

Contents

Foreword xi

Preface xiii

Contributors xv

Acknowledgments xvii

1. Molecular Basis of Cardiac Development

LAURA A. DYER, IVAN MOSKOWITZ, CAM PATTERSON

The Heart Fields and Heart Tube Formation 1

Looping and Laterality 4

Chamber Specification 6

Ventricular Septation and Myocardial Patterning 7

Conduction System Development 8

Valve Development 9

Atrial Septation 11

Arterial Pole Maturation 13

Epicardial and Coronary Vascular Development 15

Conclusions 16

Acknowledgments 17

References 17

2. Cardiac Metabolism in Health and Disease

LIONEL H. OPIE

Introduction 23

Energy Availability 23

Major Sources of Energy 23

Energy Expenditure: Work of the Heart 29

Pathological Alterations in Myocardial Energy Metabolism 30

Metabolism of Heart Failure 33

Mitochondrial Mechanisms in Heart Disease 34

References 35

3. Cardiac Atrophy and Remodeling

PAMELA A. HARVEY, LESLIE A. LEINWAND

Overview of Atrophic Cardiac Remodeling 37

Models of Atrophic Remodeling 37

Cardiac Workload Determines Cardiac Size 38

Morphological Features of the Atrophic Heart 39

Extracellular Matrix Remodeling with Cardiac Atrophy 40

Protein Homeostasis in the Healthy and Atrophic Heart 41

Metabolic Unloading of the Myocardium 42

Signaling Pathways Activated During Cardiac Atrophy 42

Molecular Alterations in Atrophic Remodeling: The Fetal Gene Program 43

Contractile Function in Cardiac Atrophy 44
Regulation of Atrophic Remodeling by microRNAs 45
Atrophic Remodeling due to Cardiac Pathology 45
Atrophic Remodeling as a Potential Therapeutic 47
Summary 47
References 48

4. The Pathophysiology of Cardiac Hypertrophy and Heart Failure

WILLIAM E. STANSFIELD, MARK RANEK, AVANI PENDESE,
JONATHAN C. SCHISLER, SHAOBIN WANG,
THOMAS PULINKUNNIL, MONTE S. WILLIS

Introduction 51

Etiology of Heart Failure 51

Physiologic Hypertrophy 53

Pathologic Hypertrophy 57

Molecular Mechanisms of Pathologic LVH 58

References 70

Ischemic Heart Disease and its Consequences

JOHN W. CALVERT

Introduction 79

Pathophysiology of Ischemia-Reperfusion Injury 79

Therapeutic Strategies to Combat Myocardial Ischemia-Reperfusion Injury 85

Clinical Trial Failure 95

Summary and Concluding Remarks 97

References 97

6. Pathophysiology of Cardiomyopathies

HARSIMRAN SAINI, SARA TABTABAI, JAMES R. STONE,
PATRICK T. ELLINOR

Introduction 101

Dilated Cardiomyopathy 101

Ischemic Cardiomyopathy 102

Idiopathic Dilated Cardiomyopathy 103

Chagas Disease-Related Cardiomyopathy 105

Alcoholic Cardiomyopathy 106

Peripartum Cardiomyopathy 107

Hypertrophic Cardiomyopathy 108

Restrictive Cardiomyopathy 109

Anderson-Fabry's Cardiomyopathy 111

Cardiac Hemosiderosis 112

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia 113

Left Ventricular Non-Compaction Cardiomyopathy	114
Role Of Genetic Testing and Future Directions	115
References	116

7. Cellular and Molecular Pathobiology of the Cardiac Conduction System

THOMAS J. HUND, SAKIMA A. SMITH, MICHAEL A. MAKARA,
PETER J. MOHLER

Overview of the Cardiac Conduction System	121
The Sinoatrial Node	122
The Atrioventricular Node	125
Bundle of His and Bundle Branches	127
Cardiac Purkinje Fibers	127
Role of Autonomic Nervous System	128
Human Conduction System Disease	129
MicroRNAs and Cardiac Conduction	132
References	132

8. Molecular Pathobiology of Myocarditis

ELISA CARTURAN, CRISTINA BASSO, GAETANO THIENE

Introduction	135
Etiology	136
Diagnosis	139
Pathogenic Mechanisms	146
Treatment	153
Consensus Statement on EMB from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology	154
References	155

9. Calcific and Degenerative Heart Valve Disease

ELENA AIKAWA, FREDERICK J. SCHOEN

Introduction	161
Normal Valve Function, Biomechanics, and Structure	161
Valve Development, Post-Developmental Adaptation, and Aging	164
Calcific Aortic Valve Disease (CAVD)	166
Mechanisms of CAVD	168
Animal Models of CAVD	172
Degenerative Mitral Valve Disease (DMVD)	172
Mechanisms of DMVD	175
Animal Models of Mitral Valve Disease	175
Future Research Opportunities in Heart Valve Disease: Key Questions	176
References	177

10. Vasculogenesis and Angiogenesis

JOSEPH F. ARBOLEDA-VELASQUEZ,
PATRICIA A. D'AMORE

Introduction	181
Vascular Development	181

Developmental Abnormalities	183
Angiogenic Component of Pathologies	186
References	191

11. Diseases of Medium-Sized and Small Vessels

J. CHARLES JENNETTE, JAMES R. STONE

Introduction	197
Normal Vessel Wall Structure	197
Vascular Cell Activation	198
Intimal Hyperplasia	199
Diabetic Vasculopathy	202
Amyloid Vasculopathy	203
Small Vessel Vasculitis	205
Kawasaki Disease	212
Giant Cell Arteritis	213
Vascular Trauma and the Hypothenar Hammer Syndrome	214
Vasospasm and Raynaud's Phenomenon	215
References	217

12. Pathophysiology of Atherosclerosis

MICHAEL A. SEIDMAN, RICHARD N. MITCHELL, JAMES R. STONE

Introduction	221
Early Lesions	222
Lipids in Atherosclerosis	222
Endothelial Activation	223
Inflammation in Atherosclerosis	224
The Atherosclerotic Plaque	225
Aortic Atherosclerosis and Atherosclerotic Aneurysms	228
The Genetics of Atherosclerosis	229
Clinical Implications	232
Laboratory and Animal Models	234
Conclusions	235
References	235

13. Genetic Diseases of the Aorta (Including Aneurysms)

MARC K. HALUSHKA

The Normal Aorta: Histology and Function	239
Gross Pathologic Changes to the Aorta	240
Demographics of Aneurysms and Dissections	241
Histopathologic Changes to the Aorta	242
Specific Genetic Syndromes and Causes of Aneurysm	244
Non-Genetic Causes of Aortic Aneurysm	249
Evidence for the TGF- β Pathway to be a Unifying Mechanism of Aortic Aneurysm	250
TGF- β Canonical and Non-Canonical Signaling in the Ascending Aorta	250
TGF- β Signaling in Ascending Aortic Diseases	251
TGF- β Signaling in the Descending Aorta	252
Biomarkers of Aneurysm	252
Treatment for Aneurysm	253
Future Directions	253
References	253

14. Blood Pressure Regulation and Pathology

RHIAN M. TOUYZ

Introduction	257
Definition of Essential (Primary) Hypertension	257
Genetics of Hypertension	259
Physiological Control of Blood Pressure	261
Cardiac Output and Hypertension	261
The Sympathetic Nervous System and Hypertension	261
The Kidney and Hypertension	261
Sodium and Hypertension	262
The Renin–Angiotensin System (RAS)	262
Angiotensin Receptors and Signaling	264
The Vascular System and Hypertension	265
Reactive Oxygen Species, Oxidative Stress, and Human Hypertension	269
New Drugs, Procedures, and Devices in the Management of Hypertension	270
Conclusions	271
Acknowledgments	271
References	271

15. Venous and Arterial Thrombosis

EVI X. STAVROU, ALVIN H. SCHMAIER

Introduction	277
Venous Thrombosis	277
Arterial Thrombosis	286
References	292

16. The Pericardium and its Diseases

POOJA GUPTA, AMAR IBRAHIM, JAGDISH BUTANY

The Pericardium and its Diseases	297
Serological Tests	299
Echocardiography	299
Pericardiocentesis and Biopsy	299
Specific Forms of Pericarditis	299
References	311

Index 315