: Daggett procedure with sutures in both ventricles

Large woven prosthesis raises the risk of thrombosis and residual shunts. The surgical outcomes can be enhanced with the use of double patch and glue (sandwich technique).[9] The clear-cut indications for surgery are concomitant need for value or bypass surgery, defect >24 mm and multiple defects, failure of TCC, surgeons' expertise, and patient preference.

Guidelines

The European guidelines favor early surgery in all patients who fail to improve with initial aggressive treatment (IC) and delayed surgery in stable patients (IIA, C) or TCC as an alternative (IIB, C).

The American guidelines argue for early emergency surgery even in stable patients and TCC in selected cases.

TIMING OF THE CLOSURE

Postmyocardial infarction ventricular septal rupture is a potentially fatal complication and it calls for an early treatment, preferably surgical and transcutaneous invisible cases. The mortality is nearly total for untreated medically managed cases. The ideal timing for closure is not yet certain due to insufficient data. The reports vary very widely, as concluded in **Figure 4**, for early and delayed surgical and TCC. Temporary stability with an aggressive approach reaps brief benefits; the patient deteriorates very rapidly. The procedure may be delayed if there is adequate cardiac output, no evidence of cardiogenic shock, absence of congestive heart failure and fluid retention, and preserved renal functions. The spontaneous closure is extremely rare, seen so far in six reported cases associated with pseudoaneurysm, thrombus, or small size closing the defect.

Device Selection

The different case series have utilized different devices mostly from the Amplatzer family—Amplatzer postinfarction muscular VSD occluder, Amplatzer muscular VSD occluder **(Fig. 3)**, Amplatzer septal occluder, occluder devices, atrial

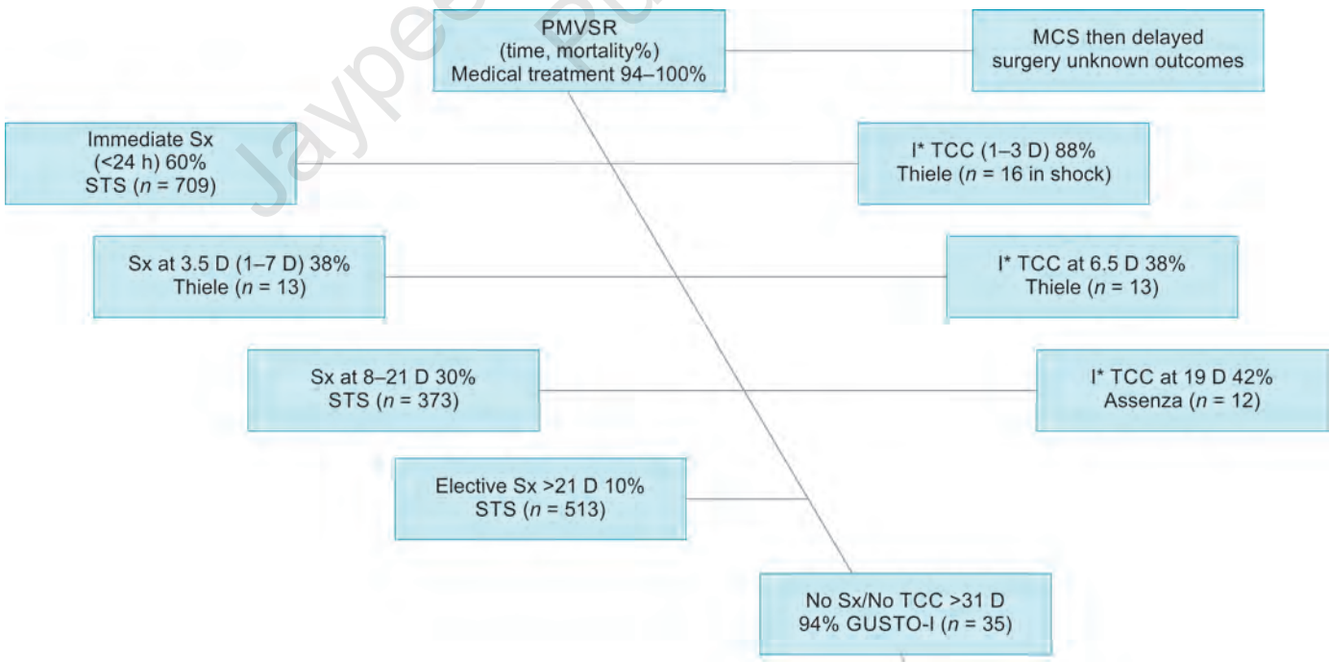


FIG. 4: Comparison of outcomes as per timing of the procedure after myocardial infarction.
(MCS: mechanical circulatory support; PMVSR: postmyocardial infarction ventricular septal rupture; STS: society of thoracic surgeons; TCC: transcutaneous closure)

septal devices, and even cribriform and Gore septal occluders. The postinfarction devices are especially designed with a longer waist disk to help track serpiginous defects and a wider disk to ensure complete closure of complex irregular defects. The defect-based 3D printed device was used in one case.

Revascularization

The benefits of revascularization before the procedure remain controversial and most series report better survival in revascularized patients.

Recurrence

The late surgical repair, more use of prosthetic material, and infarct inclusion procedures are associated with higher chances of device embolization, hemolysis, and residual shunts. The management of residual shunt is TCC.

FACTORS INFLUENCING OUTCOMES

The posterior location of PMVSR carries higher mortality than the anterior location. The higher mortality with immediate closure that is reported in many series can be attributed to the selection biases ("Trial of Life"). The surviving patients usually have a lower New York Heart Association (NYHA) class, better right ventricular and renal functions, and Euro score II.

STABILIZATION BEFORE PROCEDURE

Inotropes and Vasodilators

There is a need to stabilize the patient by decreasing the afterload yet maintaining BP in a shock patient. The vasopressors support the low cardiac output but increase the afterload and thereby increase the left-to-right shunt through the defect and myocardial oxygen demand. The vasodilators with pulmonary artery vasodilatory effects such as nitroprusside worsen the shunt, so hydralazine or phentolamine may be more effective. The diuretics may reduce the pulmonary congestion at the cost of a reduced BP, while fluid resuscitation worsens pulmonary congestion.

MECHANICAL SUPPORT DEVICES

The normal hemodynamics are not achieved by any form of mechanical support device, and the flow through pulmonary arteries is always markedly elevated because of the shunt. The primary utility of any mechanical support device is to decrease the shunt by decreasing the systemic vascular resistance and continue to have adequate filling pressures.

Intra-aortic Balloon Pump

The intra-aortic balloon pump (IABP) and vasodilatation have been proposed to be the first line to manage a stable patient. The IABP supports cardiac output by about half a liter per minute flow, boosts the coronary blood flow, and helps unload the left ventricle. However, it does not improve oxygenation and carries chances of limb ischemia with long use.

Impella

Impella increases coronary blood flow and cardiac output with support from 2.5 to 5.0 L/min, unloads the left ventricle, and decompresses pulmonary capillary wedge pressure (PCWP). It may cause right-to-left shunt with deoxygenated blood in the systemic circulation and cause limb ischemia and is contraindicated in aortic dissection and aortic valve regurgitation. It does not provide oxygenation.

Peripheral Veno-arterial Extracorporeal Membrane Oxygenator

The peripheral veno-arterial extracorporeal membrane oxygenator (pVA-ECMO) increases coronary and systemic blood flow, unloads the right ventricle, and provides oxygenation. The use may be counterproductive with an increase in the afterload of the left ventricle, decrease in native cardiac output, thromboembolism with long closure of the aortic valve, and increased left-to-right shunt. It also carries the risk of leg ischemia.

Central Veno-arterial Extracorporeal Membrane Oxygenator

The central veno-arterial extracorporeal membrane oxygenator (cVA-ECMO) likewise increases coronary and systemic blood flow, unloads the right ventricle, and provides oxygenation. Its use is associated with the need for surgical procedures with higher bleeding and infection rate.

TandemHeart

It increases coronary blood flow with systemic circulation, unloads the left atrium and ventricle, decreases PCWP, and can oxygenate. The downside is an increase in the afterload of the left ventricle, a reduction of the native cardiac output, thromboembolism with long closure of the aortic valve, and an increase in the left-to-right shunt. The associated risk of dislodgment of the inflow cannula into the right atrium would result in the right to left shunt and a loss of support. It requires a transseptal puncture for the placement of the inflow cannula into the left atrium with the associated risk of persistent patent foramen ovale and risk of leg ischemia.

ECPELLA

It increases coronary blood flow with systemic flow and oxygenates and unloads the left and right ventricles and PCWP. Like impella, it may cause right-to-left shunt with deoxygenated blood in the systemic circulation and cause limb ischemia and is contraindicated in aortic dissection and aortic valve regurgitation.

Passive Apical Left Ventricular Vent with Veno-arterial Extracorporeal Membrane Oxygenator (Generally Central)

It decompresses the left ventricle through the apical LV vent and reduces PCWP with positive aspects of cVA-ECMO. It carries the same negative aspects of cVA-ECMO.

FUTURE DIRECTION FOR RESEARCH AND TREATMENT

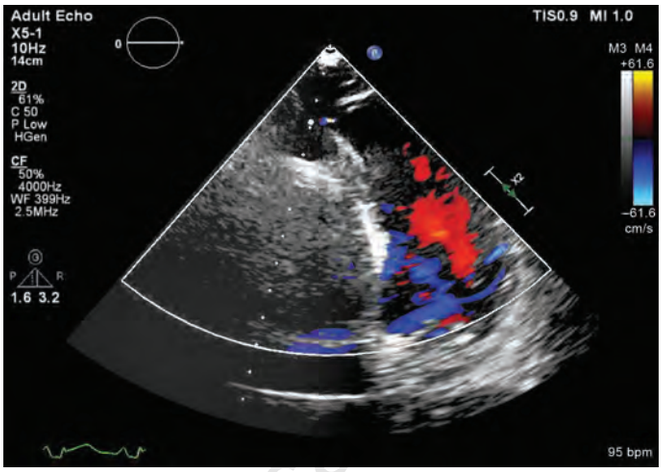
With the dearth of evidence available, there is a need for randomized controlled trial and direct comparison between the surgical and TCC. There is also a need for new devices more suited to the postinfarction friable anatomy. The future also lies in hybrid procedures that combine surgery and TCC and a rapid response national task force (something like emergency toxicology on call) for prompt guidance.

AUTHOR'S EXPERIENCE

The Advanced Cardiac Institute, Government Medical College, has received eight cases of PMVSR between 2013 and 2022. Two patients underwent successful TCC—one of posterior PMVSR **(Fig. 3)** and the other of anterior PMVSR **(Fig. 5)**. The other six were medically managed and did not survive, and none were treated by cardiac surgery.

CONCLUSION

The PMVSR still remains mostly untreated and fatal in spite of the progress made in hemodynamic support and our understanding of the defect owing to the rare incidence. The evidence to formulate a treatment approach is accumulating, yet far from enough.



Note: The apical ventricular rupture closed by the ventricular septal occluder device.

FIG. 5: Color flow mapping on echocardiography demonstrating apical-anterior postmyocardial infarction ventricular septal rupture closed by the ventricular septal occluder device.

(BPM: beats per minute)

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CHAPTER 75

Left Ventricular Remodeling after Myocardial Infarction: The Current Approach and Novel Interventions

Sandeep Bansal, Aseem Basha M

ABSTRACT

With advancements in medical management and revascularization strategies, more and more remodeled hearts add on to the increasing prevalence of heart failure with ischemic etiology. Previously, description of left ventricular remodeling was purely structural and did not include functional parameters such as left ventricular ejection fraction (LVEF), which is one of the most important predictors of mortality post myocardial infarction (MI) and a consequence of adverse remodeling. This chapter discusses the incremental value of adding LVEF to the previous structural definition of remodeling, its pathophysiology, the (un)natural course, diagnostic modalities, and strategies to prevent and reverse post MI left ventricular remodeling.

INTRODUCTION

The prevalence of heart failure (HF) with reduced ejection fraction is ever increasing despite timely revascularization in patients with acute myocardial infarction (MI). Successful revascularization strategies, although can significantly reduce mortality, do not guarantee freedom from adverse remodeling. This cardiac remodeling determines the natural course of patients developing HF post MI. Left ventricular (LV) remodeling is the end result of the pathological cascade comprising myocardial inflammation, myocardial necrosis, and replacement fibrosis, resulting in heightened wall stress and consequent LV dilatation. This description of LV remodeling is purely structural and does not include functional parameters such as LV ejection fraction (LVEF), which is one of the most important predictors of mortality post MI and a consequence of adverse remodeling. Incorporation of LVEF in the existing definition of LV remodeling may add prognostic value to patients exhibiting LV remodeling post MI. Adverse post-MI remodeling is characterized by an abnormal increase in LV end-diastolic volume (LVEDV) by 20% or more, LV end-systolic volume (LVESV) by 15% or more,[1] and an absolute reduction in LVEF by more than 5% when compared to the baseline values.[2] As of now, there is no consensus on which definition of LV remodeling is better.

EPIDEMIOLOGY

With advancements in medical management and revascularization strategies, more and more remodeled hearts add on to the increasing prevalence of HF with ischemic etiology. Advanced age, female sex, diabetes, hypertension, obesity, chronic kidney disease, and chronic obstructive pulmonary disease confer heightened predilection for development of HF post MI. LV remodeling is seen in both ST-segment elevation MI (STEMI) and non-ST segment elevation MI (NSTEMI). In the contemporary era, where STEMI is treated with primary percutaneous intervention (PCI) and guideline-directed medical therapy, nearly half of them demonstrate some degree of LV remodeling. Van der Bijl et al. reported that 48% of patients undergoing primary PCI for STEMI developed remodeling over the next 12 months. 64% of patients were early remodelers (0–3 months), 23% mid-term remodelers (3–6 months), and 13% late remodelers (6–12 months) when LVEDV of ≥20% was used to define remodelers **(Table 1)**.[3] In contrast to STEMI, patients with NSTEMI also show adverse remodeling and are associated with HF with preserved ejection fraction more often than with reduced ejection fraction. Remodeling has also been documented in patients with MINOCA (MI in absence of obstructive coronary artery disease), although to a lesser extent.[4]

TABLE 1: Prevalence of LV remodeling post myocardial infarction.

				
Nonremodeler	**Remodeler**	**Early remodeler (0–3 months)**	**Mid-term remodeler (3–6 months)**	**Late remodeler (6–12 months)**
52%	48%	52%	23%	13%

(LV: left ventricular; STEMI: ST-elevation myocardial infarction)

TABLE 2: Pathophysiology of ventricular remodeling post myocardial infarction.

Post myocardial infarction-myocyte necrosis					
Triggers a cascade of biochemical intracellular signaling processes					
Release of inflammatory mediators				**Decreased contractility**	
Alterations in the biology of the myocyte	Alterations in the biology of the nonmyocyte	Alterations in the extracellular matrix	Progressive myocyte loss	Activation of RAAS and heightened sympathetic drive	Increased natriuretic peptides
• Myocyte hypertrophy • Fetal gene expression • Negative inotropic effects • Increased oxidative stress	• Conversion of fibroblasts to myofibroblasts • Upregulation of AT1 receptors on fibroblasts • Increased matrix metalloproteinase secretion by fibroblasts	• Degradation of the matrix • Myocardial fibrosis	• Necrosis • Apoptosis	Abnormal loading conditions	
				Myocyte hypertrophy and fibrosis	Transient improvement in LV function
Alterations in LV structure and function					
• LV wall thinning • Infarct expansion • LV dilation • Increased LV sphericity		• Mitral valve incompetence • LV systolic dysfunction • Increased wall stress • Mechanical stretch			
Heart failure					

(LV: left ventricular; RAAS: renin–angiotensin–aldosterone system)

PATHOPHYSIOLOGY OF LEFT VENTRICULAR REMODELING POST MYOCARDIAL INFARCTION

During acute MI, there is a switch in metabolic fuel from fatty acids to glucose for the generation of adenosine triphosphate (ATP). Significant reduction in myocardial oxygen supply coupled with limited anaerobic metabolism reserve of infarcted heart results in massive ATP depletion, impairment of Na^+–K^+ ATPase pump, and loss of membrane integrity and cardiomyocyte death.[5,6] The ischemic event is soon followed by an intense inflammatory infiltrate with neutrophils, monocytes/macrophages, and lymphocytes in that order. Neutrophils start appearing in the first 12 hours post MI and peak over the next 3 days. Neutrophils and macrophages together eliminate cellular debris while driving inflammation by releasing proinflammatory cytokines, which further augment more proinflammatory cells causing cardiomyocyte necroptosis. After a few days, neutrophils are replaced by macrophages while T lymphocytes regulate monocyte activation, which is pivotal in the healing process. Progressive myocyte loss coupled with alterations in the biology of myocytes, nonmyocytes, and extracellular matrix together results in the disintegration of dead tissue and formation of granulation tissue comprising collagenous fibers, macrophages, and fibroblasts over 1–3 weeks post MI **(Table 2)**. Chronic inflammation and activation of inflammatory cytokines with proinflammatory cells may persist beyond 3 months, resulting in adverse chronic remodeling and consequent HF.[7] Although timely revascularization is the most effective way to reduce myocardial injury post MI, the process of myocardial reperfusion may in itself induce myocardial cell death by a phenomenon known as ischemia-reperfusion injury. Ventricular remodeling represents an adaptation to the loss of contractile function consequent to tissue necrosis and subsequent LV distension. This adds to the wall stress and myocardial oxygen consumption, thereby increasing cardiac workload while the heart is compensating to the heightened preload and afterload.

(MAL)ADAPTATIONS CONSEQUENT TO ALTERATIONS IN LEFT VENTRICULAR GEOMETRY

Elevated LV end-diastolic pressure (LVEDP) is universal in patients presenting with acute coronary syndromes. This acute elevation of LVEDP resulting from loss of contractile function coupled with increased LV volumes results in acute LV dilatation. With time, increased wall stress, ongoing inflammation, activation of the renin–angiotensin–aldosterone system (RAAS), and heightened sympathetic tone together activate apoptotic signaling pathways, leading to programmed death of cardiomyocytes. This leads to LV wall thinning and chamber dilatation, producing a spherical geometry with an increased LV mass but decreased relative wall thickness (volume overload type of hypertrophy). This increase in the radius of left ventricle (R) with consequent reduction in wall thickness (T) in an afterload excess state (P) reduces the wall stress and is beneficial in maintaining cardiac output by increasing ventricular filling volume during the initial phases (best explained by the Laplace law, wall stress = PR/2T). However, with time, these compensatory mechanisms fail in the long term, resulting in irreversible LV dysfunction and HF.[8]

(UN)NATURAL COURSE OF LEFT VENTRICULAR REMODELING POST MYOCARDIAL INFARCTION

Although timely revascularization is the most effective way to reduce myocardial injury post MI, the percentage of patients not developing remodeling (reverse remodelers) is just over 50. Patient characteristics that typify reverse remodelers include those with small infarcts, nonanterior wall infarctions, nontransmural infarctions, lesser degrees of myocardial stunning, and patent infarct-related artery (IRA) in addition to local trophic factors. Delayed revascularization, slow-flow/no-reflow phenomenon post PCI, advanced microcirculatory resistance, inadequate healing, myocardial stunning, and hibernation either in isolation or in combination incite secondary damage and elicit varying degrees of ventricular remodeling. In remodelers, varying patterns of LV remodeling have been described. Four trajectories of LV remodeling are apparent when functional parameters are incorporated into structurally remodeled hearts **(Fig. 1)**. Group 1 includes those with no LV dilatation or LVEF impairment, group 2 includes remodeling phenotype with LVEF impairment without LV dilatation, group 3 remodelers have dilated LV but without LVEF

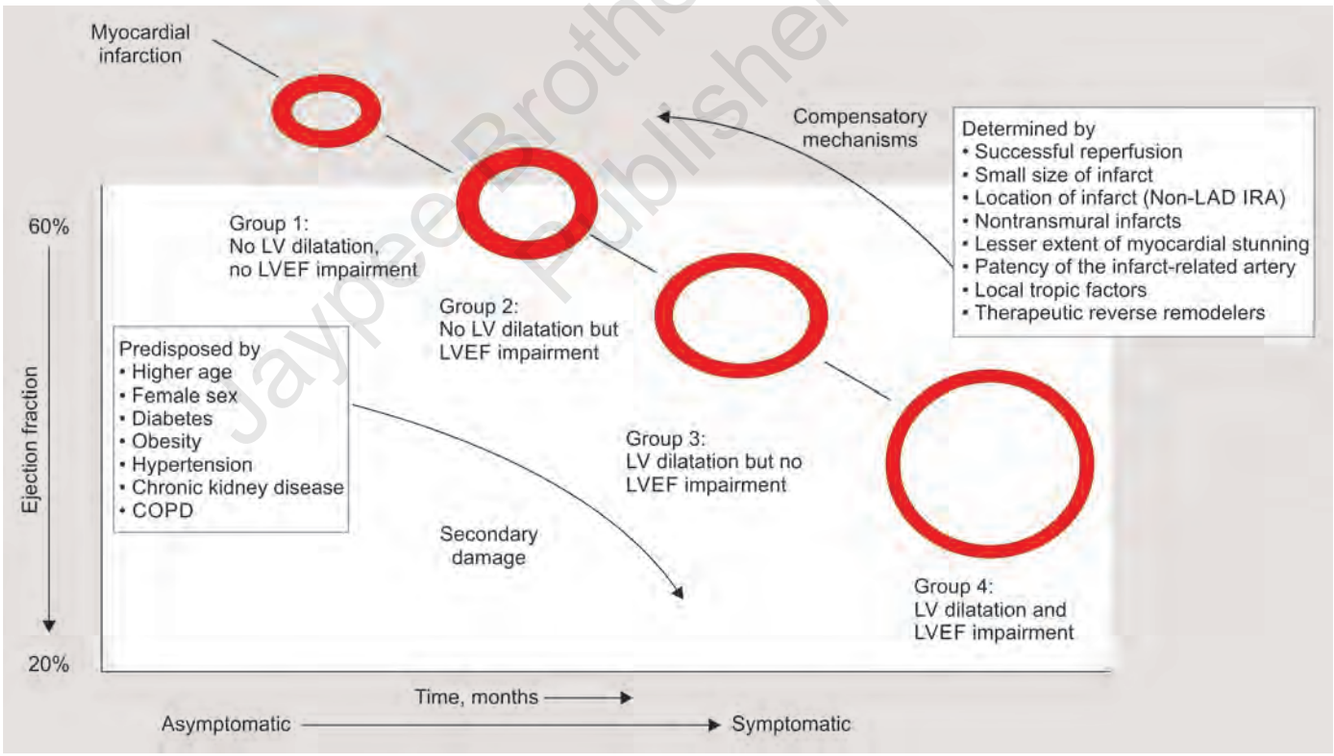


FIG. 1: Classification and trajectories of postmyocardial infarction based on LV volume and LVEF.
(COPD: chronic obstructive pulmonary disease; LV: left ventricular; LVEF: left ventricular ejection fraction; non-LAD IRA: non LAD infarct related artery)

TABLE 3: Four distinct functional LV remodeling groups and their clinical implications.

Group	Definition	Composite of all-cause mortality and HF hospitalization	All-cause mortality
Group 1: No LV dilatation, no LVEF impairment	Patients without LVEDV increase of ≥20% and no absolute reduction in LVEF of >5%	11%	10%
Group 2: No LV dilatation but LVEF impairment	Patients without LVEDV increase of >20% but with absolute reduction in LVEF of >5%	14%	12%
Group 3: LV dilatation but no LVEF impairment	Patients with LVEDV increase of ≥20% and no absolute reduction in LVEF of >5%	16%	14%
Group 4: LV dilatation and LVEF impairment	Patients with LVEDV increase of ≥20% and absolute reduction in LVEF of >5%	31%	29%

(HF: heart failure; LV: left ventricular; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction)

impairment, while group 4 patients have the worst combination of dilated LV and impaired LVEF **(Fig. 1)**. These groups have great dynamicity, and aggressive guideline-directed medical therapy can reverse the remodeling process and improve the LVEDV and LVEF in otherwise remodeled hearts.

Chimed et al.,[2] in a retrospective study of STEMI patients who were treated with primary PCI, evaluated the prognostic relevance of LVEF in remodeling hearts. In this study, at 6 months of follow-up, 63% of patients had no LV dilatation or impairment in LVEF (group 1), while those with no LV dilatation but LVEF impairment comprised of 7% of the study population (group 2). 25% of patients had dilated LV but without LVEF impairment (group 3), and 4% had dilated LV with impaired LVEF (group 4). Patients in group 4 had the highest degree of troponin rise during acute MI. During a median follow-up of 72 months, the composite of all-cause mortality and HF hospitalization occurred in 11%, 14%, 16%, and 31% in groups 1, 2, 3, and 4, respectively. All-cause mortality was 10%, 12%, 14%, and 29% in groups 1, 2, 3, and 4, respectively. This study concluded that group 4 patients had significant mortality when compared to other functional LV remodeling groups **(Table 3)**.[2]

IMAGING MODALITIES FOR LEFT VENTRICULAR REMODELING

With advancements in noninvasive cardiac imaging, assessment of LVEDV, LVESV, and LVEF is now relatively easy. This is routinely done using two-dimensional (2D) echocardiography, three-dimensional (3D) echocardiography, cardiac magnetic resonance (CMR) imaging, and radionuclide-based molecular imaging techniques. Each of these imaging modalities has its own advantages and disadvantages. Apart from the routine objective parameters of LV remodeling, global longitudinal strain and global myocardial work have been increasingly used in quantifying LV remodeling and their role in prognostication is being studied.

Transthoracic 2D echocardiography is the first investigation modality used to quantify LVEDV, LVESV, and LVEF (by summation-of-disk method) in addition to the regional wall thickness, mitral valve (MV) incompetence, and LV sphericity index along with global longitudinal strain. 3D LVEDV/LVESV and LVEF are more accurate than 2D parameters and hence preferred over the summation-of-disk method due to better reproducibility. The limitations of 3D echocardiography include limited availability, high cost, need of experienced operator, postprocessing, and need for excellent image quality. Endocardial delineation can be further enhanced with myocardial contrast echocardiography for improving accuracy and reproducibility. 4D echocardiographic assessment for estimation of global myocardial work is also being employed in the assessment of LV remodeling.[8]

Cardiac magnetic resonance imaging is the current gold standard for assessing cardiac volumes and function with features of high reproducibility and low variability. Late gadolinium enhancement (LGE) imaging techniques can additionally provide information on viability, microvascular obstruction, ischemia, blood flow, and fibrosis. Parametric mapping such as native T1 mapping (for etiology of infarction), contrast-enhanced T1 mapping for extracellular volume quantification for diffuse fibrosis, and T2* mapping for assessing intramyocardial hemorrhage/microvascular obstruction have also been used in assessing LV remodeling.[9,10] There is limited availability, longer acquisition times, artifacts, and limited suitability for patients with severe renal disease (LGE).

Nuclear radiopharmaceuticals are not routinely used to assess LV remodeling unlike echocardiography and CMR. While ^{18}F-deoxyglucose positron emission tomography (FDG–PET) can provide information on myocardial metabolism and viability, novel tracer-based approaches have emerged to detect myocardial inflammation and fibrosis. These include chemokine receptors CXCR4 and CCR2, mitochondrial 18 kD translocator protein, and somatostatin receptors.[11,12] These ligands can be a therapeutic target in the future to reverse remodeling. One such example is PET imaging with ^{68}Ga-pentixafor (CXCR4 ligand), which identifies postinfarct inflammation (when CXCR4 is overexpressed) and subsequent poor outcomes in patients with remodeling, and this concept has been used to improve LV function using CXCR4 blocker plerixafor.[13]

MANAGEMENT

Although timely revascularization is the most effective way to prevent or reduce LV remodeling, most of our patients have a significant delay in receiving reperfusion therapy. After the acute phase, changes in preload, afterload, and contractility tremendously increase myocardial oxygen consumption, and the vicious cycle of continuous myocardial injury and myocardial remodeling ensues. Previously, LV remodeling was considered to be irreversible with respect to the functional and structural changes. Rather, it is now clearly understood that LV remodeling is a dynamic process and the degree of reverse remodeling depends on the multiple factors that aid in myocardial recovery. Strategies to prevent, reduce, and reverse post-MI LV remodeling are summarized in **Table 4**.

Myocardial Revascularization

Left ventricular remodeling post MI depends on infarct size, patency of IRA, and the degree of collateral supply in the occluded area. Jeremy et al. studied the relationship between perfusion of IRA and LV volumes/LVEF and concluded that in those patients who did not receive thrombolysis, perfusion of IRA was a good predictor of LV volume change from 2 days to 1 month post MI when compared to the infarct size.[14] Timely reperfusion is associated with greater myocardial salvage and lesser myocardial stunning in the infarcted region. Even those infarcts associated with reperfusion that develop contraction band necrosis are expected to have greater tensile strength and lesser predilection to infarct expansion. The GISSI study examined the changes in LVEDV and LVESV after thrombolysis in patients with acute MI with gated radionuclide ventriculography and concluded that patients receiving thrombolytic therapy had smaller LV volumes at 6 months when compared to those who did not receive thrombolysis.[15] Primary PCI seems to be the most effective way of preventing remodeling by reducing the total infarct size, myocardial stunning, maintaining of patency of culprit artery, and improving LVEF. Reverse remodeling, which is defined as reduction in LVESV by more than 10% at 6 months post MI after successful PCI, is also associated with reduced incidence in HF and improved survival rates.[16,17]

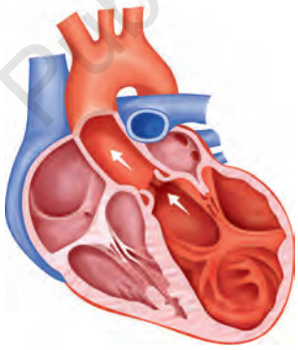
Cardiac Rehabilitation

While acute exercising activates the RAAS pathway and is detrimental, chronic exercise training has an antagonizing effect on it. Cardiac rehabilitation programs are often the most neglected part in the management of the patient post MI. Most studies have concluded that post-MI exercise training results in an overall positive impact of LV remodeling. However, intensity, duration, and timing of initiation of exercise post MI are yet to be standardized to obtain the desired outcome.[18]

Neurohormonal Blockers

Neurohormonal excess is central to the pathophysiology of LV remodeling. Blocking neurohormonal excess and thereby causing reverse remodeling and restoration of LV geometry

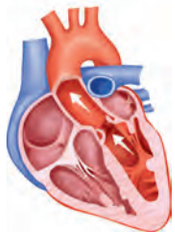
TABLE 4: Strategies to prevent, reduce, and reverse post-MI LV remodeling.



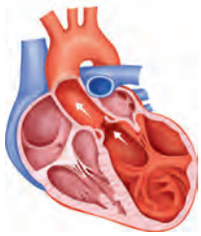
Myocardial revascularization	Post-MI cardiac rehabilitation	Neurohormonal blockers	Inflammation modulators	Transcatheter/Surgical interventions	Newer perspectives
• PCI • CABG • Thrombolysis		• ACEI/ARB • ARNI • MRA • Beta blockers • SGLT-2 inhibitors	• Statins • Canakinumab • Colchicine	• CRT • MitraClip • MV repair • MV replacement • LV reconstruction • LVAD	• Gene therapies—noncoding RNAs • Bone marrow-derived cell therapies
	 • Exercise rehabilitation				

(ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; CABG: coronary artery bypass graft; CRT: cardiac resynchronization therapy; LV: left ventricular; LVAD: left ventricular assist device; MI: myocardial infarction; MRA: mineralocorticoid receptor antagonist; MV: mitral valve; PCI: primary percutaneous intervention; RNA: ribonucleic acid; SGLT-2: sodium–glucose cotransporter-2)

TABLE 5: Impact of disease-modifying therapies on structural and functional parameters of adverse LV remodeling.



	Reverse remodeling						
LVEF ↑	1–4%	9–15%	4%	4–12%	1–6%	2–24%	3%
LVEDV ↓	12–13 mL/m^2	12.25 mL/m^2	17.3 mL		–	21 mL/m^2	26 mL
LVESV ↓	13 mL/m^2	15.29 mL/m^2	18.5 mL	4.8 mL	–	18.4 mL/m^2	16 mL
LVEDD ↓	2.4 mm	–	–		–	–	–
LVESD ↓	6.2 mm	–	–		–	–	–
LVMI ↓	–	–	–	–	2.6–13.7 g/m^2	–	–
	Adverse remodeling						



(LV: left ventricular; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVESV: left ventricular end systolic volume; LVMI: left ventricular mass index)

and function is a sensible option in our armory against adverse remodeling. This reverse remodeling is associated with reductions in mortality and morbidity.

Angiotensin-converting enzyme inhibitor (ACEI), when initiated in the early phase post MI, was associated with significant improvement in all-cause death in both short-term and long-term follow-up. The SOLVD (Studies of Left Ventricular Dysfunction) trial in asymptomatic patients with systolic dysfunction demonstrated a significant reduction in LVEDV at a mean 25 months of follow-up with enalapril when compared to placebo.[19] In symptomatic HF with reduced ejection fraction patients post MI, similar improvement in LVEDV and LVEF was documented at 1 year with enalapril when compared to placebo.[20] Trials that compared angiotensin receptor blocker (ARB) with ACEI in post-MI patients also demonstrated similar statistically equivalent improvements in LVEF, LV volumes, and clinical outcomes.[21-23] LVEF, LVEDV, and LVESV improve to the tune of 1–4%, 12–13 mL/m^2, and 13 mL/m^2, respectively, with ACEI/ARB when compared to placebo.[19,20,24] Other RAAS inhibitors, mineralocorticoid receptor antagonist (MRA), have been shown to improve LVEF, LVESV, and LVEDV after 6 and 12 months of therapy when compared to placebo. Mean improvement in LVEF, LVEDV, and LVESV occurs to the tune of 4%, 17.33 mL, and 18.5 mL, respectively, with MRA when compared to placebo.[25,26] Impressive results were obtained with the new molecule angiotensin receptor-neprilysin inhibition (ARNI), and the magnitude of reverse remodeling in LVEF, LVESV, and LVEDV was 9.4%, 12.25 mL/m^2, and 15.29 mL/m^2, respectively, when compared to enalapril.[27] Consistent results have also been obtained with beta blockers with reversal of remodeling with 4–12% improvement in LVEF and 4.8 mL reduction in LVESV.[28-32] Sodium–glucose cotransporter-2 (SGLT-2) inhibitor is another molecule that has had overwhelming success in HF with reduced as well as preserved ejection fraction. Empagliflozin has been found to switch the metabolic fuel in ischemic myocardium from glucose to free fatty acids, ketone bodies, and branched chain amino acids, thereby optimizing myocardial energetics. Improvement in LVEF has been documented to the tune of 1–6% in patients with HF, while it improves diastolic dysfunction and regresses LV mass to the tune of 2.6–13.7 g/m^2.[33-36] The ongoing EMPACT-MI (NCT04509674) and DAPA-MI (NCT04564742) trials will provide more relevant details regarding the effect of SGLT-2 inhibitor in these subsets of patients. The impact of disease-modifying therapies on structural and functional parameters of adverse LV remodeling has been summarized in **Table 5**.

Inflammation Modulators

Inflammation plays a very important role in ventricular remodeling after acute MI, making it a potential target for reversing remodeling. Statins, canakinumab, colchicine, glucocorticoids, nonsteroidal anti-inflammatory drugs, anti-integrins, complement pathway inhibitors, and metallo-proteinase blockers are a few to name. However, none of the candidate agents have been found to reproduce results from preclinical studies.[7] Statins are known for their pleiotropic effects and in rat models with large MIs, statins are associated with reduction in LVEDP and LV dilatation consequent to the reduced expression of fetal genes and collagen fibers.[37] Enhanced nitric oxide formation while on statins is the most plausible explanation for the possible improvement in LV remodeling parameters.

Transcatheter Therapies and Surgical Interventions for Reversing Left Ventricular Remodeling

Intracoronary infusion of supersaturated blood after PCI with anterior wall MI, renal denervation, transcatheter or surgical ventricular restoration, MV repair/replacement, and LV assist devices are few of the options available to reverse LV remodeling. Among these, MV interventions (MV repair/replacement, MitraClip) for mitral regurgitation, which occur as a consequence of cardiac remodeling, have been found to have significant improvement in LVEF and LVEDV.[38-40] Cardiac resynchronization therapy is also associated with improvement in LVEF, LVEDV, and LVESV to the tune of 2–24%, 21 mL/m^2, and 18.4 mL/m^2, respectively, in a carefully selected population with HF with reduced ejection fraction.[41-44] However, the magnitude of benefit seems to be more with nonischemic etiology of HF. LV assist devices also reduce and reverse LV remodeling by causing mechanical unloading and restoring neurohormonal imbalance. They are currently being used as an advanced HF therapy, as a bridge to destination/recovery/transplant.

Newer Therapies

Gene-based therapies, which induce angiogenesis and facilitate myocardial healing and regeneration, are the next way forward. Reasonable success has been obtained in preclinical studies and large clinical randomized controlled trials are in the pipeline. Genome editing technologies and bone marrow-derived cell therapies could add to the ever-increasing list of therapeutic options available for reversing the adverse remodeling post MI.[8]

CONCLUSION

Ventricular remodeling is a maladaptive pathophysiological process consisting of progressive myocardial hypertrophy, fibrosis, and myocyte death in conjunction with ventricular dilatation and/or dysfunction. Functional LV remodeling, which incorporates LV function into the existing structural definition (based on LVEDV), improves the risk stratification in patients with MI. LV dilatation in the absence of impairment of LVEF is not necessarily associated with poor prognosis, but LV dilatation in association with impaired LVEF does.

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INDEX

Page numbers followed by *b* refer to box, *f* refer to figure, *fc* refer to flowchart, and *t* refer to table.

A

A waves, abnormalities of 4
Abbott's pressure wire 445*f*
Abciximab 315, 492
Abdomen 19
Abdominal aorta 540
Abdominal aortic aneurysm 394
Abdominal pain 148
Abdominal surgery 257
Abdominal-jugular reflux 5
  false-positive 5
Abernethy malformation 308, 309*f*
Abiotrophia species 157
Ablation systems, second-generation 210
Abscess 157
  mycobacterium 162
  myocardial 162
Abundant intimal inflammatory cells 548
Academic cardiologists 261
Acetylcholine 444, 446, 473
Acetylsalicylic acid 202, 315, 400
Acid-fast bacilli 162*f*
Acinetobacter 158-160, 163
Acquired emphysema 45
Acquired right ventricular outflow tract obstruction 11
Acrocyanosis 44
Actinobacillus 157
Actinomycetemcomitans 157
Activated partial thromboplastin time 258
Acupuncture 128
Acute cardiovascular syndrome 218
Acute chest pain 60, 505*f*
  causes of 58
Acute coronary syndrome 59, 109, 111, 199, 202*t*, 228, 255, 262, 317, 325, 345, 362, 369, 395*f*, 426, 442, 454, 456, 461, 481, 487, 517, 517*t*, 520, 540, 547, 561, 570, 574*f*, 576, 583, 588, 593, 466, 469, 498, 576, 600, 605
  diagnosis of 58
  intervention 576
  percutaneous coronary intervention 498
  treatment of 498
Acute ischemic
  events, prevention of 202, 613
  stroke 494
Acute mitral regurgitation 98-100, 553, 554
  causes of 99
Acute myocardial infarction 58, 99, 133, 172, 364, 415*f*, 502, 505, 506*f*, 536, 553, 554*t*, 556*f*, 557*t*, 560, 568, 571*f*, 589, 605, 612, 622
  complications of 558*fc*
  diagnosis of 406, 553
  interventions 502
  management 553
  mechanical complications of 558, 558*b*, 558*fc*
  setting 133
  treatment of 522
Acute pulmonary embolism 592
  classification of 219, 219*t*
  diagnosis of 218
  management of 218
  risk assessment of 223
  symptoms of 220
Adaptive servo ventilation 173
Adenocarcinomas 161
Adenosine 351, 439, 445, 473, 489, 492
  continuous infusion of 439
  monophosphate-activated protein kinase 391
Adenosine diphosphate 315, 466, 593, 594
  P2Y12 inhibitors 318
  release of 200
Adenosine triphosphate 351, 391, 473, 492
  generation of 623
Adequate cardiac output 619
Adherence, interventions 125, 331, 331*t*
Admixture physiology 45
Adrenergic ganglion blocking drugs 116
Adult population 11
Advanced glycation end products 351
Advanced life support 224
Adventitious sounds 69
Adverse cardiovascular events 380, 548
Adverse pregnancy, history of 401
Aerobic activity, moderate-intensity 475
Aerobic exercise 349, 353, 377, 378
Afterload-reducing agents 104
Agatston method 94
Agitation 617
Air
  embolism 220
  pollution 189
  space edema 22
Alcohol 327
  avoidance of 173
  septal ablation 273

Aldosterone-to-renin ratio 126
Aldosteronism, primary 126
Alirocumab 341, 358, 375, 391
Alkaptonuria 85
Alternate-day dosing 375
Alternative regimen 161, 162
Alternative therapy, need for 152
Alzheimer's disease 449
Ambrisentan 239, 245
Ameliorate metabolic syndrome 128
Amino acid 192
  branched chain 627
  prohormone 407
Amlodipine 593
Amyloidosis 456
Anacrotic pulse 6
Anaerobic metabolites 504
Anatomical signs 25
Ancillary pharmacotherapy 492
Anderson–Fabry disease 456
Anemia 5, 114, 117, 244
  absence of 244
Anesthesia
  general 555
  induction of 224
Anesthetic drugs 224
Aneurysm 583
  dilatation 310*f*
Angina 87, 109, 110, 112*t*, 394, 459, 519, 593
  cause of 454
  equivalent 111
    symptoms 520
  mechanism of 111
  occurrence of 433
  sites of 111, 111*f*
  stress-induced 454
  typical 432
Anginal chest pain 455
Angiocardiography 304
Angiogram 303, 304
Angiographic catheters 298
Angiographic projections 299, 300*t*
Angiography 295, 299, 302*t*, 308, 459
  advantages 296
  following arterial switch operation, postoperative 311
Angioplasty 207
  preventive 536
  primary 508*f*, 605
Angiotensin-converting enzyme 117, 270, 293, 325, 326, 327*f*, 444, 459, 475, 518, 558
  inhibitor 121, 178, 270, 385, 476, 626, 627
Angiotensin-receptor blocker 121, 270, 385, 518, 626, 627
Angiotensin-receptor-neprilysin inhibition 128, 133, 270, 626, 627
  exploring role of 133
Animal cells 193
Ankle
  brachial index 395
  edema 117
Ankylosing spondylitis 547
Anomalous origin 15*f*
Anorexiant medications 99
Antenatal diagnosis 40, 41
Anteroapical rupture 566*t*
Antibiotic strategy, appropriate 157
Anticardiolipin 229
Anticoagulant 252, 332
  managing 252, 258
  therapy 320, 597
  treatment 227
    indication for 220
Anticoagulation 229*t*, 235, 252, 492
  initiation of 227
  therapy 329, 576
Anticomplementary therapy 514
Antidepressants 124
Antihypertensive drug therapy 211
Antihypertensive medication 206, 212
Antihypertensive treatment 350, 397
Anti-inflammatory
  agent 330, 332, 548
  properties 547
  therapy 599
  treatment 330
Anti-integrins 627
Anti-ischemic
  drugs 592*t*
  therapy 592
Antimicrobial stewardship 161, 162
Anti-mitochondrial antibody 490
Antinuclear antibodies 293
Antiplatelet 258, 315, 318, 322, 326, 498, 583
  agents 257, 315, 491, 523, 584
  managing 255
  resistance 466
    causes of 467*f*
  risk profile of 316
  starting 322
  timing protocol 256*f*
Antiplatelet therapy 134, 178, 257, 316, 319, 320, 328, 466, 484, 581, 593, 598
  alternate 468
  single 465, 598
  trial, master dual 462
Antiplatelet treatment
  chronic 469
  investigating de-escalation of 469
Antiretroviral agent 370
Antisense oligonucleotide 376
  therapy 365
Antithrombotic agents 584
  managing 252
Antithrombotic regimen 320
Antithrombotic therapy 320, 329, 541, 593*b*, 598*fc*
  effective 542
  management of 580
Antithrombotic treatment, mechanism of action of 594*f*
Anti-XA therapy 614

Anti-β-glycoprotein 229
Anxiety 189, 518
Aorta 31, 23, 38, 303*f*, 305*f*, 512
  aneurysm of ascending 68
  ascending 23-26
    dilation 68
    prominent 23
  descending 24, 302
  entire 94
  left anterior 33
Aortic angiogram, descending 301*f*
Aortic annulus, measurement of 91
Aortic arch 19, 25
  evaluation of 23
  hypoplasia of 36
  right 20*f*, 24
  transverse 23, 25
Aortic area 70
Aortic atherosclerotic disease 394
Aortic dissection 59, 228
  acute 59
Aortic ejection 71
  sound 68
Aortic knob 23, 24
Aortic override 31*f*
Aortic pressure 438, 442, 443
Aortic regurgitation 5, 48, 67, 68, 70*f*, 71, 139, 166, 166*t*, 264, 265, 266, 558
  chronic 166
  prevalence of 197
Aortic root 166
  angiogram 301*f*
  pathology 95
Aortic stenosis 13, 68-70, 70*f*, 79, 85-87, 86*t*, 93, 95, 101, 165, 177, 197, 264, 266, 456
  assessment of 86
  cause of 85, 165
  diagnosis of severe 95, 95*b*
  hemodynamic classification of 85
  history of severe 95
  low-flow 86
  low-gradient 86, 93*f*c, 95*b*
  moderate 89*f*
  natural history of 86
  noninvasive assessment of 85
  prevalence of 197
  severe 14*f*, 87*f*c, 89*f*, 92*f*
  severity 88*f*
  supravalvular 166
  systolic murmur of 101
Aortic valve 38, 94, 139, 264
  area 85, 89, 89*f*, 91*f*, 93
  bicuspid 68, 264, 265
  closure 166
  disease 9, 165, 197, 198, 198*t*, 263
    epidemiology of 197
    prevalence of 197, 198
  fistula 5
  flow 95
  orifice 89
  replacement, surgical 265
  restricted 88
Aortoarteritis, nonspecific 135
Aortopulmonary collaterals 298, 300, 302
Aortopulmonary communications 73
Aortopulmonary window 11
Apelin 242
Apical aneurysm 181
  formation 181
    pathophysiology of 181
Apical ballooning syndrome 273
Apical four-chamber view 140*f*
Apical septum 301
Apical wall motion abnormality 612
Apical-anterior postmyocardial infarction 621*f*
  ventricular septal rupture 618*f*
Apixaban 202, 228, 254, 329, 579, 597, 613
  role of 613
Apnea-hypopnea index 173
Apolipoprotein
  A 328
  A1 mimetic peptides 376
  B 355, 357, 358*t*, 361, 376, 390, 474, 540
    containing lipoproteins 368
  synthesis of 376*b*
Apoptosis 540
Arch 23
Arrhythmia 100, 172, 173, 176, 177, 274, 282, 292, 4
  malignant 532
  reperfusion-induced 507
Arrhythmogenic right ventricular
  cardiomyopathy 176, 269, 352
  dysplasia 177
Arrhythmogenic substrate 352
Arterial and venous pressure 207
Arterial blood
  deflection of 130
  gas analysis 44
Arterial compliance 271
Arterial oxyhemoglobin saturation 224
Arterial pulse 3
  evaluation of 5
  palpation of 101
  wave velocity 94
Arterial stiffening 351
Arterial switch
  changes following 15
  operation 311, 312
Arterial thrombosis 292
Arterial wall
  condition of 5
  evaluation, condition of 7
Arteriolar vasodilation 351
Arterioles 437
Arteriovenous
  anastomosis 129
  communication 73
  fistula 129

Artery
infarct-related 507, 531, 536, 624
narrowing of 73
single 439
Arthralgia 137, 239
Artificial intelligence 56, 76, 77, 79, 82
applications of 77
based electrocardiography 78
challenges of 81
current state of 81
future of 81
history of 76
principles of 77
use of 79
wider application of 82*b*
Asana 278
Asbestosis 45
Ascending aorta, leftward 26
Ascites 234
Aspergillus species 160
Aspiration 493
Aspirin 201, 315, 318, 327*f*, 328, 461, 466, 467, 579, 580, 584, 593
absence of 579
dose of 492
free antiplatelet therapy 461
monotherapy 461, 465
plus warfarin 202
resistance 467
response 467
role of 576, 580
treatment 466
Asthma 114
bronchial 113
Asymmetric dimethyl arginine 475
Asymptomatic general population 407, 409*f*
Asymptomatic latecomers 529
Atherogenesis 351
Atherogenic dyslipidemia 416
Atherogenic lipids 358
Atherogenic lipoprotein 357
number of 376
protein of 376
Atheroma components 382
Atheromatous plaque 384*f*
Atherosclerosis 152, 188, 281, 356, 362, 368, 369, 380, 390, 473, 473*fc*, 480, 547, 548, 583
development of 372, 480
leading, role in 548
multi-ethnic study of 381
pathophysiology of 355
prevention of 368
regression of 476
risk factors of 368
risk scores 406
Atherosclerotic cardiovascular disease 343, 355, 358, 361, 368, 374, 387, 390, 390*fc*, 394, 397, 399, 400, 402, 406, 409, 449, 450, 472
cause of 355
prevention of 355
risk assessment 357
risk of 357
Atherosclerotic disease 351, 368
Atherosclerotic lesions 383
Atherosclerotic plaque 380, 548
regression 384
rupture 540
Atherosclerotic process 355
Atherothrombosis 188
pathophysiology of 200
reduction of 199
Atherothrombotic vascular events 199
Athletes
heart 351
specific considerations for 483
Atorvastatin 329, 359, 500
Atretic tricuspid valve 39
Atria 353
Atrial appendage, juxtaposition of 24
Atrial arrhythmia 16, 274
Atrial fibrillation 65, 78, 93, 100, 105, 116, 117, 141, 167, 170, 172, 214, 253, 264, 319, 396, 549, 550, 576, 578, 579, 581*f*, 598, 614
absence of 199
after cardiac surgery, prevention of 550*t*
care 79
diagnosis of 320, 576
history of 271
management of 215, 576
postoperative 551
prevention of 550, 551*t*
Atrial myxoma 73
Atrial natriuretic
factor 407
peptide 242
Atrial septal defect 9, 10, 11*f*, 12, 27, 34, 38, 48, 49*t*, 50, 52*t*, 98, 166, 176, 300
closure of 10
device 28*f*
large 21*f*
left atrium 35
syndromes of 10
Atrial septum, assessment of 37
Atrial switch, after 14
Atrioventricular block 68
Atrioventricular defects 311
Atrioventricular dissociation 65
Atrioventricular septal defect 12, 14, 34, 48, 52
Atrioventricular valve 48, 64
regurgitation 69
Atypical angina 111, 432
Auscultation 56
rise and decline of 56
Auscultatory alternans 65
Auscultatory gap 7
Austin flint murmur 73, 167
Autoimmune processes 272
Automated ECG interpretation 77
Automated oscillometric blood pressure measurement 7
Autonomic dysfunction 293
Autonomic imbalance 7
Autonomic nervous system 188, 279

Autotitrating positive airway pressure 173
Avibactam 159
Aztreonam 158
Azygos vein 313*f*

B

Bacteremia 162
Bacteria 187
Bailout therapy 492
Balloon angioplasty
  plain old 475
  scoring 386
Balloon atherectomy, cutting 386
Balloon atrial septostomy 239, 296, 297*f*
Balloon dilatation 154*f*
Balloon floatation catheters 298
Balloon mitral valvotomy 139
Balloon pulmonary angioplasty 230, 240
Ball-valve mechanism 49
Bare metal 485
  stent 386, 475, 579, 601
Bariatric medicine 449
Barium swallow 24
Baroreflex activation therapy 271
Barrel chest 19
Barth syndrome 176
Bartonella
  diagnosis of 158
  species 160
Baseline electrocardiogram abnormalities 434
Batch size 77
Beats per minute 621
Becker and van Mantgem classification 555*t*
Becker's sign 166
Bedside
  cardiology 1
  echocardiography 514
  evaluation 502
  transthoracic echocardiography 554
Bempedoic acid 331, 358, 377, 391, 392
  coenzyme A 377
Beraprost 239
Beriberi 5
Berylliosis 45
Beta-blockers 128, 183, 207, 242, 326, 327*f*, 330, 370, 476, 483, 558, 592
  use of 592
Beta-hemolytic streptococcal pharyngotonsillitis 144
Beta-lactamase 159
Bias–variance tradeoff 77
Bidirectional functional Glenn shunt 313*f*
Bifurcation lesions 440
Bilateral pleural effusion 562*f*
Bile acid 372
  sequestrants 372
Bileaflet
  mitral valve 154*f*
  valve 149*f*, 150*f*
Bilevel positive airway pressure 173
Biodegradable polymer sirolimus-eluting stent 134
Biofluids 194
Biolimus-eluting stents 475
Biological tissue valves 146
Biomarker
  release, timing of 590*f*
  use of 405
Bioprosthetic valve degeneration 266
Bisferiens pulse 6
Bisoprolol 128, 592
Bivalirudin 492
Biventricular hypertrophy 11, 52
Blalock–Thomas shunt 16, 31
Blalock–Thomas–Taussig shunt 309, 309*f*
Bleeding 523
  academic research consortium 319, 320
  high risk of 596
  major 315, 464*f*
  minor 315
  prevention 599
  risk of 316
  severe 315, 316
  time, modified 7
  treatment 599
Bleeding risk 321*t*, 580, 599
  assessing high 315
  high 253, 315
  increased 203
  minor 253
  stratification of 253*b*
Blood
  contains electrolytes 261
  flow 625
  glucose, fasting 281
  loss, observed 200
  pools 505
  supply, source of 554
  volume 139
    variation of 261
Blood pressure 3, 6, 54, 121, 123, 124, 127, 205, 219, 224, 225, 279, 281*f*, 349, 350, 358, 398, 418, 563, 592
  checkups, regular 368
  control, benefits beyond 213
  cuffless 262
  diastolic 208*f*, 349, 398
    ambulatory 214*f*
  elevated 410
  high 321, 368
  history of high 368
  level 122
  measurement, inaccurate 125
  monitoring, ambulatory 122, 123
  normal 410
  recording 3
  reduction 350*f*
  sensitivity of 418
  systolic 124, 208*f*, 210*f*-213*f*, 326, 349, 398, 406, 434, 561, 592
Body mass index 122, 170, 188, 321, 327, 369, 381, 402, 455, 466, 469

Body surface area 271, 302
Boerhaave syndrome 59
Bombe 19, 76
Bone morphogenetic protein 244
Boot-shaped heart 49, 49*f*
Bosentan 237, 239, 245
Bovine pericardial valves 146
Brachial artery 283
Brachial vein, left 307*f*
Bradyarrhythmias 116
Bradycardia 592
Bradykinin 473
Brain natriuretic peptide 245, 405, 407, 409
  assessment 103
  genes 407
Brain stroke, prevention of 549
Branch pulmonary artery 31
  anatomy 33*f*
Branched-chain alpha-ketoacid 195
  dehydrogenase 195
Branched-chain amino transferase 195
BRAVE-2 trial 531
Breast cancer 342
Breath
  mimicking, shortness of 481
  shortness of 110, 126
Breathing 58
Breathlessness 113, 562*f*
Bridging agent 252
Bridging antiplatelet therapy 256
Bridging glycoprotein 256
Bridging strategy 256
Broken heart syndrome 273
Bromocriptine 99
Bronchial situs 24
Bronchitis, chronic 45
Bronchopulmonary dysplasia 46
Brucella
  diagnosis of 158
  species 160
Brugada syndrome 116, 176
Budd–Chiari syndrome 117
Buddhist meditation 278
Bupropion 400
Burkholderia capaciae 157, 158
Burkholderia pseudomallei 157
Bypass surgery 568

C

Cabergoline 99
Cachexia 117
Calcific aortic valvular stenosis 363
Calcifications, types of 380
Calcified plaque, signature of 382
Calcium 127
  antagonists 602
  arc, center of 382
  around aortic valve 25
  blockers 183
  channel blocker 121, 127, 236, 459, 483, 484, 492, 592, 593
  elevated 381
  nodule 385
Caloric restriction 127
Canagliflozin 128
Canakinumab 328, 330, 476, 627
  anti-inflammatory thrombosis 473
Cancer 221, 224
  cells 243
Candida 158, 162
  albicans 162
  auris 158
    infections 163
  endocarditis 162
Candidemia, delayed resolution of 162
Cangrelor 257, 596
Capillary 437
  filling time 46
  fragility, test for 7
  leakage following reperfusion 504*f*
  rarefaction 504
Car air
  conditioning 186
  purifiers 186
Carbapenem-resistant strains 158, 159
Carbohydrate 123, 192, 416, 417
  cravings 417
  high 418
  with protein, replacing 418
Carbon 193
  monoxide 235
Cardiac abnormalities 369
Cardiac amyloidosis 79, 273
Cardiac anomaly, incidence of 24*t*
Cardiac arrest 223, 224, 291
Cardiac arrhythmia 576
Cardiac auscultation 74, 167
Cardiac axis 9
Cardiac catheterization 33, 296, 308, 606
  basic principles 296
Cardiac causes 115
Cardiac chambers 92
  right-side 74
Cardiac complications 266, 353
Cardiac computed tomography 177
Cardiac crux, internal 41
Cardiac cycle 261, 442*f*
  entire 443
Cardiac damage, biomarkers of 352
Cardiac disease 100
  meditation in 279*f*
Cardiac disorders 176*t*
Cardiac dysfunction, presence of 178
Cardiac dyspnea 114
Cardiac events 281
  risk of 435
Cardiac health 277, 282
Cardiac index 245
Cardiac intervention, sign of previous 27

Cardiac lesions 34
different 24
Cardiac magnetic resonance imaging 77, 86, 95, 177, 183, 432, 433, 446, 458, 532, 561, 612, 613
Cardiac malformations 26
Cardiac malignant deposits, secondary 560
Cardiac malpositions 24
Cardiac metabolism 195
Cardiac metastases 177, 178
Cardiac mortality 472
Cardiac murmurs 161
Cardiac muscle stretch 407
Cardiac myocyte 492
specific troponins 406
Cardiac output 225, 233, 260
decreased 557
Cardiac rehabilitation 282, 328, 518, 626
exercise-based 326
facilities 328
Cardiac remodeling 409, 622
Cardiac resynchronization therapy 106, 270, 626
Cardiac risk
factors 327
reduce 414
Cardiac rupture 560
causes of 560
Cardiac sarcoidosis 79, 274
Cardiac shunts 307
Cardiac silhouette, enlarged 25
Cardiac specific troponin 589
Cardiac status, detecting 76
Cardiac structure
anatomy of 19
arrangement of 19
interpretation of 19
Cardiac surgery 470, 555
Cardiac symptoms 109
interpretation of 109
significant 117
Cardiac syncope
causes of 115
history of 115
Cardiac tamponade 5, 228
Cardiac total anomalous pulmonary venous connection 35*f*
Cardiac transplant 555
Cardiac troponin 406
determinants of 407
use of 406
Cardiac tumors, primary 560
Cardiac valves 169
Cardiobacterium hominis 157
Cardiogenic pulmonary edema 114
Cardiogenic shock 148, 220, 226, 523, 533, 536, 537, 555, 557, 589, 609, 609*f*
Cardiology 79, 449, 547
preventive 323
Cardiometabolic conditions 293
Cardiometabolic disease 449, 449*b*, 450
Cardiometabolic medicine 449, 450*f*
Cardiometabolic risk, reducing 413
Cardiometabolic syndrome 413, 420, 449
Cardiomyocytes 504
Cardiomyopathy 5, 68, 114, 176, 269, 271, 291, 454
dilated 176, 178, 269, 352, 452, 456
nonclassified 269
primary 455
secondary 456
specific 271
symptom of 269
type of 175
Cardioprotective agents 330
Cardioprotective properties 415
Cardioprotective therapies 326*f*
Cardiopulmonary exercise testing 237, 248
Cardiopulmonary resuscitation 227, 563
Cardiovascular clinical manifestations 292
Cardiovascular complication 171*f*
Cardiovascular death 203, 358, 408, 468, 494
Cardiovascular disease 121, 170, 171, 185, 186, 192, 205, 274, 277, 293, 341*f*, 349, 361, 377, 396-401, 405, 406, 413, 415*f*, 449, 452, 454, 520, 525, 547, 548, 549*t*, 576
applications of 194
development of 279
incidence of 188, 414*f*
management of 283
meditation for 281
mortality of 288, 414*f*
epidemiology of pollution-induced 186
nature of 186
primary prevention of 394, 397
risk factors for 414
risk of 188, 547
secondary prevention of 547
types of 214
Cardiovascular disorders 3
Cardiovascular event 410, 547
major 418
risk for 411
Cardiovascular health 349
study 271
Cardiovascular manifestations, long-term 293
Cardiovascular mortality 172, 203, 405, 547
rates 414
Cardiovascular outcomes 475
Cardiovascular protective agents 330
Cardiovascular risk
factors 279, 521
history of 201
prediction 195
reducing 328*t*
stratification 405
Cardiovascular silhouette 22
Cardiovascular societies 396*t*
Cardiovascular system 283, 293*f*, 349, 446*f*
Carditis 137
diagnosis of 137, 139*t*
Carey coombs murmur 73
Carina shift 440

Carotid artery
external 152
internal 152
thrombosis 383
upstroke 101
Carotid baroreceptor
activation therapy 129
stimulation 129
Carotid bifurcations 540
Carotid bulb 129
Carotid intima-media thickness 335, 338, 395, 397
Carotid sinus stimulation, effects of 129
Carpentier classification system 100, 100*f*
Carpopedal spasm 7
Carvallo's sign 69, 168
Carvedilol 128, 592
Caspofungin 162
CAT RX
advantages of 494
mechanical aspiration system 494*f*
Catabolic pathway 195
Catabolize 192
Cathepsins 541
Catheter 298, 438
based invasive indices 438
diagnostic 298*t*
manipulation 298
multi-purpose 298
Catheterization 304, 425
Ceasing cigarette smoking 369
Cefazolin 161
Cefepime 158
Cefiderocol 160
Ceftazidime 158-160
Ceftolozane 159
Ceftriaxone 158
Cell
adhesion molecules 500
dead 505
subsequent 293
Cellular necrosis 505
Cellular proliferation 339
Central cyanosis 44
Central executive network 280
Central nervous system 201, 279
Central pulmonary arteries 20
Central venous pressure 5
Cerebral angiogram 154
Cerebral embolism 110
Cerebrovascular accidents 117, 321
Cerebrovascular disease 172, 394
Cervical cone biopsy 253
CETP gene 341
Chain amino acids 195
Chemotherapeutic agent 370
Chest
auscultation 59
deformity 45
discomfort 109, 110
radiograph 49, 50*f*, 102
X-ray 49*f*, 50*f*, 220, 234, 617
Chest pain 58, 206, 273, 292, 511*f*
atypical 111
character of 432*t*
differential diagnosis of 112*t*
nonanginal 432, 562*f*
type of 59
Chitra mitral tilting disk 152*f*
Chitta vritti nirodha 278
Chlamydia
endocarditis 158
species 160
Chlorthalidone 122
Choanal atresia 45, 46
Cholecystitis 59
Cholesterol 326, 328, 336, 356, 371*t*, 389
absorption inhibitor 600
exposure 370*f*
high 279
oxidation 377
synthesis 374
total 281, 397, 401, 402, 416, 520
treatment trialists 329, 356
Chordae tendineae rupture 99
Choussat criteria 313*t*
Chromosomal locations 339
Chronic coronary syndrome 326, 461
Chronic diseases 283
Chronic inflammatory
diseases 400
disorders 547
Chronic kidney disease 122, 123, 126, 293, 358, 381, 390, 396, 399, 450, 466, 467, 469, 596, 601, 622
Chronic mitral regurgitation 99, 100
treatment of 105
Chronic obstructive pulmonary
disease 45, 59, 113, 114, 293, 386, 396, 456, 622, 624
vascular disease 135
Chronic renal
failure 7
insufficiency cohort 123
Chronic thromboembolic pulmonary hypertension 226, 230
treatment of 230
Cigarette smoking 381
Cingulate cortex, anterior 280
Cirrhosis 5
Classic peripheral stigmata 157
Clinical cardiac examination 87
Clinical probability, assessment of 220
Clonidine patch 128
Clopidogrel 134, 202, 257, 328, 466, 467, 469, 492, 593, 594*f*-596*f*
absorption 468
bioactivation 468
platelet inhibition 465
plus aspirin 134
resistance 466, 467, 594
response, deceased 469
responsiveness 468

Close cardiac diagnoses 64
Cloxacillin 161
Coagulation cascade 200*f*
Coagulation profiles 281
Coarctation of aorta 6, 14, 126
  signs of 26
Coarctation stent 28*f*
Cobra catheter 298
Cocaine 583, 592
Coconut oil 416
Coenzyme 385
Coexisting anomaly, characterization of 37
Cohort studies 372
Colchicine 328, 514, 547-550, 550*t*, 627
  clinical trials of 548, 549
  low-dose 548
  mechanisms of 549*t*
  ongoing clinical trials of 550
Colchicum autumnale 547
Colcot trial 549
Colistimethate 159
Colistin 159
  plus 159
Collagen turnover 548
Collateral flow 26
Colonic polypectomy 253
Color Doppler flow imaging 618
Combination therapy 244
Common arterial trunk 16, 27
Common femoral
  artery 153
  vein 153
Communicable disease 337
Communication, abnormal 309*f*
Community 402
Comorbid lifestyle factors 327
Comorbidity 214
Competitive athletes 351
Complement pathway inhibitors 627
Complementary therapy, role of 281
Compression ultrasonography 222, 223
Computed tomography 33, 86, 94, 395, 432, 438, 458, 613
  angiography 126, 382, 433
  comparing effectiveness of 133
  coronary angiography 583
  pulmonary angiography 220-222, 228, 230
Computers 57
Concomitant P2Y12 inhibitor 580
Cone-beam CT 230
Congenital bicuspid aortic valve 85, 88
Congenital coronary artery fistula 74
Congenital emphysema 45
Congenital extrahepatic portosystemic shunt 308
Congenital heart defects 175
Congenital heart disease 9, 18, 30, 46, 109, 110, 114, 176, 177, 265
  diagnosis of 48*t*
  postoperative cyanotic 308
  secondary prevention in 331
Congenital hypoplasia 207
Congestive cardiac failure 5, 114
Congestive heart failure 45, 141, 144, 213, 253, 282, 407, 591
Connective tissue disorders 161
Consciousness, loss of 115
Conservative management 178
Conservative therapy 607
Conservative treatment, role of 564
Constrictive pericarditis 6
Contemporary cardiology 54
Continuous noninvasive techniques 7
Continuous positive airway pressure 124, 170, 173
  therapy 476
Contraception 235
Contralateral kidney 207, 208
Contrast nephropathy, risk factors for 535*b*
Convex left heart border 24*f*
Convolutional neural network 76, 77, 78*f*, 80
COPPS POAF sub-study 550
COPPS-2 trial 550
Coronary anatomy 301
Coronary angiogram 485, 510*f*
  coregistration 442*f*
Coronary angiography 81, 426, 429, 437, 481, 484, 517, 555, 583, 589
  primary 513*f*
Coronary anomaly 14
Coronary artery 31, 312*f*, , 516, 540, 569, 569*f*
  anatomy 568, 569*t*
    delineation of 37
  aneurysm 583, 586, 586*f*c
    management of 584, 586
  blockages 262
  blood flow 437
  bypass 519
  bypass graft 106, 253, 317, 427, 441, 452, 472, 484, 518, 523, 550, 566*t*, 576, 583, 485, 586, 591, 626
    surgery 599
  circulation 175
  dominance 568
  ectasia 583, 584
  involvement of 516
  left 15*f*, 60, 510, 569
  nonostial left main 439
  occluded right 512*f*
  proximal right 573*f*
  single 616
  stenting 577, 578
  surgery study 433
Coronary artery calcification 380, 385, 386
  detect 382
  epidemiology of 381
  types of 382, 383
Coronary artery calcium 338, 353, 400, 400*t*, 401
  progression, medical therapies for 385*t*
Coronary artery disease 56, 60, 80, 69, 99, 106, 109, 110, 121, 170, 172, 177, 199, 262, 264, 265, 325, 340*f*, 343, 344*f*, 380, 409, 427, 431, 433*t*, 439, 444, 449, 452, 453, 472, 484, 535, 547, 549, 576, 591
  absence of 177, 269
  diagnosis of 431, 432*t*
  history of 370

malignant 364
management of 133
prevention in 325
risk factors for 588
risk stratification of 380
significance of 427
stable 431
treatment of 431
Coronary artery dissection
natural history of spontaneous 516
pregnancy-associated spontaneous 517
prevalence of spontaneous 517*t*
treatment of spontaneous 518
Coronary artery occlusion 522
left main 569, 570*f*
Coronary artery stenosis 394
intermediate 445
localization of 262
regression of 281
Coronary artery system 454*f*
functional anatomy of 453
Coronary atheroma 500
Coronary atherosclerosis 351, 472, 474
Coronary blood flow 518, 605
effect of 480
Coronary bypass grafting 265
Coronary calcification
clinical significance of 382
pathophysiology of 380
risk factors for 381*t*
Coronary calcium 395, 399
Coronary cath lab 439
Coronary circulation 438
segmental anatomy of 569*f*
Coronary computed tomography angiography 480
Coronary cusps, right and left 88
Coronary ectasia 583
Coronary endothelial function 475
Coronary events
acute 113*t*, 114*t*, 385, 600
major adverse 133
Coronary flow
reserve 60, 444-446, 455, 458
velocity 458
velocity
ratio 457
reserve 440
Coronary heart disease 99, 107, 110, 186, 237, 281, 325, 326, 341*f*, 342, 356, 369, 370, 380, 394, 400, 405, 521
risk of 279, 361
Coronary intervention 583
Coronary lesions, calcified 386*t*
Coronary magnetic resonance angiography 584
Coronary microcirculation 456
Coronary microvascular
disease 443, 446
dysfunction 60, 444, 444*f*, 452-454, 455*f*, 456, 458, 458*fc*, 458*t*, 459
causes of 457*f*
classification of 452*t*
extent of 453*f*
endothelial dysfunction 472
syndromes 447
Coronary physiology
evaluating 427
indices 446*t*
invasive 438*fc*
noninvasive 438*fc*
Coronary pressure, resting distal 443
Coronary risk prediction tools 338*t*
Coronary sinus 25, 307
Coronary stenosis 281
Coronary stenting 320
Coronary thrombus 489, 491*f*
Coronary vasculature 437
Coronary vasospasm 481
Coronavirus disease-2019 (COVID-19) 54, 291, 291*f*, 292, 293, 293*f*, 548
complication of 292
diagnosis of long 292
era 56
infection 292
acute 293
long-term 292
pandemic 56, 132, 394
Cor-pulmonale 5
Corrigan's pulse 6
Corrigan's sign 166
Corticosteroids 370, 399
Cortisol 280
Corynebacterium diphtheriae 157
Cough 58, 109, 110, 117
Counterclockwise loop 13*f*
Counterpulsation, enhanced external 459
Coxiella burnetii 157
C-reactive protein 283, 293, 330, 406, 474, 549, 613
high-sensitivity 243, 328, 590
Creatine kinase 391
myocardial band 112, 499
Creatine phosphokinase 372
Creatinine
clearance 317
kinase 406
Critical valvular pulmonary stenosis 50*f*
Culprit artery 568, 571*t*, 572*f*, 572*fc*, 574, 575
crucial role in 572
Culprit vessel 535
Culprit-only lesion 599
Cushing's syndrome 126
Cut pigtail catheter 298
Cyanosis 19, 44-46, 109, 306
cardiac cause of 47*t*
cause of 46, 51, 52*t*
hematologic causes of 46
metabolic causes of 46
neurological causes of 46
provokes erythrocytosis 297
respiratory cause of 47*t*

Cyanotic congenital heart disease 30, 46-48, 50*fc*, 53*fc*, 295, 299
classification of 295, 296*t*
diagnosis of 9, 52*t*, 295
hemodynamic classification of 48*t*
management of 9, 295
Cyanotic heart disease 304
Cyclic adenosine monophosphate 467
Cyclooxygenase 467
inhibitors 315
Cyclopentyltriazolopyrimidines 467
Cyclosporine 124
CYP2C19 LOF alleles 469
CYP2C19-negative 468
Cysteine residues 473
Cytochrome P450 374, 376, 467
isoenzymes 374
Cytosolic calcium 243

D

Dabigatran 228, 258, 579
Daggett technique 555
Dapagliflozin 270
Daptomycin 161
Dasatinib 244
David technique 555
D-dimer testing 221
de Musset's sign 166
Deep vein thrombosis 218, 221, 229, 386
De-escalation, unguided 134
Defective autophagy 387
Degenerative calcific valve 165
Dehydration 115
Dehydroepiandrosterone 242
Delayed activation wave 574
Deoxygenated blood 45
Deoxyribonucleic acid 370
Depression 188, 283, 434, 518, 602
circulatory 592
Descending artery
left posterior 569
posterior 569
Device
implantation 258
selection 619
Device-guided slow breathing 128
Dextrocardia 9, 20*f*, 24, 47
Dharana 278
Dhyana 278
Diabetes 116, 253, 293, 372, 409, 449, 455, 466, 469, 622
absence of 132
diagnostic criteria for 398*t*
management 330
mellitus 46, 80, 122, 133, 264, 277, 283, 317, 357, 381, 390, 398, 399, 435, 521, 523, 588, 591, 596, 601
type 2 172, 342, 408
uncontrolled 389
presence of 132
treatment of 450
Diabetic patient 410, 510*f*
category of 398
Diabetology 449
Diagnostic testing strategy 458*fc*
Dialysis, duration of 381
Diametric stenosis 427
Diaphoresis 517
Diaphragm, position of 19
Diarrhea 238, 239
Diastolic dysfunction 68, 177, 353
development of 481
Diastolic function 176, 273
Diastolic murmur 71
causes for 167
Diastolic sounds 167
Dicrotic pulse 6
Dietary modification 327
Dietary quality 189
Dietary salt restriction 127
Diet-heart hypothesis 414
Diffuse ectasia 584*f*
Diffuse fibrosis 353
Digoxin 235
Dihydropyridine 117, 592
derivatives 602
Diluted thrombin time 258
Dipeptidyl peptidase, inhibitors of 244
Direct stenting 495
Direct thrombin inhibitors 597
Disability, years lived with 413
Disability-adjusted life years, number of 413
Discharge, risk stratification on 599
Disease-modifying therapy 627*t*
Disequilibrium 342
Disopyramide 459
Disparity 525
Distal coronary
artery 456
pressure 438, 442
Distal pulmonary arteries 234
Distal vessel 494
Diuretic therapy 104
Dobutamine 482, 590
echocardiography 85, 86, 93, 93*fc*
Dock's murmur 72, 167
Downstream stenosis 440
Doxazosin 128
Drug 192
addicts 592
adherence 211
eluting 485
therapy, triple 247*t*
Drug-drug interaction 374, 467
Dual antiplatelet 576
theory 581
Dual antiplatelet therapy 199, 202, 252, 255, 256, 316, 319, 328, 461-464, 466, 576, 578, 580, 584, 594, 595, 598
advent of 612

duration of 461
score 316
shortened duration of 461
short-term 463
Dual antithrombotic therapy 577, 581*f*, 582
Dual drug therapy 247*t*
Dual pathway inhibition 199
Dual-chamber pacing 184
Ductal dependent systemic circulation 42
Ductus arteriosus 37
Duke treadmill score 434
Duroziez's sign 166
Dynamic auscultation 101
Dynamic resistance exercise 350
Dysautonomia 7
Dysfunctional energy 502
Dyslipidemia 277, 355, 368, 370, 372, 374, 381, 399, 416, 454, 455
management of 374, 375, 391, 391*t*, 500
secondary 373
forms of 370
Dyspnea 109, 110, 114, 59, 110, 113, 115, 117, 147, 239, 520
differential diagnosis of 114*t*
exertional 87, 142
special types of 114
Dysrhythmia 291

E

Ear lobes 44
Early diastolic
murmurs 71
sounds 68
Early intensive
rosuvastatin therapy 499
strategy 599
Early reperfusion therapies 553
Ebstein's anomaly 16, 27, 41, 49, 175-177
Ebstein's severity 41
Ebstein's syndrome 311
Echinocandins 163
Echocardiogram 79, 272
Echocardiography 30, 34, 50, 56, 103, 222, 226, 234, 248, 584, 613, 618
assessment 273
evaluation 87
Economic burdens 405
Eco-nutritional diseases 189
Ectopic beats 116
Edema 109, 110, 234, 419, 505
Edge-to-edge clip plays 105
Edoxaban 228, 254, 258, 329
Ehlers–Danlos syndrome 518
Eikenella species 157
Eisenmenger syndrome 11, 237
Ejection fraction
normal 265
reduced 132, 270, 450
Ejection sounds 68
Ejection systolic murmur 49, 71, 165
Electrical conduction 260
Electrical device implantation 258
Electrocardiogram 49, 51*f*, 52*t*, 102, 182, 234, 431, 433, 442, 532, 589, 591, 617
limitations of 574
Electrocardiography 50, 177, 260
Electrolyte abnormality, detection of 79
Electronic nicotine delivery system 400
Electronic stethoscopes 55
Elizabethkingia endocarditi 158
Embolic protection device 495
Embolized thrombus 155*f*
Embryology 175
Emergency
balloon mitral valvotomy 142*f*
department care 104
medical service 600
procedures 258
surgery 151
toxicology 621
Empagliflozin 132, 270, 450
End organ failure, absence of 555
End-diastolic
frames 511*f*
murmur 48
volume 98, 264
wall thickness 507*f*
Endocardial fibroelastosis 177, 178
Endocardial ischemia, role of 175
Endocarditis 160
atypical infective 157
culture negative 160
Endocrine 368
disorder 369
Endogenous neurohormonal systems 236
Endogenous triglycerides 389
Endomyocardial biopsy 274
Endomyocardial morphogenesis 175
Endoplasmic reticulum 243, 387
Endothelial cell 503
infiltration 293
Endothelial dysfunction 188, 454, 472, 474-477
assessment of 475, 475*t*
biomarkers of 475
clinical implications of 474, 474*f*c
mechanisms of 474
plays 401
role of 476
Endothelial function 282, 472, 498
assessment of 474
Endothelial shear stress 474
Endothelial turnover 541
Endothelin 474
A 237
antagonist 237
B 237
receptor antagonist 235, 247
Endotheliocytes 504

Endothelium 390, 454
derived
hyperpolarizing factors 474
vasoconstrictors 474
vasodilators 473
loss of 454
End-stage disease 271, 455
End-stage heart disease 278
End-systolic
diameter 104
volume 98
Endurance exercise, chronic 353
Enoxaparin 492
Enterobacteriaceae 163
Enterococcus faecalis 157
Environment and cardiovascular health 185
Enzyme 391, 467, 589
pathway 375
reductase 374
Enzyme-linked immunosorbent assay 221
Eosinophilic endomyocardial disease 178
Eosinophilic myocarditis 177
Epicardial artery 281, 437
Epicardial coronary artery 439, 605
normal 459
Epicardial flow indices 443
Epicardial spasm 444
Epicardial stenosis severity, overestimation of 437
Epicardial tissue 482*f*
Epicardial vessels 437
Epicardium 483*f*
Epidermal growth factor 243
Epigenetic changes 288
Eplerenone 122
Epoprostenol 238, 239, 245
Eptifibatide 315, 492
Erb's palsy 46
Erectile dysfunction 449
Ergotamine 99
Erosion 540
Esophageal rupture 59
Esophagus 24
Estimated glomerular filtration rate 208, 255, 358, 409, 427, 591
Estimating coronary flow directly 443
Estradiol 241
Estrogen 218
Estrogen-containing
contraceptives 273
oral contraceptive agents 218
Ethical disparities 521
Ethnicity 362, 395
Everolimus-eluting stent 542
Evinacumab 341, 358, 359, 375, 391, 392
Exercise 127, 349, 377, 419
capacity 238, 433
enhances 326
chronic 351
concurrent 353
damage previously normal heart 352
effects of 352*f*
electrocardiogram 433, 434
testing 433, 434*t*
electrocardiography 432
intolerance 117
physiological effects of 350, 351
stress testing, current status of 431
testing 103
types of 349
Exertional dyspnea, symptoms of 273
Exogenous hormone 518
Extended-spectrum beta-lactamase 158, 159
Extensive disease 162
Extra virgin olive oil 415
Extracardiac disease 575
Extracardiac structure 19
Extracellular edema 514
Extracellular matrix 472
Extracorporeal membrane oxygenation 219, 225, 227, 555, 562
veno-arterial 620
central 620
peripheral 620
Extreme kyphoscoliosis 45
Eye 126
movement, nonrapid 124
Ezetimibe 329, 331, 358, 365, 372, 375, 376, 399, 600

F

Fabry's disease 85
Factors influencing vascular tone 473*f*
False lumen 517
Familial hypercholesterolemia 357, 358, 370, 392, 399, 540
genetic diagnosis of 372
Familial hyperlipidemia 472
Fast-myocardial infarction program 532
Fatal bleeding 201, 202
rates of 203
Fatigue 109, 110, 115, 117
chronic 419
Fats in oils, composition of 416*t*
Fatty liver 449
Felodipine 593
Femoral artery, superficial 155*f*
Fetal echo 40, 41
Fiber 127, 417
Fibrinogen 468, 489
Fibrinolysis 155*f*, 607, 609
contraindications to 226
Fibrinolytic therapy 151, 155*f*, 529, 553, 605, 607, 609*f*
trialists 607
Fibrinopeptide A 200
Fibroatheroma 382, 541
Fibrosis 236, 625
Fibrotic transformation 230
Fibrous 382
plaque 382
Figure of eight 23*f*
Film, exposure of 19

First diagonal branch 572
First medical contact 606
First septal branch 572
Fistula 28*f*
Flail mitral leaflet, partial 99
Flash pulmonary edema, acute 619
Flexible stenotic valve 166
Florid pulmonary edema 617
Flower myocardial infarction trial 134
Flow-limiting obstruction 425
Fluorodeoxy glucose 490
Flushing 238
Fluvastatin 359
Foam cells 541, 548
Fogarty balloon 155*f*
  embolectomy 154
Fondaparinux 225, 492
Food additives 192
Foot, soles of 44
Force, volume, and tension, causes of 5
Fosfomycin 159
Fourier trial data 389
Fractional flow reserve 425, 428, 429, 433, 438, 440-442, 444, 446, 482, 484
  role of 439
  testing, method of 440
  use of 134
Framingham heart study 271
Free thyroxin 126
Free wall rupture 554, 560
  diagnosis of 561
  management of 563*fc*
  surgical repair techniques of 563*fc*
Free-fatty acids 392
Friedrich's sign 5
Frontopolar prefrontal cortex 280
Fungi 160

G

Gadolinium 178, 613
Gallavardin phenomenon 166
Gamma-aminobutyric acid 279, 280
Garlic extract 385
Gas chromatography-mass spectrometry 193
Gastritis 517
Gastroesophageal reflux 517
Gastrointestinal bleeding 593
Gastrointestinal conditions 59
Gender 362
  difference 271
    causes for 521, 521*f*
  specific risk 401
Gene
  mutations 176*t*
  therapy 459, 476, 628
General cardiology 119
General supportive measures 235
Genesis and timing 64
Genetic 176
  risk factors 338
  risk score 335
  testing, role of 177
Genome 342, 628
  wide association studies 343
  wide polygenic risk score 343
Genotyping 466
  infarct 469
  role of 466
  score 469
Giant aneurysm 583, 585*f*
Giant cells, multinucleated 274
Gibson's murmur 73*f*
Glenn shunt 39
Global left hemodynamic load 93
Glomerular filtration rate, dysfunction-reduced 381
Glucagon-like peptide 328
Glucocorticoids 627
Glucose
  challenge test 544
  disorders 381
  insulin-potassium infusion 514
  metabolism 214
  tolerance 279
Glycated hemoglobin 122, 328, 402, 590
Glycemic index 420
Glyceryl trinitrate 444, 446
Glycoprotein 255, 257, 257*f*, 489, 491, 585, 585*f*, 593, 597
  inhibitors 257, 315, 492, 597
G-protein 242
G-protein-coupled receptor 242
  pathways 242
Graham Steell murmur 72, 167, 168
Great artery 41, 401
  congenitally corrected transposition of 14, 48
  corrected transposition of 47, 305, 305*f*
  dextro-transposition of 14, 36, 37. 37*f*, 38, 38*f*, 303, 305
  imaging transposition of 37
  L and D transposition of 303
  level of 304
  single 40*f*
  transposition of 16*f*, 24*f*, 26*f*, 48, 49, 52, 53
  types of 33
Great vessel
  left transposition of 14
  transposition of 298
Groundnut oil 416
Growth factor
  beta, transforming 244
  receptors 243
Guanfacine 128
Guideline-directed medical therapy 60, 106, 271, 601
Guillain–Barré syndrome 46
GUSTO bleeding 316
Gut microbiome 195
Gynecological bodies 401

H

Haemophilus 157
aphrophilus 157
parainfluenzae 157
Hair and skin, poor quality of 419
Half-moon sign 482, 482*f*
Hammer pulse 166
Headache 206, 238, 239
Healed plaque rupture 382
Healthcare
centers 402
quality and research 337
system 125, 281
Healthy diet 327
Healthy fat 413, 414
Healthy food 328*t*
Healthy lifestyle 186
Heart 126, 208, 368
ailments of 110
catheterization, left 618
dilated 27*f*
healthy 416
rupture, risk of 561
strong 402
structurally normal 306, 308
team 558
tissue 194, 293
transplantation 106, 178, 233
univentricular 39
Heart attack
ready 530
trial, prevent 123
Heart block 617
complete 50
Heart disease 45, 170, 238, 266, 278
hypertensive 177, 178
infiltrative 456
mechanism of 278
pericardial 110
risk factors of 369
Heart failure 47, 67, 80, 102, 105, 116, 122, 132, 170-173, 177, 194, 195, 213, 269, 270, 291, 292, 405, 449, 453, 455, 456, 503*f*, 509*f*, 520, 521, 523, 524, 532, 554, 578, 602, 608, 623, 625
acute 502, 507
decompensated 178
advanced 271
chronic 110, 224, 547
diagnosis of 116
etiology of 77
events, reducing 133
left-sided 141
management of 411
manifestations of 141
medications 272
pathogenesis of 177, 195, 213
prevalence of 292, 622
refractory 508*f*
right 234, 243
risk of 186
severe 607
signs of 100
symptoms of 100, 117*t*, 272
taming 132
trials in 132
vasodilator 270
Heart rate 125, 139, 207, 353, 561, 592, 593
reduce 330
variability 279
Heart sound 4*t*, 64
first 64, 165
fourth 49, 59, 64, 67, 67*f*
second 49, 65
third 66, 67*f*, 101
Hematologists 252
Hemi vertebra 19
Hemodynamic
causes 147
guided management 133
information 260
insignificant shunt 555
instability 272
suspected pulmonary embolism 228
measurements 238
parameters 262
stabilization 226
support 555
Hemopericardium 555*f*
Hemoptysis 109, 110, 117
Hemorrhage 382, 384, 505
intracerebral 202, 580
intramyocardial 505, 625
Hemorrhagic bleeding, nonintracranial 608
Hemostatic causes 147
Heparin 597
unfractionated 151, 219, 227, 266, 594, 597, 598
Hepatic adjustment 201
Hepatic aminotransferases 237
Hepatic lipase progressively hydrolyze triglycerides 376
Hepatic vein congestion 117
Hepatocytes 374
Hepatology 449
Hereditary hemorrhagic telangiectasia 45
Hess's tourniquet test 7
Heterogeneous mixture 185
Heterozygous familial hypercholesterolemia 370, 376
Hexosamine biosynthesis pathway 195
Hickman's catheters 158, 163
High output states, causes of 5
High thrombotic risk 254
High-density lipoprotein 280, 337, 351, 356, 369, 371, 390, 397, 402, 416
cholesterol 389, 402, 406
High-intensity
interval training 419
statin 358, 384, 500
Hill's sign 7, 166
Histoplasma species 160

Holosystolic mitral regurgitation murmur 102
Holosystolic murmur 70*f*, 102, 167
Holt-Oram syndrome 19
Home sleep apnea test 170
Homograft cadaveric valves 146
Homozygous familial hypercholesterolemia 365, 370
  treatment of 376
Honey-combing pattern 49
Hormone 242
  circulating 241
  replacement therapy 124, 270, 365, 401
Hospital readmissions 270
Host-exam trial 463
Hounsfield unit 382
Human atheromata 542*f*
Human environment 187*f*
Human immunodeficiency virus 400
Human monoclonal antibodies 372
Hydralazine 128
Hydrochlorothiazide 385
Hydrogen 193
Hydrolyze penicillins 158
Hydrostatic mechanisms triggers 350
Hydroxyestrone 241
Hyperbaric oxygen therapy 514
Hypercalcemia 381, 382
Hypercapnea 172
Hypercholesterolemia 336, 340, 368, 369, 371, 397
  awareness of 356
  detection of 370
  diagnosis of 370
  management of 371
  primary 365
  severe 356
Hypercoagulable state 147
Hyperdynamic states 69
Hyperechoic tissue, superficial 383*f*
Hyperemia 425, 438, 445, 457
  maximal 438
Hyperemic medications, elimination of 442
Hyperemic microvascular resistance 458
Hyperglycemia 588
Hyperhomocysteinemia 589
Hyperinflation, unilateral 49
Hyperinsulinemia 588
Hyperlipidemia 588
Hyperoxia test 46
Hyperparameters 77
Hyperparathyroidism, secondary 384
Hyperphosphatemia 381, 382
Hypertension 5, 116, 126, 171, 205, 237, 253, 264, 277, 280, 283, 350, 368, 381, 397, 449, 454, 521, 523, 588, 591, 622
  arterial 372
  causes of secondary 126*t*
  classification of 398*t*
  clinical 129
  drug-resistant 7, 124*t*
  early stages of 280
  episodic 7
  exercise pulmonary 234
  intracpulmonary 306*f*
  isolated systolic 398
  management of 121
  masked 7
  mediated organ damage, assess for 126
  mild-to-moderate 210
  orthostatic symptoms with 7
  persistent pulmonary 48, 49
  primary 368
  radiance 212
  refractory 122, 122*f*
  renal denervation for 129
  resistant 122
  screen for secondary 125
  secondary 121
  stop 127
  symplicity 210
  systemic 68, 456
  systolic 123
  treatment of 214, 369
    targets of 398*t*
  uncontrolled 121, 122*f*
  whitecoat 7
Hyperthyroidism 126
Hypertriglyceridemia 588
  treatment of 359
Hypertrophic cardiomyopathy 4, 78, 80, 99, 166, 176, 178, 181, 269, 273, 452, 454, 455, 457
  apical form of 177
  type of 178
Hypertrophic obstructive cardiomyopathy 116
Hyperuricemia 123, 589
Hyperviscosity 147
Hypocapnia 220
Hypokalemia 115
Hyponatremia 115
Hypoplastic heart syndrome
  left 41, 48, 175, 311
  right 52
Hypoproteinemia 117
Hypotension 5, 93, 592
Hypothalamic–pituitary–adrenal axis 279, 280
Hypothyroidism 117, 126
Hypovolemia 228
Hypoxemia 172
Hypoxia, correction of 226
Hypoxic coagulation necrosis 616

I

Iatrogenic coronary microvascular dysfunction 456
Idarucizumab 258
Idiopathic pulmonary
  arterial hypertension, management for 236
  fibrosis 236
Iliofemoral arteries 540
Iloprost 239
Imatinib 244

Immune modulatory 243
Immunoglobulin G 490
Immunomodulatory agents 514
Impedance cardiography
  emerging role of 260
  lies, role of 262
  principle of 260
Impella 620
Implancardioverter defibrillator 80, 184, 270, 282
Incident cardiomyopathy, detection of 79
Inclisiran 341, 359, 392
Indapamide 128
Index angina 112
Infarct exclusion technique 619
Infarct inclusion technique 619
Infarcted tissue 561
Infarction 58, 59, 68, 195
  etiology of 625
Infection 221, 396, 583
  recurrent 419
Infectious disease 187
Infective endocarditis 99, 146, 157, 168, 198
  atypical organisms causing 158
Inflammation 200*f*, 221, 362, 416, 505, 557
  chronic 623
  modulators 627
Inflammatory bowel disease 342
Inflammatory cytokines 283
  activation of 623
Inflammatory diseases, acute 161
Inflammatory mediators 243
Inflammatory metabolic hypothesis 271
Inflammatory substance 548*t*
Inflation-deflation cycles 514
Influenza
  season 547
  vaccine 133, 547
Inhibits thrombin 597
In-hospital mortality 114*t*, 524
Initial anticoagulation 225
Initial upfront combination therapy 246
Inotropes 620
Inotropism 593
Inspiratory increase 5
Instantaneous wave-free ratio 442
Insulin
  dependent 317
  growth factor 544
  receptor 351
    substrate 351
  resistance 279, 417, 418
    syndrome 281
  signaling 351
Intact interventricular septum 14
Intact ventricular septum 34, 48, 50, 52
Intensity 65, 359*t*, 391*t*
Intensive care unit, prolonged 557
Interatrial septum 298, 300
Intercostal space 49, 165
Interheart risk score 337
Interleukin 279, 362, 548, 549
Internal body states 280
Internal carotid artery, right 153*f*
Interquartile range 213
Interrupt anticoagulation 252
Interrupting sedentary spells 419
Interruption, timing of 253, 256
Interstitial lung diseases 45
Interventional cardiology 81
Interventional therapy 239
Interventricular septal rupture 553
Interventricular septum 295, 298, 533
  anterior 506*f*
  mid anterior 512*f*
Intimal hyperplasia 454
Intimal-luminal interface 382
Intra-aortic balloon 104
  pump 562, 620
Intracardiac thrombosis, extent of 495
Intracoronary Doppler 484
Intracoronary nitroglycerin 481
Intracoronary thrombolysis 492
Intracoronary thrombus 490
  large 489
  pathophysiology of 489, 490*f*
Intracranial hemorrhage 200
  bleeding 608
Intramural hematoma 517, 616
  large 561
Intraprocedural bleeding 252
Intravascular lithotripsy 385
Intravascular ultrasound 230, 383, 384, 481, 490, 500, 583
Intravenous antiplatelet agents 514, 596
Intravenous fluid 562*f*
Intravenous infusion 257
Intravenous unfractionated heparin 225
Invasive coronary
  angiography 60, 433
  imaging 133
Invasive hemodynamic indices 438
Invasive hyperemic indices 438, 443
Invasive management 178
Invasive methods 475
Invasive nonhyperemic indices 441
Invasive procedure, timing of 599
Inversion-recovery gradient echo 183
Ion channel 243
  disease 351
Iron
  deficiency 244
  infusion 244
Irreversible injury 502
Ischemia 15, 59, 99, 208, 426, 443, 453, 481, 530, 570, 593, 625
  degree of 426*f*
  diagnosis of 433, 589
  guided approach 599
  reperfusion injury 505, 623
  signs of 483

Ischemic cascade 502
schema of 503*f*
Ischemic electrocardiogram 457
Ischemic episodes 599
Ischemic events 591
low risk of 596
Ischemic heart disease 114, 115, 122, 186, 262, 335, 336*f*, 390, 397, 401, 435, 588, 627
prevalence of 402
spectrum of 588*f*
Ischemic stroke 394, 466, 608, 614
moderate-to-severe 317
Ischemic syndromes, strategies for 550
Isolated aortic
regurgitation 197, 198
stenosis 198
Isoleucine 195
Isomerism 9
left 10
Isometric handgrip exercise 128
Isometric resistance exercise 350
Isosorbide mononitrate 128
Isotretinoin 370

J

Jaundice 110
Jaw pain 239
Joint replacements 218
Jowar flour 420*f*
Judkins right catheter 298
Jugular vein, internal 3, 296
Jugular venous pressure 3, 102, 234
Jugular venous pulse 3, 48, 49
measurement 5
waveforms 4, 4*t*, 5
Juvenile mitral stenosis 139, 139*t*
Kaplan–Meier survival curves 428*f*
Kerley's A line 22*f*
Kerley's B line 22, 22*f*
Keto diets 415
Kexin type 9 399, 468
Kidney 126, 207, 208, 368
ability 208
biopsy 253
function 253
injury, acute 297
transplant surgery 207
Kingella species 157
Klebsiella 157, 158
pneumoniae 158
Korotkoff sounds 6, 125
Kussmaul's sign 5

L

Labetalol 128
Landolfi's sign 166
Large electronic health data, analysis of 125
Large thrombus burden, management of 491*fc*
Laryngomalacia 45
Late diastolic murmurs 73
Late gadolinium enhancement 625
Late reperfusion
benefits of 531
trials of 531
Leaders free trial 319
results of 320*t*
Leaflet
opening of 150
perforation 98
Left anterior descending artery 481*f*, 506*f*, 510*f*, 511*f*, 569
coronary 569, 572, 572*fc*
occlusion 570, 571*f*
Left atrial
damage 92
enlargement 11
fistula 307
Left atrium 35, 39, 48, 49, 52, 70, 72, 104, 105, 307, 506, 509, 510, 512, 513, 554
size of 25
small 34
Left bundle branch block 434, 608
Left circumflex
artery 508*f*, 510, 569, 572
coronary artery 569
Left intercostal space 48
Left obtuse marginal branches 569
Left pulmonary artery 40, 300-302, 305, 311
injection 305*f*
Left upper sternal border 48
Left ventricle 31, 37, 39, 48, 70, 72, 106, 300, 302, 304, 305, 307, 312, 503, 505, 506, 509-513, 554, 558
double outlet 48
dysfunction 272, 274, 435
ejection
fraction 622
performance 94
end-diastolic volume 622
systolic
dysfunction 91
function, abnormalities of 103
thrombus, prevention of 613
Left ventricular
apical aneurysm 181
assist device 106, 558, 626
dysfunction 627
ejection fraction 80, 86, 87, 91, 105, 132, 172, 173, 264, 409, 490, 624, 625, 627
measurement of 91
ejection time 261
end-diastolic
diameter 265, 627
volume 625, 627
end-systolic
diameter 105, 142, 265, 627
volume 627
failure 557, 589
free wall rupture 553

geometry 624
hypertrabeculation 178
hypertrophy 11, 14*f*, 182*f*, 397
presence of 433
noncompaction 175
noncompaction cardiomyopathy 175-178
benign 176
dilated 176
outflow tract 86
obstruction 89*f*, 181, 558
pseudoaneurysm 557
pulsus alternans 6
remodeling 622, 625, 626
systolic dysfunction 92*f*
detection of 78
thrombus 177, 612-614
Left ventriculography 183, 183*f*
Left-axis deviation 52
Leg pain 238
Legionella species 161
Leptin's effect 283
Lesion
intermediate 437
nonflow-limiting 425
nonprimary 440
primary 440
reduction, coronaries for 385
severity alone 425
Lethal injury 503
Lethal reperfusion injury 533
Leucine 195
Levocardia 9
Life, literature to 420
Lifestyle
change, power of 413
measures 397, 398, 401
modifications 371
Light transmission aggregometry 468
Limb 49*t*
ischemia 620
pain 110
sudden onset of 117
Linoleic acid 415
Lipid 192, 351, 382
genes 340
goals 358
management 361
measure 357
metabolism 391
parameters 357
peroxidation 283
screen for 359
targets 357
Lipid lowering 329
medication 381
therapy 374, 600, 601
effect of 364*t*
efficacy of 391*t*
treatment 123
Lipid profile 355, 357, 390
fasting 357
Lipid-rich
plaques 495
substances 548
Lipoprotein 328, 339, 355-357, 361-365, 376, 392, 402, 406
elevated 359, 364
intermediate-density 355, 356
lipase 376, 389, 392
management 330
measurement of 362
mediates calcific aortic valvular stenosis 363
molecules 389
pathogenicity of 362
Liquid chromatography 193
mass spectrometry 193
Liquid nitrogen 194
Liver 36*f*
disease 45
enzymes 391
function test 237
midline 20*f*
Loading dose 499
LODOCO1 trial 549
Lomitapide 372, 376
Loop diuretics therapy 178
Loudness 65
Lovastatin 329, 359, 377
Low carbohydrate 413, 416
Low immunity 419
Low thrombotic risk 254
Low transaortic flow 95
Low-density lipoprotein 279, 336, 337, 355, 356, 361, 364, 371, 391, 392, 399, 400, 402, 415, 472, 490, 520, 548
atherogenic risk of 389
cholesterol 328, 339, 355, 356, 358, 359, 364, 368, 370, 375, 389-391, 406, 590
atherogenic risk of 389
interpretation of 390
treatment goals of 358*t*
concentration 363
oxidized 490
reduction 498
Lower cardiovascular events 614
Lower limb fractures 218
Lower mortality 591
Lower total cholesterol 371
Lowered aspirin efficacy 467
Low-fat carbohydrates 416
Low-molecular-weight heparin 225, 227, 254, 266, 492, 594, 597
Luminal stenosis 439
Lung 235
diseases 233
fissures 22
hypoplasia 45
increases 302
scintigraphy 222
transplantation 245
vascularity, evaluation of 20

Lupus anticoagulant 229
Lutembacher syndrome 74
Lymphocyte counts 293
Lysosomal acid lipase 376

M

Machine learning 76, 77
  application of 56
Macitentan 239, 247
Macrophages 541, 623
Magnesium 127, 514
Magnetic resonance angiography 222
Maintenance therapy, chronic 465
Major adverse cardiac event 443, 485, 490, 498, 543, 544, 578, 580
Major adverse cardiovascular event 320, 386, 409, 516
Malassezia restricta 160
Malondialdehyde concentration 283
Mammary artery, internal 26, 298
Marantic endocarditis 161
Marfan syndrome 99, 518
Mass spectrometry-based metabolomics 193
Massive pulmonary embolism 219
Maternal mortality 266
Matrix metalloproteinases 541
Mean arterial pressure 124
Mean pulmonary artery pressure 233, 234
Means–Lerman scratch 69
Mechanical alternans 6
Mechanical cardiopulmonary support, use of 224
Mechanical circulatory support 558, 619
  and oxygenation 224
Mechanical complications 523, 553, 558
Mechanical heart valves 266
Mechanical support devices 620
Mechanical thrombectomy 494
Mechanical valve 146, 147
  dysfunction of 147
    diagnosis of 148
    mechanisms of 147
  obstruction 152
Mechanical ventilation 224
Mechanistic genetic pathways 341
Mederi 277
Mediastinitis 59
Mediastinum, superior 19
Medical care 104, 325
Medical therapy 104, 266, 270, 427, 428*f*, 483
Medication adherence 211
Meditation 277-282
  effect of 281*f*
  role of 279
  type of 278, 280
  understanding 277
Mediterranean diet 371, 415
Mediterranean fats 414
Menopause 401
Mental status, altered 224
Mental stress, constant 588
Meropenem 160
Mesenteric infarction 177
Messenger ribonucleic acid 376, 380
Metabolic derangements 114
Metabolic equivalent 349
Metabolic flexibility 194
Metabolic syndrome 172, 271, 280, 283, 336, 400, 588
Metabolites 192
  group of 193
Metabolize 192
Metabolomics 192, 195
  workflow of 194*f*
Metaiodobenzylguanidine 126
Metal electrodes 468
Metalloproteinase blockers 627
Metanalysis 266
Methacrylate
  ball 146
  tube 146
Methemoglobin 46
Methysergide 99
Metoprolol 592
  succinate 128
MGuard stent 495
Microcirculatory resistance 456
  index of 444, 458
Micrognathia 45
Microribonucleic acid 467, 476
Microsomal triglyceride transfer protein inhibitor 376
Microtubule depolymerization 549
Microvascular angina 444, 459*f*
Microvascular dysfunction syndromes 452
Microvascular obstruction 533, 625
Microvascular resistance, index of 444, 446
Microvascular spasm 444
Mid-cavitary hypertrophic obstructive cardiomyopathy 181
Mid-cavitary obstruction 181, 182
Mid-muscular defects 555
Mid-ventricular
  hypertrophy 183*f*
    obstructive cardiomyopathy, management of 184
    severe 183*f*
  muscular apposition 182
  obstruction 181
Migraine 396, 518
Milking effect 481
Mill wheel murmur 69
Mind-body therapies 277
Mineralocorticoid receptor antagonist 122, 626
Minerals 192
Minnesota coronary experiment 414
Mipomersen 365, 372, 376
Mitigate edema 505
Mitochondria 243, 387
  calcium uniporter 243
  metabolic dysfunction 243
  oxidative stress 387
  reactive oxygen species 195
  superoxide dismutase 474

Mitophagy 387
Mitral annulus 98
Mitral bileaflet valve 147*f*
Mitral damage, left 92
Mitral intervention 153
Mitral leaflet
  anterior 34, 138
  posterior 138
Mitral prosthesis 149*f*
Mitral regurgitation 65, 67, 69, 70, 98, 100*f*, 105, 107, 139, 143*f*, 167, 168, 263, 266, 554, 558, 627
  chronic
    compensated 98
    decompensated 99
    severe secondary 106*fc*
  clinical approach to 98
  complications of 107
  etiology of 107
  murmur of 72, 102
  percutaneous treatment of 106
  primary 104, 105
    etiology 99
  secondary 104, 106
    etiology 99
  severe 103*f*, 560
    chronic primary 105*fc*
  surgical treatment for secondary 105
  treatment of 106
Mitral stenosis 68, 72, 73, 110, 117, 139, 141*f*, 143*f*, 167, 263, 266
  adult 139*t*
  classical murmur of 167
  opening snap of 67
Mitral valve 25, 100, 106, 139, 264, 625, 626
  affects, closure of 65
  annulus, calcification of 99
  clefts 99
  disease 99, 167
    degenerative 99
    distal to 25
  double-orifice 107
  fenestrations 99
  morphology 104
  orifice area 139
  pathology, aggressive 264
  prolapse 68, 168, 264
  replacement 104
  surgery 100, 264, 265
M-mode echocardiography 618
Modern electronic stethoscopes 55
Modern-generation surgical valves 146
Molecular imaging 613
Molecular mimicry 293
Monacolin 377
  K 377
Monascus
  fermentation 377
  floridanus 377
  pilosus 377
  purpureus 377
  ruber 377
Monoamine oxidase 124
Monoarthritis 137
Monoclonal antibodies 328, 358
Monocyte chemotactic protein 362
Monogenic risk factors 339
Monounsaturated fatty acids 327, 415
Morbidity, cause of 401
Morphine 592
Morphogenetic protein 380
Morphology matching 541
Mortality 172
  cause of 401, 406
Müller's maneuver 168
Müller's sign 166
Multicentric trials, absence of 288
Multidisciplinary team 558
Multidrug-resistant *Candida auris* 163
Multidrug-resistant strains 160
Multifactorial disease 540
Multiorgan
  damage 213
  dysfunction 557
Multiple thrombus 584*f*
Multivessel disease 536
Murmur 64, 69, 102, 166
  continuous 73
  faint 167
  innocent 9, 71
  intensity of 72, 167, 169
  mid-diastolic 72, 72*f*
  mid-systolic 101
    ejection 168
  shorter 168
  systole-diastolic 47
  systolic 69, 168*t*
Muscle
  fibers 484
  loss 419
  related symptoms 377
  symptoms, statin-associated 375
Muscular symptoms 375
Musculoskeletal disorders 59
Mustard oil 416
Myalgia 239, 375
  incidence of 392
Mycobacteria, rapidly-growing 162
Myectomy 273
Myocardial blood flow 455
Myocardial bridge 480, 481, 481*f*, 482, 484*t*, 485, 485*t*
  diagnosis of 483
  investigations for 483, 484*t*
  prevalence of 483
Myocardial cell 503
Myocardial contractility 236
Myocardial deformation 532
Myocardial disease 109, 110, 452, 459
  absence of 454, 459
  presence of 455
Myocardial dysfunction 87, 177

Myocardial edema 503, 505, 506, 511
detection of 505
natural history of 511
pathogenesis of 504
reduction of 514
reperfusion-induced 504*f*
Myocardial energetics 627
Myocardial fibrosis 352, 353
Myocardial flow, absence of 511*f*
Myocardial forms, primary 175
Myocardial free wall rupture, types of 554*f*
Myocardial heart disease 110
Myocardial infarction 58, 59, 113*t*, 114, 122, 133, 177, 186, 200, 271, 281, 293, 315, 320, 337, 341*f*, 358, 375, 386, 394, 425*f*, 428*f*, 440, 441, 453, 466, 490, 495, 508, 520, 533, 542, 553, 555*f*, 560, 568, 572*f*c, 578, 584, 591, 600, 608*f*, 616, 619*f*, 622, 626
acute
anterior 510*f*
inferior 109, 503*f*, 509*f*, 574*f*
anterior 505*f*
wall 570, 585*f*
bleeding, thrombolysis in 315
causes of 516
first episode of 616
inferior 555
wall 493, 572, 572*f*, 572*f*c, 573*f*, 585*f*
inferolateral wall 562*f*
pathophysiology of acute 520
phenotypes of acute 507*f*
risk of 472
risk score 113
very low incidence of 425
Myocardial injury 58, 59, 291, 406
markers of 223
postreperfusion 505*f*
Myocardial ischemia 58, 68, 195, 282, 425, 459, 472, 504, 507, 548, 557
syndromes 447
Myocardial necrosis 529
amount of 591
Myocardial oxygen consumption 623, 626
Myocardial perfusion 435, 493
imaging 431
Myocardial reperfusion injury 502
Myocardial response 265
Myocardial revascularization 626
Myocardial rupture 555*t*, 560
typical presentation of 561
Myocardial salvage 529, 531
Myocardial swelling 505
Myocardial thickening, abnormal 506
Myocardial tissue characterization 95
Myocardial water content, infarct-related 507*f*
Myocarditis 79, 291, 292, 560
acute 6
diagnosis of 292
Myocyte 623
damage 294
volume 505
Myonecrosis 375
Myopathy 375
Myopericarditis 292, 517
Myositis 375
Myxomatous
degeneration 98, 99
mitral valve disease 98
valve disease 99

N

N-acetyl-seryl-aspartyl-lysyl-proline 125
Nasal cannula, high-flow 223
Natriuretic peptide 242
B-type 405, 406
C-type 474
pro-B-type 219
system, evolution of 407
Natural cell death 540
Nausea 239, 517
Nebivolol 592
Necrosis 382, 540
Necrotic core 548
reduction of 498
Negative concordance 9
Negative predictive value 431, 432
Neointimal hyperplasia 386
Neo-spiritual movements 278
Nephrectomy, bilateral 207
Nephrology 449
Nephropathy 435
Neural language processing 77, 79
Neural network 77
Neural receptors 206
Neurohormonal blockers 626
Neurohormonal imbalance 627
Neurohormonal regulation 242
Neurosurgical emergency procedures 258
Neutropenia 176
Neutrophil 623
counts 293
extracellular traps 542
New aldosterone antagonists 129
Newer oral anticoagulant 576, 579, 581
Newer therapeutic agents 392
Newer therapies 628
Niacin 365
high-dose 365
Nicorandil 492, 514
Nicotinamide adenine dinucleotide phosphate 474
Nicotine 369
Nicotinic acid 365
Nilotinib 244
Nitrates 592, 602
Nitric oxide 124, 236, 283, 351, 473, 514
Nitrogen 193
Nitroglycerin 439, 492, 558
Nitroprusside 492
Noise 189
pollution 189

Nonadherence
assessment of 125
challenge of 124
factors responsible for 125
Nonalcoholic fatty liver disease 396, 449, 450
Nonalcoholic steatohepatitis 449, 450
Nonatherosclerotic disease 518
Nonbacterial thrombotic endocarditis, diagnosis of 162
Noncommunicable disease 277, 395, 530
risk factors for 188
Noncontrast echocardiography 182
Non-cytochrome P450 375
Nondihydropyridine derivatives 592
Nonhepatic gamma-carboxyglutamic acid 380
Non-high-density lipoprotein 335, 336
cholesterol 358*t*
Nonhypertrophied left ventricular 454
Noninfectious disease 160
Noninsulin dependent 317
Noninvasive anatomical imaging 432
Noninvasive functional imaging 431
Noninvasive methods 457, 475
Noninvasive tests 431, 589
Noninvasive ventilation 224
Nonischemic cardiomyopathy 291
Nonmyocytes 623
Nonobstructive coronary artery 443, 453, 454
Nonobstructive thrombus 154
Nonocclusive technique 7
Non-ST segment elevation myocardial infarction 622
Non-ST-elevation 588, 600
myocardial infarction 316, 330, 441, 588, 598, 605
acute 574
Nonsteroidal anti-inflammatory drug 124, 467, 535, 581, 593, 627
Nonsustained ventricular tachycardia 172
Nonsystem delays 530
Nonthrombotic pulmonary embolism 220
Nontuberculous mycobacteria 161, 162
Nonvalvular atrial fibrillation 578
Non-vitamin K
antagonist 225
oral anticoagulant 225, 227, 229
oral anticoagulant 253, 258*fc*
resumption of 254*t*
Noonan's syndrome 168
Norepinephrine 124, 213
Normal curvilinear density, absence of 23
Norwegian guidelines 397
Nosocomial endocarditis 158
Notched rib, bilateral 19
Novel oral anticoagulant 594, 598, 612
N-terminal pro-brain natriuretic peptide 590
Nuclear cardiology 79
Nuclear magnetic resonance 415
Nuclear radiopharmaceuticals 625
Nuclear scan, abnormal 425*f*
Nucleic acid 192, 365
Nucleotide-binding oligomerization domain 549
Nutraceutical agents 371, 377
Nutrition 449
Nutritional habits 371

O

Obesity 114, 122, 277, 283, 368, 369, 372, 400, 449, 588, 622
apple-shaped 588
management 369, 450*f*
secondary causes of 369
Obstruction 625
Obstructive coronary artery disease 458, 622
absence of 454
pretest probabilities of 432*t*
Obstructive sleep apnea 123, 124, 171, 171*f*, 172, 214, 401, 449, 450
behavioral therapy for 173*t*
cardiovascular complication of 171
signs of 171, 171*f*
symptoms of 171, 171*f*
treatment for 170, 173*t*
Obtuse marginals 569
Occluded artery trial 531
Occluder devices 619
Odyssey alternative trial 375
Ohm's law 437
voltage 260
Ointment 592
Olive oil 416
Omega-3 415
fatty acids 415
Omega-6 415
Omnicarbon tilting disk valve 151*f*
Onyx ONE trial 462
Oozing rupture 565*t*
Opiate addiction, history of 592
Optical coherence tomography 543
Optimal antiplatelet 320
Optimal coherence tomography 383
Optimum medical therapy 429
Oral anticoagulant 577, 581, 581*f*, 583, 598
direct 200, 201*t*, 202*t*, 254*f*, 329, 580
role of direct 199
ximelagatran 199
Oral antiplatelet drugs 593
Oral colchicine 599
Oral contraceptive 370
pill 124, 401
Oral factor Xa inhibitors 597
Oral therapy 247
Oral vitamin K antagonist, dose-adjusted 319
Organ damage, hypertension-mediated 121, 123
Organic acids 192
Orifice area, effective 146
Orlistat 126
Orthopnea 114, 117
Orthostatic hypotension 115
Oscillatory wall shear stress 480
Osler's maneuver 7
Osler–Weber–Rendu syndrome 45

Osteocalcin 380
Osteopontin 380
Osteoporosis 449
Osteoprotegerin 381
Ostia 440
Ostium secundum 10
Outflow tract obstruction 36
Outlet chamber, left-sided 24*f*
Out-of-hospital cardiac arrest 81
Oxidative phosphorylation 474
Oxidative stress 281, 283
Oxygen
  hemoglobin dissociation curve 45*f*
  species, reactive 474
  supplementation 223
  supply, inadequate 507
  therapy 223

P

P wave 9
P2Y12 inhibitor 469, 593, 601
Pacemaker, temporary 296
Paclitaxel-eluting stent 386, 475
Palm oil 416
Palpitation 109, 110, 116, 292
Pan-systolic murmur 48
Papillary muscle
  anterolateral 554
  dysfunction 99, 167, 619
  rupture 553, 554, 560, 618
    differential diagnosis of 618*t*
Parachute mitral valve abnormality 99
Paradise ultrasound catheter 212, 212*f*
Paradoxical embolism 220
Paradoxical jet flow 182
Paraganglioma 126
Parasites 187
Parasitic disease 187
Parasternal heave 49
Parasternal long axis 88
Parasternal short axis 31, 88
Parathyroid hormone abnormalities 381, 382
Paravalvular leak 146
Paraventricular nucleus 206
Parenteral anticoagulation 225
Paris bleeding score 317*t*
Paroxysmal bouts 124
Paroxysmal nocturnal dyspnea 114, 117
Paroxysmal phenotype 282
Paroxysmal supraventricular tachycardia 116
Partial anomalous pulmonary drainage 25
Passive apical left ventricular vent 620
Patches 592
Patent arterial duct 11
Patent ductus arteriosus 21*f*, 28, 28*f*, 47, 48, 73, 73*f*, 302
Pathological cell death 540
Patient's mothertongue 109
PCSK9 inhibitors 358, 365
Peak metabolic equivalents 377
Pedal edema 116
Pediatric dyslipidemia, treatment of 372
Pediatric population 401
  care for 372
Pelacarsen 365
Peptides 192
Percutaneous balloon
  angioplasty 241*f*
  mitral valvuloplasty 263, 264
Percutaneous catheter 226
  directed treatment 226, 228
Percutaneous coronary intervention 106, 134, 200, 255, 256, 316, 326, 385, 425, 426, 426*f*, 428, 452, 456, 461, 466, 469, 484, 485*t*, 494, 498, 504, 506*f*, 507, 509*f*, 511*f*-513*f*, 518, 523, 529, 535, 536, 538, 538*b*, 543, 549, 553, 576, 579, 583-586, 600, 608, 609*f*
  primary 491, 491*fc*, 535, 536*f*, 560, 607, 609
Percutaneous coronary, guidelines for 530
Percutaneous device, steps of 556*f*
Percutaneous double-orifice mitral valve repair 107
Percutaneous intervention 134, 475
  primary 622, 626
Percutaneous myocardial ablation 184
Percutaneous nephrostomy 227
Percutaneous procedures 564
Percutaneous transluminal
  coronary angioplasty 385, 386, 456, 492
  pulmonary angioplasty 135
    role of 135
Percutaneous transvenous mitral commissurotomy 139*t*, 144
Peregrine system 205
  infusion catheter 211, 212*f*
Perfusion 222, 223
  scintigraphy 228
Pergolide 99
Pericardial disease 109, 110
Pericardial friction rub 69
Pericardial knock 67
Pericardiocentesis 253
Pericarditis 58, 69, 292
Pericardium 561
Perindopril 330
Peripartum cardiomyopathy 269, 272
  etiology of 272
Peripheral artery 126
  disease 270, 394, 591
    diagnosis of 79
  valve 264
Peripheral balloons 153
Peripheral cardiovascular system 3
Peripheral cyanosis 44
Peripheral embolism 177
Peripheral vascular disease 466
Peripheral vasculature 494
Periprocedural anticoagulation 492
Periprocedural bleeding 252
Peroxisome proliferator 392
Persistent ductus arteriosus 49
Pests 187

Pexelizumab, assessment of 554
Pharmaceutical industry 402
Pharmacoinvasive percutaneous coronary intervention 607
Pharmacoinvasive strategy 606
  strength of 609
Pharmacologic agents, classes of 124*t*
Pharmacologic stress testing 432
Pharmacological intervention 371
Pharmacotherapy 328
Phenotyping, role of 466
Pheochromocytoma 126
Phlebostatic axis 3
Phosphodiesterase 247
  inhibitors 237, 315
Phospholipase, lipoprotein-associated 548
Phosphoprotein, vasodilator-stimulated 467
Phosphorus 381
Photon emission computed tomography, single 484
Physical activity 326, 349, 400, 476
Physical examination 59
Physical exercise, peripheral adaptation to 351
Physical inactivity 277, 368, 369
Physiologic parameters 445
Physiological aberration 123
Phytosterols 377
Pierre Robin sequence 45
Piezoelectric crystal 211
Pigtail catheter 298
Piperacillin 158, 159
Pitavastatin 329, 359, 374
Placebo 247
Plaque
  and thrombus, distal embolization of 490
  calcified 385
  mechanism of formation of 540
  morphology 382
  volume, estimation of 338
Plaque erosion 540-543, 543*t*, 545
  incidence of 540
  management in 542
  mechanisms of 541
Plaque rupture 540, 542*f*, 543, 544*f*
  mechanisms of 541
  transpires 541
Plasma 221
  aldosterone 418
  d-dimer 228
  glucose, random 544
  insulin 420
  lipids 351
  renin activity 125, 126
  troponin, elevated 223
Plasminogen activator 226, 541
Platelet 467, 489
  accumulation of 489
  activation 200*f*, 466, 468
  aggregation 466, 468, 492
    pathway of 492
  counts 293
  derived growth factor 243
  function analyzer 468
  function testing, current place of 469
  glycoprotein 489
  hyperactivation 416
  inhibition 469
  poor plasma 468
  reactivity 147
    high on-treatment 467
    treatment 466, 468
  treatment 470
Platypnea 114
Plausible molecular mechanisms 282
Pleural effusion 22, 113
Pleuritic pain 58, 111
Pleurotus ostreatus 377
Pneumonia 113, 114, 235, 386
Pneumothorax 113
  pain of 59
  secondary 59
Pollutants 192
Polyarthralgia 137
Polycystic ovarian
  disease 401
  syndrome 449
Polygenic risk scores 341, 342, 343*f*
Polymer technology 461
Polymyxin 159
  B 159
  E 159
Polysplenia 20*f*
Polytetrafluoroethylene 585*f*
Polyunsaturated fatty acids 327, 371, 414
Pooled cohort equation 396
Poor sleep quality 124
Porcine xenograft valves 146
Positional therapy 173
Positive predictive value 432
Positive-pressure ventilation 224
Post-arterial switch operation 311*f*, 312*f*
Post-coronavirus disease-2019 291, 292, 294
Postcorrective surgery 16, 27
Posterior wall infarction 573
Post-fontan 18
  completion 312*f*
Postganglionic neurons 207
Post-Glenn shunt 312*f*, 313*f*
Post-Glenn surgery 45
Postischemic regional contractility 514
Postmenopausal women 242, 273
Post-myocardial infarction 623*t*
  classification of 624*f*
  complications 523
  myocyte necrosis 623
Post-myocardial infarction ventricular septal rupture 616, 617*f*, 618, 619
  differential diagnosis of 618*t*
  posterior 617*f*
Post-myocardial ventricular septal rupture 618

Postpercutaneous coronary intervention 520
Postpericardiotomy syndrome 551
Postprandial lipemia 378
Post-pulmonary artery band 314*f*
Postsurgical changes 11, 16
Post-tetralogy of Fallot 309*f*-311*f*
Post-traumatic stress disorder 188
Postural tachycardia syndrome 292
Potassium 127
Potts shunt 240
Pranayama 278
Prasugrel 257, 328, 492, 594, 594*f*, 595, 595*f*
Pravastatin 329, 359, 500
Prazosin 116
Precapillary hypertension 22
PRECISE-DAPT score 316, 317*f*
Predators 187
Prediction tools 337*t*
Predilection site 540
Pre-ejection period, role of 261
Pregnancy 7, 139, 221, 267
  hemodynamics of 139
  hypertensive disorders of 401
Pre-hospital
  care 104
  thrombolysis 530
Premature beats 65
Premature cardiac deaths 345
Premature coronary artery disease 335, 337*t*, 345
  prevalence of 336*f*
Premature deaths 335
Premature menopause 401
Pre-percutaneous coronary intervention 612
Preprocedural planning 296
Preserved ejection fraction 132, 271, 456
Pressure 3
  gradient 87, 93
  wire 438
Pretest probability 431
Preventive medicine 402
Previous surgery, signs of 19
Prinzmetal's variant angina 602
Probiotics 371
Procedural anticoagulation 492
Progestogen 218
Proinflammatory cells 623
Proinflammatory milieu 456
Proliferation 236
Prominent vasodilator substances 351
Prophylactic administration 599
Prophylaxis 613
Proprotein convertase subtilisin 375, 391, 399, 476
Pros and cons 442
Prostacyclin 124, 315, 473
  analogs 238
  receptor agonists 238
  urinary metabolites 238
Prostaglandins 351
Prostanoids 246
Prostate biopsy 153
Prosthetic patch placement 562*f*
Prosthetic valve 161, 266
  history of 146
  malfunction 154
  stuck 146, 152
  thrombosis 142
    management of 151
    prevention of 154
Protease activated receptor 315
Protein 127
  containing 380
  high 418
  intake, insufficient 419
  kinase 242
  PCSK9 inclisiran 376
Proteomics 192
Prothrombin concentrate complexes 258
Prothrombin time 258
Prothrombotic states 406
Proton-pump inhibitors 581
Provocative tests 457
Proximal isovelocity surface area 104
Pseudoaneurysm 553, 554
  management of asymptomatic 564
  repair of 564
  type 561
Pseudohypertension 7
Pseudomonas 158, 159, 163
  aeruginosa 157
Pseudopheochromocytoma 123
Pseudoresistance, exclude 124
Pseudoresistant hypertension, causes of 124*f*
Psoriasis 400, 547
Psychological ailments 58
Psychological stress, pathophysiology with 279
Psychoneuroimmunology, stress-related 282
Psychosocial stress 277, 401
Pulmonary angiography 222
Pulmonary apoplexy 141, 142*f*
Pulmonary arteriovenous malformation 45, 48, 307, 308, 308*f*
  types of 308*t*
Pulmonary artery 15*f*, 32*f*, 33, 37*f*, 38*f*, 41*f*, 48, 49, 53, 298, 300, 302-305, 307, 555
  aortic origin of 304
  band 313, 314, 314*f*
  catheterization effectiveness 4
  denervation 240
  dilatation 167
  dilated main 21*f*
  endothelial cells 243
  hypertension 48, 49, 52, 53, 71, 80, 100, 142, 239, 244, 245
    moderate 219
    severe 138*f*
  hypoplastic branch 33
  infarction 59
  mechanical obstruction of 230
  pressure 100, 233, 226
    reveal elevated 98

right descending 20
smooth muscle cells 243
systolic pressure 139
thrombus 230
wedge pressure 233, 234
Pulmonary atresia 16, 33, 34, 177, 302, 303*f*, 311*f*
Pulmonary atrioventricular fistula 27
Pulmonary blood flow 33, 45, 50, 53
causes of decreased 23
decreased 23
unprotected 39
Pulmonary blood supply 304
Pulmonary capillary wedge pressure 620
Pulmonary conditions 59
Pulmonary disease 45
chronic 224
Pulmonary dyspnea 114
Pulmonary edema 22, 113, 117
acute 101, 141
Pulmonary ejection sound 68
Pulmonary embolism 58, 59, 113, 114, 218, 221*t*, 229*t*, 386
acute high-risk 225*t*
classification of 219
diagnosis of 222*t*, 230
emergency treatment of high-risk 228
high-risk 227*t*
low-risk 220, 227*t*
management of low-risk 229
risk factors for 218
rule-out criteria 221
severity index 223
signs of acute 220
treatment of intermediate-risk 229
Pulmonary endarterectomy 230
Pulmonary function test 7
Pulmonary hemodynamics 244
Pulmonary hypertension 9, 36, 135, 167, 170, 172, 233, 234
development of 105
diagnosis of 234
hemodynamic classification of 234*t*
management of primary 233, 235
pharmacotherapy for 239*t*
primary 247, 248
severe 12*f*, 139
signs of 239
symptoms of 239
treatment of 240
Pulmonary infarction 220
Pulmonary medicine 449
Pulmonary microvascular bed 230
Pulmonary obstruction 226
Pulmonary oligemia 20*f*
Pulmonary regurgitation 72, 168, 310
functional 167
murmurs of 72
Pulmonary reperfusion 224
Pulmonary resistance, total 245
Pulmonary sequestration 45
Pulmonary stenosis 9, 13, 26, 45, 48, 49*t*, 50, 52, 53, 69, 304
Pulmonary trunk 23
Pulmonary valve 139, 168
absent 27
stenosis 68
syndrome 47
Pulmonary vascular
damage 92
normal 20
occlusive disease 306
resistance 52, 172, 233, 234, 245, 247
Pulmonary vasodilator testing 236
Pulmonary vein 300, 306
course of right upper 25
flow 104
isolation 550, 551*t*
obstruction 21
right 25*f*
stenosis 36
Pulmonary venous
high 618
hypertension 21, 22, 25, 48, 50
wedge angiogram 302*f*
Pulmonic atresia 39
Pulmonic stenosis 39, 71, 166, 177
Pulmonic valve closure 166
Pulse 5
character, types of 6
large-volume 166
oximetry, role of 49
rate comparison 6
Pulsus alternans 6, 7
causes of 6
Pulsus bisferiens 6
causes of 6
Pulsus celer 6
Pulsus durus 6
Pulsus magnus 6
Pulsus mollis 6
Pulsus paradoxus 6, 7
Pulsus parvus 6
Pulsus tardus 6
Pump failure, severe 273
P-wave morphology 9
Pyramidal processing 80
Pyruvate dehydrogenase kinase 243

Q

Q fever 157
QRS complexes 51*f*
QT syndrome 116
Quincke's pulse 166
Quinquennial trends 336*f*

R

Racial disparities 521
Radiation exposure 495
Radiofemoral delay 6

Radiofrequency
ablation 550
system, first-generation 208
catheter positioning 209*f*
Ramipril 330
Randomized clinical trials, absence of 484
Randomized controlled trial 201, 202, 280, 320, 385, 386
Rankin scale, modified 321
Reactive hyperemia-peripheral arterial tonometry 475
Receptor tyrosine kinases 243
Recombinant tissue 226
Recording extra leads, role of 589
Recurrent ischemic episodes, prevention of 591
Red blood cell 51, 504, 593
Red yeast rice 377
Reflux esophagitis 59
Regional wall motion abnormality 112
Regular exercise, benefits of 350*f*
Regular physical activity 350, 351, 353
Regurgitant orifice area, effective 104, 264
Regurgitation 37, 157
severity of 264
Rehabilitation 518
medicine 449
Reinfarction 525, 607
Renal adjustment 201
Renal afferent sympathetic nerves, activity of 207
Renal angiography 209
Renal artery 205, 207, 209*f*, 210*f*, 211, 368
adventitia 205
intervention, previous 208
stenosis 126, 207, 208
vessels 210
Renal blood flow 129
Renal denervation 129, 214
ablation systems 211
clinical results of 208
reinnervation after 213
therapy 205, 212*f*, 215
Renal disease, severe 625
Renal disorder 117
Renal end-stage disease, prevention of 271
Renal etiology 381
Renal failure 382
Renal function 201, 599
Renal impairment 225
Renal nerve ablation 211
Renal parenchymal disease 126
Renal replacement therapy 538*f*
Renal sympathetic
denervation 129
nervous system
anatomy of 207
physiology of 207
Renal transplantation 400
Renin secretion 207
Renin-angiotensin
inhibitors 125
system 127, 236, 410
Renin–angiotensin–aldosterone system 207, 242, 293, 351, 381, 623, 624
inhibitors of 330
Reperfusion 605
injury 503*f*, 514, 533
strategies 605
practical considerations of 606
types of 605
therapy 561
after 507*f*
treatment 226, 227
Rescue thrombolytic therapy 229
Residual cholesterol risk 328
Residual risk 591
Residual shunt 556*f*
Residual stenosis, severe 605
Resistance exercise 353
Resistance-training machines 350
Resistant arterial hypertension 128
Resistant hypertension 121, 122*f*, 123, 130, 170, 171
apparent treatment 123
causes of 130
device-based treatment of 129
epidemiology of 122
evaluation of 124
management of 121, 126, 127*fc*
medication-related 123
pharmacological treatment of 128
prognosis of 122
treatment 123*t*
Respiration, effect of 5
Respiratory depression 592
Respiratory distress, severe 51
Respiratory failure 220
Respiratory movements 111
Respiratory support 223
invasive ventilation for 554
Response to clopidogrel differs 469
Restenosis, rate of 484
Resting full-cycle ratio 442
Restrictive cardiomyopathy 269
Restrictive left ventricular noncompaction cardiomyopathy 177
Restrictive lung diseases 113
Retinal evaluation 76
Retrograde pigtail catheter 303*f*
Retrograde venous catheter 305*f*
Retrosternal chest discomfort 589
Revascularization 426
strategies 522
Reverse Berman catheter 298
Rheolytic thrombectomy 491
device 493*f*
Rheumatic cohort 197
Rheumatic etiology 139, 263
Rheumatic fever 136, 144
acute 136, 137, 139*t*, 144
prevalence of 136
prevention and control of 143, 144*fc*

Rheumatic heart disease 85, 99, 136, 137*f*, 139, 140*f*, 141, 142, 143*f*, 144, 198, 263, 264
decline of 143
juvenile 139
prevalence of 136, 137
prevention and control of 143
Rheumatoid arthritis 547
Rho-associated protein kinase 242
Rhythm disturbances 109, 110
Rib
crowding of 19*f*
notching 26*f*
Ribonucleic acid 328, 358, 361, 372, 626
role of 476
therapeutic drugs 365
Right acute marginal branch 569
Right atrial
appendage 298
pressure 4, 5
Right atrium 16, 35, 39, 52, 306, 307, 510
dilated 138*f*
Right bundle branch block 13*f*, 17*f*, 18*f*, 434, 572
incomplete 52
Right coronary artery 74, 509*f*, 512, 516, 554, 569, 572, 583, 585*f*
branch of 589
Right dominant circulation 568
Right heart 296
catheterization 233, 248, 555, 618
Right interventricular posterior branch 569
Right posterolateral branch 569
Right pulmonary
arteriovenous malformation 312*f*
artery 40, 302, 306, 308, 311
aortic origin of 306, 306*f*
stenosis 311*f*
Right ventricle 35, 38, 39, 49, 52, 106, 219, 225, 298, 300, 302-305, 503, 505, 510, 512, 558
double outlet 18, 33, 45, 48, 52, 53, 303, 303*f*, 304
double-chambered 11
entry 299*f*
failure, treatment of 225*t*
types of double-outlet 304
Right ventricular
angiogram 300*f*
branch 569
damage 92
dysfunction, markers of 223
failure, pharmacological treatment of acute 224
hypertrophy 49, 51*f*, 52, 236
myocardial infarction 4
outflow tract 30, 32, 298, 301-303, 308, 310, 311
Right-axis deviation 52
Riociguat 239
Risk strata 224
Rivaroxaban 200-203, 228, 254, 319, 579, 597, 598, 614
vascular dose 199
very-low-dose 254
Romano–Ward syndrome 176*t*
Root angiogram 301*f*
Rostral ventrolateral medulla 206
Rostrolateral prefrontal cortex 280
Rosuvastatin 329, 359, 500
Rotational atherectomy 386
Rupture 565*t*
chordae tendineae 98
exclusion of 541
fibrous cap 543
plaque 541, 544
lesions 544
posterolateral 566*t*
propensity of 561
sinus of valsalva aneurysm 74
Rytand murmur 73

S

S1
factors affecting intensity of 65*b*
splitting of 66*b*
S2
factors affecting intensity of 66*b*
fixed splitting of 66
splitting of 66*b*
wide splitting of 66
Saline placebo 244
Salt 418
and fluid intake, restriction of 235
and water retention 207
sensitivity 418
Saphenous venous graft 441, 485
lesions 441
Sarcoidosis 45, 560
Sarcolemmal rupture 504*f*
Sarcopenia 419
SARS-COV-2 infection 294
Satherosclerotic vascular disease 200
Saturated fat 414
Sawing wood murmur 47
Schwarz classification 483, 484*t*
Scimitar syndrome 25
Scleroderma 45, 99
Sedentariness 419
Sedentary lifestyle 588
Seizures 115*t*
Selection biases 175
Selective serotonin reuptake inhibitor 124
Selexipag 239, 247
Septal branches 569
Septal devices 620
Sequential combination therapy 246
Serial lesions 439
Serine
carbapenemases 158
protease inhibitors, type 9 390
Serine-threonine kinases 242
Serotonin 242, 473, 489
norepinephrine reuptake inhibitor 124
Serum creatinine 51, 122

Sesame oil 416
Severe acute respiratory syndrome 548
  coronavirus 2 291
Sex differences 264*t*, 522
Sex hormones 241
Sex-based differences 270
Sharp pain 58
Sheart failure 551
Shock 173, 291
  refractory 555
  signs of 532
  symptoms of 532
  team 558
Short polymers 417
Short stature 176
Shunt lesions 25
Shunt
  anatomical localization of 25
  left-to-right 12*f*, 555
  lesions, left to right 69
  right-to-left 45, 240*f*, 295
  systemic vein 45
  systemic-to-pulmonary 233, 239
Sibutramine 126
Sildenafil 239
Silent ductus 74
Simmons catheter 298
Simon Broome criteria 370
Simplified pulmonary embolism severity index 224*t*
Simvastatin 329, 359
Single-gene mutations 335
Single-nucleotide polymorphism 339, 339*t*, 342*t*, 343, 362, 467
Single-photon emission computed tomography 222, 432, 441
Single-vessel disease, severe 427
Sinoatrial node dysfunction 15
Sinus
  bradycardia 292
  rhythm 550
  tachycardia 116, 292
  venosus 10
Sirolimus-eluting stent 386, 475
Sisotope
  applications to metabolomics 193
  probes 194
Situs inversus 9
Six-minute walk distance 245, 247
Skeletal abnormality 19
Skeletal myopathy 176
Skin discoloration 110
Sleep apnea 170, 395
  evaluation of 170
  suspected 172
  testing for 173*fc*
Sleep deprivation 123
Sleep disorders 401
Sleep testing, diagnostic 173
Sleep-endoscopy, drug-induced 173
Slow-wave sleep 124
Small mural thrombus 612
Small side branch 440
Smart-choice trial 463
Smartphones 57
Smokeless 326
Smoking 277, 326, 327, 336, 368, 369, 400, 406, 588
  cessation 475, 476
  current 317
  habit 372
  management of cessation of 369
Smooth muscle cell 362, 452, 472
  creation of 540
  death of 381
S-nitrosylation 473
Social isolation 189
Sodium and water retention 207
Sodium-glucose cotransporter 270, 626
  effects of 132
  inhibitors 128, 476
Soft tissue 19
Solitary track nucleus 206
Soluble guanylate cyclase stimulator 238
Spectral wave Doppler 618
Spinal cord
  injury 218
  stimulation 459
Spinal muscular atrophy 46
Spironolactone 122, 128
Spontaneous coronary artery 517
  dissection 293, 516, 517, 522, 524
Spontaneous reperfusion 505*f*
Stable angina, chronic 588
Stable chest pain 60
Stable coronary
  artery disease 200, 549
  microvascular dysfunction 456
Stable heart failure 550
Standard Berman angiographic catheter 298
Standard medical therapy 549
Standard statin
  group 500
  therapy 500
Staphylococcus aureus 157, 161
Starr-Edwards ball-cage 154
Start dual antithrombotic therapy 580
Start statin 498
Statin 326, 327*f*, 358, 364, 391, 399, 459, 476, 498, 514, 523, 583, 627
  continue high-dose 500
  dose of 359*t*, 399*t*
  high-dose 498
  intolerance 374, 375, 375*b*
  therapy 329*t*, 372, 374, 391
    alternatives to 391
Steerable radiofrequency catheter 208*f*
ST-elevation criteria 569
ST-elevation myocardial infarction 453, 462, 489, 499, 520, 521, 524, 525*f*, 529, 532*fc*, 535, 537, 540, 561, 562*f*, 568, 588, 605, 606*f*, 608, 614, 616
  diagnosis 492

management of 605, 606, 609
pathophysiology of 522
reperfusion strategies 522
setting 463
trial, multivessel 134
Stenosis 37, 437, 494
moderate 439
Stenotic lesions 5
Stent 28
deferred 495
design 461
drug-coated 462
drug-eluting 255, 386, 484, 485, 579, 581, 594, 605
implantation 508*f*
restenosis 462
selection 593
thrombosis 386, 461, 464*f*, 468, 547
risk of 580
Stenting strategy 495
Sternotomy 19
Steroids 514
Stethoscope 56, 166
discovery of 54
future of 57
parts of 55*f*
relevance of 54
technology
advances in 55
evolution of 55*t*
Stomach bubble 20*f*
left-sided 20*f*
right-sided 20*f*
STOPAMI-3 531
STOPDAPT-2 462
Strain 589
global longitudinal 86
susceptible 160
Stream trial 607
Strenuous exercise 352*f*
Streptococcus viridans 157
Streptokinase 226
Stress 283
acute 282
and negative affect 279
meditation for managing 279
cardiomyopathy 269, 273
chronic 188, 282
echocardiography 431, 432, 590
perfusion 590
thallium 590
Stressful life events 279
Stroke 110, 122, 146, 148, 153, 177, 291, 329, 405, 415*f*, 577, 607, 612
history of 203
preventing 210
volume 261
ST-segment
changes 433
depression 572
elevation 574*f*, 602
resolution 493
ST-segment elevation myocardial infarction 112, 492, 494, 518, 520, 536, 553, 609*f*
acute 608
cardiogenic shock 609
complications of 533
Study cohort 608*fc*
Subclinical carditis 137, 144
Subclinical neuromuscular disorder 178
Subendothelial dendritic cells 541
Submassive pulmonary embolism 219
Subpulmonary edema 22
Subpulmonary stenosis 311*f*
Sudden cardiac arrest 181
recognition 81
Sudden cardiac death 11, 172, 177, 351, 455, 521, 588
prevention of 351
risk of 172, 351
Sugar and carbohydrates 416
Sugar sweetened beverages 403
Sunflower 416
Superoxide dismutase 283
Supplemental oxygen therapy 235
Supra-aortic stenosis 312*f*
Supracardiac total anomalous pulmonary venous 50*f*
connection 36*f*
Supraventricular arrhythmia 177, 292
Supraventricular tachycardia, incidence of 274
Surgery vs. transcutaneous closure 619
Surgical care 105
Surgical embolectomy 226
Surgical management 586
Surgical pulmonary embolectomy 228
Surgical therapy 484
Survival to hospital discharge 226
Sutureless technique 563, 564, 564*f*
Switching therapy 375
Sympathetic nerve activity, levels of 206
Sympathetic nervous system 124, 205, 206*f*, 351
role of 205
Sympathomimetic amines 124
Sympathovagal tone 288
Symplicity flex
ablation catheter 208*f*
catheter 213
Symplicity spyral catheter 210*f*, 212
Syncopal episode, history of 115
Syncope 87, 109, 110, 115, 115*t*, 148, 273
Syndrome X 588
Synthetic prostacyclin 238
Systematic coronary risk estimation 396, 406
Systemic collateral arteries 23
Systemic endothelin antagonists 474
Systemic hypoperfusion 557
Systemic inflammatory disorders 547
Systemic insulin 351
sensitivity 351
Systemic lupus erythematosus 99, 400, 547

Systemic metabolic alterations 244
Systemic sclerosis 243, 547
Systemic thromboembolism 146, 612
Systemic thrombolysis 226
Systemic vascular resistance 124, 236
Systemic vein drainage 306
Systolic ambulatory blood pressure 214*f*
Systolic dysfunction 78
Systolic functions 176
Systolic pressure 484
Systolic pulmonary arterial pressure 105
Systolic sound, nonejection 68

T

T lymphocytes regulate monocyte activation 623
Tachyarrhythmias 116, 369
Tachycardia 16, 141, 369, 593
Tadalafil 239, 245, 247
Tai chi, effect of 283
Takayasu arteritis 135
Takotsubo cardiomyopathy 273, 456, 517, 522
TandemHeart 555, 620
Target lesion failure 385
Taussig–Bing anomaly 34
Tazobactam 158, 159
Technical analysis 19
Technical limitations 568
Technological advances, advent of 143
Tele-electrocardiogram 530
Tension pneumothorax 59
Terazosin 116
Tetrahydrobiopterin 474
Tetralogy of Fallot 16, 27, 31, 31*f*-33*f*, 48, 48*f*, 49*f*, 51*f*, 52, 72, 168, 176, 299, 300, 301, 301*f*, 302*t*, 304, 309-311
  postoperative 308
  postsurgical 17*f*
Tetrapolar electrodes 261
  placement of 261*f*
Therapeutic anticoagulation 147, 227
Therapeutic intravascular ultrasound 240
Therapeutic lifestyle intervention 358
Therapeutic options 146
Therapeutic window strategy 469
Thermodilution technique 445
Thiazolidinedione 128
Thienopyridine 466
  third-generation 467
  treatment 469
Thin-cap fibroatheromas 541
Thoracic aneurysm, descending 394
Thoracic aorta, descending 25
Thoracotomy 19
Thrombectomy 493
  catheters 493
  manual 493
Thrombin, generation of 489
Thrombocytopenia, heparin-induced 147
Thromboelastography 468
Thromboembolic recurrence 229
Thromboembolism 177
Thrombolysis 113, 147, 200, 351, 457, 493, 508, 580, 533, 561, 586, 591, 608*f*
  failed 607
  guidelines for 529
  indication for 529
  trials, meta-analysis of 226
Thrombolytic agent 607
  first-generation 226
Thrombolytic regimens 226*t*
Thrombolytic therapy 151, 226, 522, 529, 607
Thrombosis 236, 320, 362, 541
  acute 221
  risk of 252
Thrombotic complications 467, 468
  development of 466
Thrombotic events 579
Thrombotic risk 328, 580
  moderate 254
  stratification of 254*t*
Thromboxane 594
  A2 466, 474, 489
Thrombus 613
  aspiration catheter 492
  burden, large 489, 493
  disappearance of 151
  formation 613
    risk of 597
  grading of 490, 490*t*
  removal, method of 493
  small 613
Thumb 19
Thyroid-stimulating hormone 126
Thyrotoxicosis 5
Ticagrelor 134, 257, 328, 492, 595, 596*f*
  monotherapy 596
  plus aspirin 134
  therapy 202
Tico trial 463
Tight pinhole stenosis 49
Tirofiban 315, 492
Tobacco 336
  cessation 327
Torque-controlled catheters 298
Tortuous right internal carotid artery 153*f*
Total anomalous
  pulmonary venous connection 21, 23*f*, 25, 30, 34, 35, 35*f*, 36*f*, 45, 48, 49, 52, 53, 304, 305, 305*f*, 306
  systemic venous connection 45, 48
Total cavo pulmonary connection 39
Total ischemic time 606
Total occlusion, chronic 440
Total systolic time 261
Toxins 192
Toxoplasma, rubella, cytomegalovirus, herpes 46
Tracheobronchial tree 20
Tracheobronchitis 59
Transannular patch 310

Transcatheter
aortic valve 106
replacement 86, 94*f*, 197
closure 555
management 152
pulmonary valve replacement 310
release 152, 155*f*
therapy 627
Transcendental meditation 128
Transesophageal echocardiogram 146, 148
Transesophageal echocardiography 31, 34, 86, 103, 223, 556, 613, 618
Transferrin saturations 244
Transient ischemic attack 177, 203, 291, 329, 394, 577, 578, 614
Transmicrovascular fluid 505
Transthoracic echocardiography 85, 103*f*, 138*f*, 140*f*-143*f*, 177, 295, 613
two-dimensional 182
Transthoracic pulmonary artery denervation 240
Transthyretin 273
amyloid cardiomyopathy 273
Traube's sign 166
Trauma 99
Treadmill, role of 590
Trepopnea 114
Treprostinil 238, 239
Triacylglycerolemia 378
Tricuspid annular plane systolic excursion 223
Tricuspid atresia 17, 18*f*, 27, 39, 39*f*, 177
Tricuspid damage 92
Tricuspid regurgitation 52, 69, 101, 167, 265, 618
severe 139, 140*f*
Tricuspid stenosis 72, 141*f*, 168
Tricuspid valve 16, 39, 41, 162*f*, 168, 264
repair 139
Tricyclic antidepressant 124
Triflusal 315
Triglyceride 281, 326, 356, 371*t*, 416, 491, 520
glucose index 416
level 402
lowering 330
rich lipoproteins 392
risk 328
lipoproteins 339
Triple combination therapy 246
Tropheryma whipplei 161
Troponin 405, 406, 409
high-sensitivity 409, 410
Troponin, significance of 407
Trousseau's sign 7
True aneurysm 553
Truncus arteriosus 40, 40*f*, 41*f*
Tuberculosis 560
Tumor
malignant 255
necrosis factor 283, 362, 549
T-wave
complex 574
precordial instability 574
Twice-beating pulses 6
TXA2 generation 466
Typical machine learning model, development of 77*fc*
Tyrosine kinase 124

U

Ultrafine particles 186
Unequal saturation, cause of 49*t*
Unhealthy
diet 277
lifestyle 372
Univentricular atrioventricular connection 39
Unscoronary disease 462
Upfront combination therapy 246
Upfront triple therapy 247
Upper airway surgery 173
Upper reference limit 590
Upstream administration 498
Ureteral stent placement 227
Uric acid 51
Urinary routine and microscopic examination 126
Urine 126
Urokinase 226

V

Vaborbactam 160
Vaccine developmental strategies 143
Valine 195
Valve
diseases 114
involvement 139
lesion 110
morphological assessment of 88
replacement 147
Valvular disease 109, 110
degenerative 165
rheumatic 165
Valvular dysfunction, acute 228
Valvular heart disease 69, 110, 115, 117, 146, 165, 197, 198, 263, 265
management of 267
prevalence of 263
severity of 165
trends of 197
Valvular lesions
common 264*t*
severity of 267
Valvular pathology 161
Valvular surgery 99
Valvulo-arterial impedance 95
Vancomycin 161
Vardenafil 238
Varenicline 400
Vascular access 296
Vascular aneurysm repair 255
Vascular disease 59, 253, 435
Vascular endothelial growth factor 124, 272, 473

Vascular end-stage disease, prevention of 271
Vascular injury 380
Vascular pedicle 23
Vascular remodeling 339
Vascular smooth muscle cell 381, 455, 490
Vascular tone 473
Vasculitis 583
Vasoactive agents 457
Vasoactive intestinal peptide 242
Vasodilator 492, 554, 620
Vasoreactivity testing, acute 236
Vasospastic angina 602
Vein, ascending vertical 36*f*
Velocity time integral 88
Vena cava
  filters 227
  inferior 5, 49, 52, 219, 235, 306, 309
  interrupted inferior 296
  interruption 227
  junction of superior 9
  left superior 48, 306, 307, 307*f*
  superior 40, 49, 52, 305
Venous thromboembolism 218, 229, 291, 319
  predisposing factors for 219*b*
Venous thrombotic manifestations 292
Ventilation 222, 223, 228
Ventricular arrhythmia 15, 178, 282, 292, 455, 459, 502
  risk for 184
Ventricular distention 589
Ventricular dysfunction 263
Ventricular dyssynchrony 590
Ventricular function 36
Ventricular relation, determination on 24
Ventricular remodeling 628
  post myocardial infarction, pathophysiology of 623*t*
Ventricular septal defect 9, 11, 28, 30-34, 38, 45, 48, 49, 49*t*, 52, 69, 71, 101, 167, 300, 302, 304, 309, 618
  large 21*f*
  moderate-to-large 11
  types of 33
Ventricular septal rupture 176, 521, 524, 553-555, 554*f*, 556*f*, 557*t*, 560
  management of 555
  risk of 523
Ventricular tachycardia 116, 557
Vertebra, fused 19
Very-low-density lipoprotein 355, 356
Vijaya's echo
  criteria 138
  score 139*t*
Viral myocarditis 272
Viral origin, antigens of 293
Virtual-histology intravascular ultrasound 384
Viruses 187
Vis-à-vis lesser degrees 129
Viscera, abdominal 58
Visceral situs 24
Vitamin 192
  D 374
  K 202, 578
    agonist 329
    antagonist 178, 225, 227, 229, 320, 576, 578-580, 594, 612
Volanesorsen 376, 392
Volume conductors 261
Vomiting 617
von Willebrand factor 200, 489

W

Waist circumference 402
Warburg metabolism 243
Warburg phenotype 243
Warfarin 266, 267, 598, 614
  embryopathy 266
  triple therapy 320
Waterfall right hilum 21
Wave intensity analysis 442
Weakened cell membrane 504
Weakness 520
Wearable and mobile technologies 79
Weight loss 126, 173, 475, 476
  reduces 418
Weight management 327
Wells rule 220
White blood cell, shortening of 283
White thrombus 489
Whitecoat effect 125
Williams syndrome 168
Wolff-Parkinson-White syndrome 66*t*, 116
  delta wave 16
Worsened insulin resistance 418
Wrist blood pressure 7

X

X chromosome 270

Y

Y-chromosome 241
Yoga 128, 277
  exponents of 278
  philosophy 277
Yogasana 278, 280, 281

Z

Ziehl-Neelsen stain 162*f*
Zotarolimus-Eluting stents 475