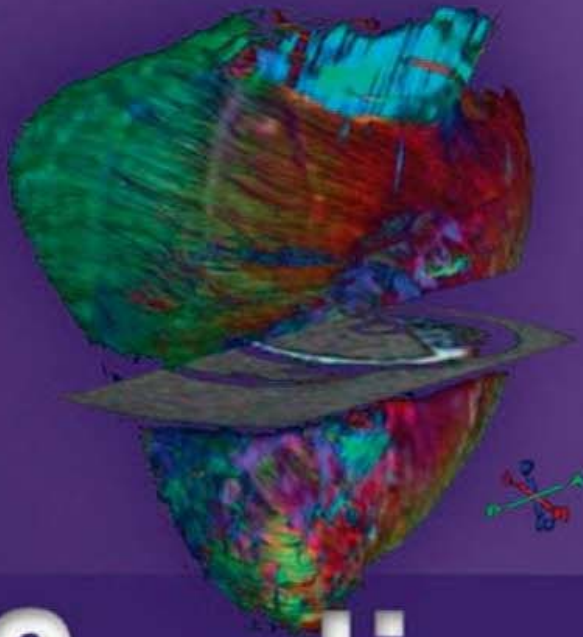
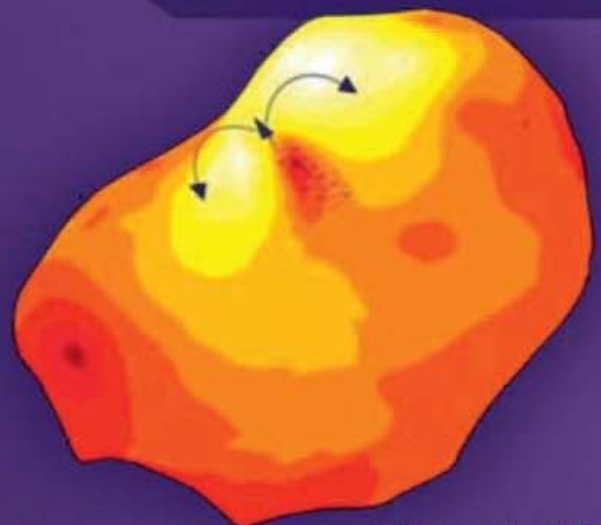


Zipes / Jalife / Stevenson



Cardiac Electrophysiology

From Cell to Bedside



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Seventh Edition

Cardiac Electrophysiology

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Douglas P. Zipes, MD

Distinguished Professor, Emeritus Professor of Medicine, Pharmacology, and Toxicology, Emeritus Director, Division of Cardiology and the Krannert Institute of Cardiology, Indiana University School of Medicine; Editor-in-Chief, PracticeUpdate/Cardiology, Editor-in-Chief, Trends in Cardiovascular Medicine, Indianapolis, IN, United States

José Jalife, MD

Cyrus and Jane Farrehi Professor of Cardiovascular Research, Department of Internal Medicine; Professor, Department of Molecular and Integrative Physiology; Co-Director, Center for Arrhythmia Research, University of Michigan, Ann Arbor, MI, United States; Senior Investigator, Fundación Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain

William G. Stevenson, MD

Director, Cardiac Arrhythmia Program, Cardiovascular Division, Brigham and Women's Hospital; Professor of Medicine, Harvard Medical School, Boston, MA, United States

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

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CONTRIBUTORS

Philip Aagaard, MD, PhD

Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic Foundation, Cleveland, OH, United States

Chapter 124: Catheter Ablation: Clinical Aspects

Dominic James Abrams, MD, MRCP

Director, Inherited Cardiac Arrhythmia Program, Department of Cardiology, Boston Children's Hospital, Boston, MA, United States

Chapter 74: Atrial Tachycardia in Adults With Congenital Heart Disease

Hugues Abriel, MD, PhD

Professor of Molecular Medicine, Managing Director, Institute of Biochemistry and Molecular Medicine, University of Bern, Bern, Switzerland

Chapter 18: Microdomain Interactions of Macromolecular Complexes and Regulation of the Sodium Channel $Na_v1.5$

Wayne O. Adkisson, MD

Assistant Professor, Division of Cardiovascular Medicine, University of Minnesota Medical Center, Minneapolis, MN, United States

Chapter 67: Head-up Tilt Table Testing

Esperanza Agullo-Pascual, PhD

Postdoctoral Fellow, Leon H. Charney Division of Cardiology, New York University School of Medicine, New York, NY, United States

Chapter 22: The Intercalated Disc: A Molecular Network That Integrates Electrical Coupling, Intercellular Adhesion, and Cell Excitability

Francisco J. Alvarado, PharmD

Graduate Student, Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, MI, United States

Chapter 53: Inheritable Phenotypes Associated With Altered Intracellular Calcium Regulation

Ahmad S. Amin, MD, PhD

Department of Clinical and Experimental Cardiology, Heart Centre, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Chapter 52: Inheritable Potassium Channel Diseases

Charles Antzelevitch, PhD

Executive Director, Cardiovascular Research, Lankenau Institute for Medical Research; Director of Research, Lankenau Heart Institute, Wynnewood, PA, United States

Chapter 51: Genetic, Ionic, and Cellular Mechanisms Underlying the J Wave Syndromes

Justus M.B. Anumonwo, PhD

Department of Internal Medicine and of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, MI, United States

Chapter 4: Structural and Molecular Bases of Cardiac Inward Rectifier Potassium Channel Function

Luciana Armaganijan, MD, MHS, PhD

Cardiologist Specialized in Electrophysiology, Dante Pazzanese Institute of Cardiology, São Paulo, Brazil

Chapter 115: Prevention of Stroke in Atrial Fibrillation: Warfarin and New Oral Anticoagulants

Arash Arya, MD

Department of Electrophysiology, Heart Centre, University of Leipzig, Leipzig, Germany

Chapter 85: Ventricular Tachycardia in Patients With Dilated Cardiomyopathy

Samuel Asirvatham, MD

Consultant, Department of Cardiovascular Diseases, Consultant, Department of Pediatrics and Adolescent Medicine, Mayo Clinic College of Medicine, Rochester, MN, United States

Chapter 61: Electroanatomical Mapping for Arrhythmias

Felipe Atenza, MD, PhD

Associate Professor of Medicine, School of Medicine, Universidad Complutense de Madrid; Senior Electrophysiologist, Department of Cardiology, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Chapter 46: Body Surface Frequency-Phase Mapping of Atrial Fibrillation

Peter H. Backx, DVM, PhD

Professor of Biology, York University, Toronto, ON, Canada

Chapter 3: Voltage-Gated Potassium Channels

Lisa M. Ballou, PhD

Research Assistant Professor, Department of Physiology and Biophysics, Stony Brook University Medical Center, Stony Brook, NY, United States

Chapter 11: Inhibition of Phosphoinositide 3-Kinase and Acquired Long QT Syndrome

Elise Balse, PhD

UPMC Univ Paris 6, INSERM UMR1166, Sorbonne University, Faculty of Medicine Pitié-Salpêtrière, Paris, France

Chapter 20: Macromolecular Complexes and Cardiac Potassium Channels

Sujata Balulad, MD

Helmsley Electrophysiology Center, Mount Sinai Medical Center, New York, NY, United States

Chapter 138: Renal Sympathetic Denervation

Andrea Barbuti, PhD

Associate Professor, Department of Biosciences, Università degli Studi di Milano, Milan, Italy

Chapter 25: Stem Cell–Derived Sinoatrial-Like Cardiomyocytes as a Novel Pharmacological Tool

Gust H. Bardy, MD

Clinical Professor of Medicine, University of Washington School of Medicine, Seattle Institute for Cardiac Research, Seattle, WA, United States

Chapter 118: Subcutaneous Implantable Cardioverter Defibrillators

Guillaume Bassil, MD

New York–Presbyterian Hospital/Weill Cornell Medical College, New York, NY, United States

Chapter 39: Pulmonary Vein Ganglia and the Neural Regulation of the Heart Rate

David G. Benditt, MD

Professor, Division of Cardiovascular Medicine, University of Minnesota Medical Center, Minneapolis, MN, United States

Chapter 67: Head-up Tilt Table Testing

Omer Berenfeld, PhD

Associate Professor, Internal Medicine and Biomedical Engineering, University of Michigan, Ann Arbor, MI, United States

Chapter 35: Computational Approaches for Accurate Rotor Localization in the Human Atria

Donald M. Bers, PhD

Distinguished Professor and Chair, Department of Pharmacology, University of California Davis, Davis, CA, United States

Chapter 16: Excitation–Contraction Coupling

Ofer Binah, PhD

Professor, The Ruth and Bruce Rappaport Faculty of Medicine, Technion—Israel Institute of Technology, Haifa, Israel

Chapter 26: Gene Therapy and Biological Pacing

Frank Bogun, MD

Associate Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, United States

Chapter 80: Premature Ventricular Complexes

Rossana Bongianino, MSc

Molecular Cardiology Laboratories, ICS Maugeri, IRCCS, Pavia, Italy

Chapter 56: Gene Therapy to Treat Cardiac Arrhythmias

Noel G. Boyle, MD, PhD

UCLA Cardiac Arrhythmia Center, David Geffen School of Medicine, UCLA Health System, Los Angeles, CA, United States

Chapter 123: Catheter Ablation: Technical Aspects

Patrick M. Boyle, PhD

Assistant Research Professor of Biomedical Engineering, Johns Hopkins University, Baltimore, MD, United States

Chapter 36: Modeling the Aging Heart

Günter Breithardt, MD

Professor Emeritus of Medicine and Cardiology, Department of Cardiovascular Medicine, University Hospital Münster, Münster, Germany

Chapter 101: Drug-Induced Ventricular Tachycardia

Marisa Brini, PhD

Department of Biology, University of Padova, Padova, Italy

Chapter 5: Mammalian Calcium Pumps in Health and Disease

Peter R. Brink, PhD

Distinguished Service Professor, Emeritus, Department of Physiology and Biophysics, Stony Brook University, Stony Brook, NY, United States

Chapter 15: Biophysical Properties of Gap Junctions

Chapter 26: Gene Therapy and Biological Pacing

Pedro Brugada, Prof., Dr.

Chairman, Cardiovascular Division, UZ Brussel—VUB, Brussels, Belgium

Chapter 92: Brugada Syndrome

Eric Buch, MD

Member, Cardiology, Adult Cardiac Catheterization Laboratory, Holter Laboratory, Pacemaker/ICD Clinic, UCLA Cardiac Arrhythmia Center, David Geffen School of Medicine, UCLA Health System, Los Angeles, CA, United States

Chapter 123: Catheter Ablation: Technical Aspects

Feliksas F. Bukauskas, PhD, Dr. Habil

Professor, Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY, United States; Institute of Cardiology, Lithuanian University of Health Sciences, 50009 Kaunas, Lithuania

Chapter 8: Molecular Organization, Gating, and Function of Connexin-Based Gap Junction Channels and Hemichannels

Hugh Calkins, MD

Director of the Arrhythmia Service, the Clinical Electrophysiology Laboratory, and the Arrhythmogenic Right Ventricular Dysplasia Program at Johns Hopkins, Baltimore, MD, United States

Chapter 87: Ventricular Tachycardias in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

David J. Callans, MD

Associate Director of Electrophysiology, Penn Medicine, University of Pennsylvania, Philadelphia, PA, United States

Chapter 64: Intracardiac Echocardiography for Electrophysiology

Sean M. Caples, DO, MSc

Consultant, Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, United States

Chapter 110: Sleep-Disordered Breathing and Arrhythmias

Ernesto Carafoli, MD

Venetian Institute for Molecular Medicine, Padova, Italy

Chapter 5: Mammalian Calcium Pumps in Health and Disease

William A. Catterall, PhD

Professor and Chair, Department of Pharmacology, University of Washington, Seattle, WA, United States

Chapter 1: Voltage-Gated Sodium Channels and Electrical Excitability of the Heart

Marina Cerrone, MD

Research Assistant Professor, Leon H. Charney Division of Cardiology, New York University School of Medicine, New York University School of Medicine, New York, NY, United States

Chapter 22: The Intercalated Disc: A Molecular Network That Integrates Electrical Coupling, Intercellular Adhesion, and Cell Excitability

Arnaud Chaumeil, MD

Department of Cardiology, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France

Chapter 128: Epicardial Approach in Electrophysiology

Caressa Chen, BS

Stanford Cardiovascular Institute, School of Medicine, Stanford University, Stanford, CA, United States

Chapter 30: Cardiac Remodeling and Regeneration

Lan S. Chen, MD

Professor of Clinical Neurology, Department of Neurology, Riley Hospital for Children, Indiana University, Indianapolis, IN

Chapter 40: Neural Activity and Atrial Tachyarrhythmias

Peng-Sheng Chen, MD

Medtronic Zipes Chair of Cardiology; Director, Krannert Institute of Cardiology; Chief, Division of Cardiology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, United States

Chapter 40: Neural Activity and Atrial Tachyarrhythmias

Jianding Cheng, MD, PhD

Department of Forensic Pathology, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, Guangdong, China; Division of Cardiovascular Medicine, Department of Medicine, University of Wisconsin, Madison, WI, United States

Chapter 98: Sudden Infant Death Syndrome

Nipavan Chiamvimonvat, MD

Roger Tatarian Endowed Professor of Cardiovascular Medicine, Department of Internal Medicine, University of California Davis, Davis; Staff Cardiologist, Department of Veterans Affairs, Northern California Health Care System, Mather, CA, United States

Chapter 24: Feedback Mechanisms for Cardiac-Specific MicroRNAs and cAMP Signaling in Electrical Remodeling

David J. Christini, PhD

Professor, Department of Medicine, Division of Cardiology, Weill Cornell Medicine, New York, NY, United States

Chapter 32: Global Optimization Approaches to Generate Dynamically Robust Electrophysiological Models

Aman Chugh, MD

Associate Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, United States

Chapter 77: Preexcitation, Atrioventricular Reentry, and Variants

Andreu M. Climent, PhD

Hospital General Universitario Gregorio Marañón, Department of Cardiology, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

Chapter 46: Body Surface Frequency–Phase Mapping of Atrial Fibrillation

Ira S. Cohen, MD, PhD

Leading Professor, Department of Physiology and Biophysics, Stony Brook University Medical Center, Stony Brook, NY, United States

Chapter 11: Inhibition of Phosphoinositide 3-Kinase and Acquired Long QT Syndrome
Chapter 26: Gene Therapy and Biological Pacing

Stuart J. Connolly, MD

Professor, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Chapter 115: Prevention of Stroke in Atrial Fibrillation: Warfarin and New Oral Anticoagulants

Lebron Cooper, MD

Professor and Chair, Department of Anesthesiology, University of Tennessee Health Science Center College of Medicine, Memphis, TN, United States

Chapter 132: Anesthesiology Considerations for the Electrophysiology Laboratory

Eric M. Crespo, MD

Director of the Interventional Electrophysiology Laboratory, Hartford Hospital, Hartford, CT

Chapter 65: Exercise-Induced Arrhythmias

Lia Crotti, MD, PhD

Assistant Professor, Molecular Medicine, University of Pavia, Pavia; Vice-Director, Center for Cardiac Arrhythmias of Genetic Origin, IRCCS Istituto Auxologico Italiano, Milano, Italy

Chapter 93: Long and Short QT Syndromes

Thomas A. Csepe, BSc

Department of Physiology & Cell Biology and Davis Heart & Lung Research Institute, The Ohio State University Wexner Medical Center, Columbus, OH, United States

Chapter 28: Mechanisms of Normal and Dysfunctional Sinoatrial Nodal Excitability and Propagation

Frank Cuoco, MD, MBA, MS

Associate Professor of Medicine, Division of Cardiology, Director, Cardiac Electrophysiology, Medical University of South Carolina, Charleston, SC, United States

Chapter 121: Newer Applications of Cardiac Pacemakers and Extracardiac Stimulation

Anne B. Curtis, MD

SUNY Distinguished Professor, Charles and Mary Bauer Professor and Chair, Department of Medicine, University at Buffalo, Buffalo, NY, United States

Chapter 107: Sex Differences in Arrhythmias

Ralph J. Damiano, Jr., MD

Evarts A. Graham Professor and Chief, Division of Cardiothoracic Surgery, Washington University School of Medicine, St. Louis, MO, United States

Chapter 133: Surgery for Atrial Fibrillation and Other Supraventricular Tachycardias

Dawood Darbar, MD

Chief and Professor of Medicine and Pharmacology, University of Illinois at Chicago, Chicago, IL, United States

Chapter 112: Standard Antiarrhythmic Drugs

Mithilesh K. Das, MD

Professor of Clinical Medicine, Cardiology/Medicine, Krannert Institute of Cardiology, Indianapolis, IN, United States

Chapter 59: Assessment of the Patient With a Cardiac Arrhythmia

Chapter 60: Differential Diagnosis of Narrow and Wide Complex Tachycardias

Andre d'Avila, MD, PhD

Director, Cardiac Arrhythmia Service, Hospital Cardiologico, Florianopolis, Santa Catarina, Brazil

Chapter 138: Renal Sympathetic Denervation

Mario Delmar, MD, PhD

Patricia and Robert Martinsen Professor of Cardiology, Professor of Medicine and Professor of Cell Biology, Leon H. Charney Division of Cardiology, New York University School of Medicine, New York, NY, United States

Chapter 22: The Intercalated Disc: A Molecular Network That Integrates Electrical Coupling, Intercellular Adhesion, and Cell Excitability

Eva Delpón, PhD

Professor, Department of Pharmacology, School of Medicine, Complutense University of Madrid, CIBERCV, Madrid, Spain

Chapter 21: Reciprocity of Cardiac Sodium and Potassium Channels in the Control of Excitability and Arrhythmias

Chapter 54: Pharmacological Bases of Antiarrhythmic Therapy

Marco Denegri, PhD

Molecular Cardiology Laboratories, ICS Maugeri, IRCCS, Pavia, Italy

Chapter 56: Gene Therapy to Treat Cardiac Arrhythmias

Arnaud Denis, MD

Centre Hospitalier Universitaire de Bordeaux, Hôpital Cardiologique du Haut Lévêque, Bordeaux, France

Chapter 125: Ablation for Atrial Fibrillation

Nicolas Derval, MD

Centre Hospitalier Universitaire de Bordeaux, Hôpital Cardiologique du Haut Lévêque, Bordeaux, France

Chapter 125: Ablation for Atrial Fibrillation

Isabelle Deschênes, PhD

Professor of Medicine, Physiology and Biophysics, and Biomedical Engineering, Case Western Reserve University; Director, Heart and Vascular Research Center, MetroHealth Medical Center, Cleveland, OH, United States

Chapter 9: Structure–Function Relations of Heterotrimeric Complexes of Sodium Channel α - and β -Subunits

Abhishek Deshmukh, MD

Senior Associate Consultant, Department of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, MN, United States

Chapter 61: Electroanatomical Mapping for Arrhythmias

Luigi Di Biase, MD, PhD, FACC, FHRS

Section Head, Electrophysiology, Director of Arrhythmia Services, Associate Professor of Medicine, Albert Einstein College of Medicine at Montefiore Hospital, New York, NY; Senior Researcher, Electrophysiology, Texas Cardiac Arrhythmia Institute at St. David's Medical Center; Associate Professor, Biomedical Engineering, University of Texas, Austin, TX, United States; Assistant Professor, Cardiology, University of Foggia, Foggia, Italy

Chapter 124: Catheter Ablation: Clinical Aspects

Timm M. Dickfeld, MD, PhD

Professor of Medicine, Maryland Arrhythmia and Cardiology Imaging Group (MACIG), Division of Cardiology, University of Maryland School of Medicine, Baltimore, MD, United States

Chapter 62: Computed Tomography for Electrophysiology

Hans Dierckx, PhD

Department of Physics and Astronomy, Ghent University, Belgium

Chapter 34: Theory of Rotors and Arrhythmias

Borislav Dinov, MD

Department of Electrophysiology, Heart Centre, University of Leipzig, Leipzig, Germany

Chapter 85: Ventricular Tachycardia in Patients With Dilated Cardiomyopathy

Sanjay Dixit, MD

Associate Professor, Medicine, Cardiovascular Division, Hospital of The University of Pennsylvania; Director, Cardiac Electrophysiology, Cardiology-Medicine, Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, United States

Chapter 134: Surgery for Ventricular Arrhythmias

Dobromir Dobrev, MD

Director, Institute of Pharmacology, Faculty of Medicine, University Duisburg-Essen, Essen, Germany

Chapter 42: The Molecular Pathophysiology of Atrial Fibrillation

Remi Dubois, PhD

Associate Professor, Ecole Supérieure de Physique et de Chimie Industrielles – ParisTech; Team Manager, Signal Processing, Electrophysiology and Heart Modeling Institute, Bordeaux, France

Chapter 47: Panoramic Mapping of Atrial Fibrillation From the Body Surface

Lars Eckardt, MD, PhD

Professor, Department of Cardiology and Angiology, Division of Electrophysiology, Münster, Germany

Chapter 101: Drug-Induced Ventricular Tachycardia

Andrew G. Edwards, PhD

Senior Research Scientist, Simula Research Laboratory; Senior Research Scientist, Institute for Experimental Medical Research, Oslo University Hospital Ullevål, Oslo, Norway

Chapter 33: Calcium Signaling in Cardiomyocyte Models With Realistic Geometries

Kenneth A. Ellenbogen, MD

Kontos Professor of Medicine, Division of Cardiology, Virginia Commonwealth University School of Medicine, Richmond, VA, United States

Chapter 73: Atrial Tachycardia**Patrick T. Ellinor, MD, PhD**

Associate Professor of Medicine, Harvard Medical School; Cardiac Arrhythmia Service, Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, United States

Chapter 49: Genetics of Atrial Fibrillation**N.A. Mark Estes III, MD**

Professor of Medicine, Tufts University School of Medicine; Director, Cardiac Arrhythmia Center, The CardioVascular Center, Tufts Medical Center, Boston, MA, United States

Chapter 108: Sudden Cardiac Deaths in Athletes, Including Commotio Cordis**Larissa Fabritz, MD**

Reader in Cardiovascular Sciences, Institute of Cardiovascular Sciences, University of Birmingham; Consultant, Department of Cardiology, University Hospitals Birmingham, Birmingham, United Kingdom

Chapter 113: Innovations in Antiarrhythmic Drug Therapy**Vadim V. Fedorov, PhD**

Associate Professor, Department of Physiology & Cell Biology and Davis Heart & Lung Research Institute, The Ohio State University Wexner Medical Center, Columbus, OH, United States

Chapter 28: Mechanisms of Normal and Dysfunctional Sinoatrial Nodal Excitability and Propagation**Antonio B. Fernandez, MD**

Assistant Professor of Medicine, Department of Medicine, University of Connecticut, Farmington, CT, United States; Director, Cardiac Intensive Care Unit, Division of Cardiology, Hartford Hospital, Hartford, CT, United States

Chapter 65: Exercise-Induced Arrhythmias**Elvis Teijeira Fernández, MD**

Fellow in Electrophysiology, Bordeaux Hospital University Center, Bordeaux, France

Chapter 111: Ventricular Assist Devices and Cardiac Transplantation Recipients**David Filgueiras-Rama, MD, PhD**

Assistant Health Scientist, Group Leader, Myocardial Pathophysiology Area, Fundación Centro Nacional de Investigaciones Cardiovasculares, Carlos III (CNIC); Cardiac Electrophysiologist, Cardiology, Hospital Clínico San Carlos; Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCv), Madrid, Spain

Chapter 41: Sympathetic Innervation and Cardiac Arrhythmias**Michael C. Fishbein, MD**

Piasky Professor of Pathology and Medicine, Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States

Chapter 40: Neural Activity and Atrial Tachyarrhythmias**Glenn I. Fishman, MD**

William Goldring Professor of Medicine, Director, Leon H. Charney Division of Cardiology, New York University School of Medicine, New York, NY, United States

Chapter 29: Cell Biology of the Specialized Cardiac Conduction System**David S. Frankel, MD**

Assistant Professor Medicine, Fellowship Program Director, Cardiovascular Division, Electrophysiology Section, Hospital of the University of Pennsylvania, Philadelphia, PA, United States

Chapter 84: Ischemic Heart Disease**Paul Friedman, MD**

Director, Cardiac Implantable Device Lab, Division of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, United States

Chapter 117: Implantable Cardioverter Defibrillator: Clinical Aspects**Antonio Frontera, MD**

Centre Hospitalier Universitaire de Bordeaux, Hôpital Cardiologique du Haut Lévêque, Bordeaux, France

Chapter 125: Ablation for Atrial Fibrillation**Apoor S. Gami, MD**

Cardiac Electrophysiologist, Advocate Medical Group, Elmhurst, IL, United States

Chapter 110: Sleep-Disordered Breathing and Arrhythmias**Paul Garabelli, MD**

Assistant Professor of Medicine, Heart Rhythm Institute, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States

Chapter 44: Role of the Autonomic Nervous System in Atrial Fibrillation**Alfred L. George, Jr., MD**

Professor and Chairman, Department of Pharmacology, Northwestern University Feinberg School of Medicine, Chicago, IL, United States

Chapter 50: Mechanisms in Heritable Sodium Channel Diseases**Edward P. Gerstenfeld, MD**

Professor of Medicine, Division of Cardiology, Department of Medicine, University of California San Francisco, San Francisco, CA, United States

Chapter 81: Outflow Tract Ventricular Tachyarrhythmias: Mechanisms, Clinical Features, and Management**Sigfus Gizurarson, MD, PhD**

Consultant, Department of Cardiology, Landspítali University Hospital, Reykjavik, Iceland; Consultant, Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden

Chapter 48: Mechanisms of Human Ventricular Tachycardia and Human Ventricular Fibrillation**Michael R. Gold, MD, PhD**

Michael E. Assey Professor of Medicine, Division of Cardiology; Medical University of South Carolina, Charleston, SC, United States

Chapter 121: Newer Applications of Cardiac Pacemakers and Extracardiac Stimulation

Jeffrey J. Goldberger, MD

Chief, Cardiovascular Division; Professor of Medicine,
Department of Medicine, University of Miami Miller School
of Medicine, Miami, FL, United States

Chapter 99: Sudden Cardiac Death in Adults

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Drugs on Sudden Cardiac Death**

Andrew Grace, MB, PhD

Cambridge University Health Partners, Cambridge, United
Kingdom

**Chapter 118: Subcutaneous Implantable Cardioverter
Defibrillators**

Full Prof. Guido Grassi

Medical Clinic, San Gerardo Hospital, Milano-Bicocca
University, Monza, Italy

Chapter 136: Baroreceptor Stimulation

Ruth Ann Greenfield, MD

Clinical Cardiac Electrophysiologist, Division of Cardiology,
Durham VA Medical Center, Durham, NC, United States

**Chapter 122: Remote Monitoring of Cardiac Implantable
Electronic Devices**

Wendy L. Gross, MD, MHCM

Assistant Professor of Anesthesiology, Harvard Medical School;
Vice Chair, Planning and Analytics Director of Non OR
Services, Department of Anesthesiology, Perioperative and
Pain Medicine, Brigham and Women's Hospital, Boston,
MA, United States

**Chapter 132: Anesthesiology Considerations for the
Electrophysiology Laboratory**

Blair P. Grubb, MD

Professor of Medicine and Pediatrics, Division of Cardiovascular
Medicine, The University of Toledo, Toledo, OH, United
States

Chapter 104: Postural Orthostatic Tachycardia Syndrome

María S. Guillem, PhD

ITACA UPV, ITACA Institute, Universitat Politècnica de
València, Valencia, Spain

**Chapter 46: Body Surface Frequency–Phase Mapping of
Atrial Fibrillation**

Sándor Györke, PhD

Professor, Physiology and Cell Biology, The Ohio State
University, Columbus, OH, United States

**Chapter 6: Structural and Molecular Bases of
Sarcoplasmic Reticulum Ion Channel Function**

Michel Haïssaguerre, MD

Professor of Medicine, CHU Bordeaux, University of Bordeaux,
LIRYC, Bordeaux, France

**Chapter 47: Panoramic Mapping of Atrial Fibrillation
From the Body Surface**

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Chapter 129: Ventricular Fibrillation

Johan Hake, PhD

Department of Bioengineering, University of California San
Diego, La Jolla, CA, United States; Simula Research Labora-
tory, Oslo, Norway

**Chapter 33: Calcium Signaling in Cardiomyocyte Models
With Realistic Geometries**

Henry R. Halperin, MD, MA

David J. Carver Professor of Medicine, Professor of Radiology
and Biomedical Engineering, Johns Hopkins University,
Baltimore, MD, United States

**Chapter 63: Computed Tomography and Magnetic
Resonance Imaging for Electrophysiology**

Brian J. Hansen, BSc

Department of Physiology & Cell Biology and Davis Heart &
Lung Research Institute, The Ohio State University Wexner
Medical Center, Columbus, OH, United States

**Chapter 28: Mechanisms of Normal and Dysfunctional
Sinoatrial Nodal Excitability and Propagation**

Stéphane Hatem, MD, PhD

UPMC Univ Paris 6, INSERM UMR1166, Sorbonne
University; Faculty of Medicine Pitié-Salpêtrière,
Department of Cardiology, Assistance Publique - Hôpitaux
de Paris, Pitié-Salpêtrière Hospital, Paris, France

**Chapter 20: Macromolecular Complexes and Cardiac
Potassium Channels**

David L. Hayes, MD

Mayo Clinic; Rochester, MN, United States

Chapter 119: Implantable Pacemakers

Jordi Heijman, PhD

Assistant Professor, Department of Cardiology, CARIM
School for Cardiovascular Diseases, Maastricht University,
Maastricht, The Netherlands

**Chapter 42: The Molecular Pathophysiology of Atrial
Fibrillation**

Todd J. Herron, PhD

Associate Research Scientist, Department of Internal Medicine,
Cardiovascular Medicine and Molecular & Integrative
Physiology, Ann Arbor, MI, United States

**Chapter 57: Highly Mature Human iPSC-Derived
Cardiomyocytes as Models for Cardiac
Electrophysiology and Drug Testing**

Gerhard Hindricks, MD

Professor and Head, Department of Electrophysiology, Heart
Centre, University of Leipzig, Leipzig, Germany

**Chapter 85: Ventricular Tachycardia in Patients With
Dilated Cardiomyopathy**

Mélèze Hocini, MD

Associate Professor, CHU Bordeaux, University of Bordeaux,
LIRYC, Bordeaux France

**Chapter 47: Panoramic Mapping of Atrial Fibrillation
From the Body Surface**

Chapter 125: Ablation for Atrial Fibrillation

Chapter 129: Ventricular Fibrillation

Stefan H. Hohnloser, MD

Professor of Cardiology, Department of Cardiology,
J.W. Goethe University, Frankfurt, Germany

Chapter 69: T-Wave Alternans

David R. Holmes, Jr., MD

Professor of Medicine, Division of Cardiovascular Diseases, Mayo
Clinic College of Medicine, Rochester, MN, United States

Chapter 139: Left Atrial Appendage Closure

Masahiko Hoshijima, MD, PhD

Associate Adjunct Professor, Center for Research in Biological Systems and Department of Medicine, University of California San Diego, La Jolla, CA, United States

Chapter 33: Calcium Signaling in Cardiomyocyte Models With Realistic Geometries

Thomas J. Hund, PhD

Associate Professor, Department of Biomedical Engineering, The Ohio State University College of Engineering, Columbus, OH, United States

Chapter 23: Function and Dysfunction of Ion Channel Membrane Trafficking and Posttranslational Modification

Mathew D. Hutchinson, MD

Professor of Medicine, Sarver Heart Center, University of Arizona; Banner University Medical Center, Tucson, AZ, United States

Chapter 64: Intracardiac Echocardiography for Electrophysiology

Leonard Ilkhanoff, MD

Inova Medical Group, Manassas, VA, United States

Chapter 114: Impact of Nontraditional Antiarrhythmic Drugs on Sudden Cardiac Death

Jodie Ingles, GradDipGenCouns, MPH, PhD

Conjoint Senior Lecturer, Centenary Institute of Cancer Medicine and Cell Biology, Central Clinical School, Sydney Medical School, University of Sydney, Sydney, NSW, Australia

Chapter 71: Genetic Testing

James E. Ip, MD

Assistant Professor, Department of Medicine, Weill Cornell Medicine, New York, NY, United States

Chapter 79: Junctional Tachycardia

Warren M. Jackman, MD

George Lynn Cross Research Professor, Heart Rhythm Institute, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States

Chapter 78: Electrophysiological Characteristics of Atrioventricular Nodal Reentrant Tachycardia: Implications for the Reentrant Circuits

Nicholas Jackson, BMedSc, MB BS, FRACP

Staff Specialist, Department of Cardiology, John Hunter Hospital; Conjoint Lecturer, School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia

Chapter 48: Mechanisms of Human Ventricular Tachycardia and Human Ventricular Fibrillation

Pierre Jaïs, MD

Professor of Medicine, CHU Bordeaux, University of Bordeaux, LIRYC, Bordeaux, France

Chapter 47: Panoramic Mapping of Atrial Fibrillation From the Body Surface

Chapter 111: Ventricular Assist Devices and Cardiac Transplantation Recipients

Chapter 125: Ablation for Atrial Fibrillation

Chapter 128: Epicardial Approach in Electrophysiology

José Jalife, MD

Cyrus and Jane Farrehi Professor of Cardiovascular Research, Department of Internal Medicine; Professor, Department of Molecular and Integrative Physiology; Co-Director, Center for Arrhythmia Research, University of Michigan, Ann Arbor, MI, United States; Senior Investigator, Fundación Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain

Chapter 21: Reciprocity of Cardiac Sodium and Potassium Channels in the Control of Excitability and Arrhythmias

Chapter 43: Myofibroblasts, Cytokines, and Persistent Atrial Fibrillation

Bong Sook Jhun, PhD

Instructor, Cardiovascular Research Center, Rhode Island Hospital; Department of Medicine, The Warren Alpert Medical School of Brown University, Providence RI, United States

Chapter 7: Organellar Ion Channels and Transporters

Roy M. John, MD, PhD

Director, Cardiac Arrhythmia Research; Associate Director, Electrophysiology Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, MA, United States

Chapter 89: Ventricular Arrhythmias in Heart Failure

Chapter 106: Atrioventricular Block

Monique Jongbloed, MD, PhD

Clinical Anatomist and Cardiologist, Leiden University Medical Center, Leiden, The Netherlands

Chapter 102: Ventricular Arrhythmias in Congenital Heart Disease

Luc Jordaens, MD, Dsc, PhD

Prof. Dr. Cardiology, University Ghent, Ghent, Belgium; Prof. Dr. Clinical Electrophysiology, Erasmus MC, Rotterdam, The Netherlands

Chapter 90: Arrhythmias and Conduction Disturbances in Noncompaction Cardiomyopathy

Jonathan M. Kalman, MBBS, PhD

Director of Cardiac Electrophysiology, Department of Cardiology, Royal Melbourne Hospital; Professor of Medicine, Department of Medicine, University of Melbourne, Melbourne, VIC, Australia

Chapter 72: Sinus Node Abnormalities

Chapter 75: Typical and Atypical Atrial Flutter: Mapping and Ablation

Timothy J. Kamp, MD, PhD

Professor of Medicine, Cell and Regenerative Biology, Tuchman Chair in Cardiology, Co-Director Stem Cell and Regenerative Medicine Center, University of Wisconsin–Madison, Madison, WI, United States

Chapter 58: Cardiac Repair With Human Pluripotent Stem Cell-Derived Cardiovascular Cells and Arrhythmia Risk

Mohamed H. Kanj, MD

Associate Director, Electrophysiology Laboratories, Robert and Suzanne Tomsich Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH, United States

Chapter 116: Implantable Cardioverter Defibrillators: Technical Aspects

Suraj Kapa, MD

Consultant, Department of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, MN, United States

Chapter 61: Electroanatomical Mapping for Arrhythmias

Beverly Karabin, RN, PhD, CNP

Certified Nurse Practitioner, Division of Cardiovascular Medicine, The University of Toledo, Toledo, OH, United States

Chapter 104: Postural Orthostatic Tachycardia Syndrome**Ioannis Karakikes, PhD**

Stanford Cardiovascular Institute and Department of Cardiothoracic Surgery, School of Medicine, Stanford University, Stanford, CA, United States

Chapter 30: Cardiac Remodeling and Regeneration**Demosthenes G. Katritsis, MD, PhD**

Director, Cardiology, Athens Euroclinic, Athens, Greece; Hon. Consultant Cardiologist, Cardiology, Guy's and St Thomas' Hospitals, London, United Kingdom

Chapter 105: Progressive Conduction System Disease**Kuljeet Kaur, PhD**

Department of Internal Medicine, Center for Arrhythmia Research, University of Michigan, Ann Arbor, MI, United States

Chapter 43: Myofibroblasts, Cytokines, and Persistent Atrial Fibrillation**Paulus Kirchhof, MD, FESC, FHRS**

Professor of Cardiovascular Medicine, Institute of Cardiovascular Sciences, University of Birmingham and SWBH and UHB NHS Trusts, Birmingham, United Kingdom; Chairman, AFNET, Münster, Germany

Chapter 113: Innovations in Antiarrhythmic Drug Therapy**André G. Kléber, MD**

Visiting Professor, Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States

Chapter 27: Cell-to-Cell Communication and Impulse Propagation**George J. Klein, MD, FRCG(C)**

Professor of Medicine, Department of Medicine, Western University, London, ON, Canada

Chapter 66: Cardiac Monitoring: Short- and Long-Term Recording**Peter Kohl, MD, PhD, FHRS, FAHA**

Scientific Director, University Heart Centre Freiburg/Bad Krozingen; Director, Institute for Experimental Cardiovascular Medicine, Medical School of the University of Freiburg, Freiburg, Germany, Chair in Cardiac Biophysics and Systems Biology, National Heart and Lung Institute, Imperial College London, London, England, United Kingdom

Chapter 14: Cardiac Stretch-Activated Channels and Mechano-Electric Coupling**Jayanthi N. Koneru, MBBS**

Assistant Professor, Division of Cardiology, Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA, United States

Chapter 73: Atrial Tachycardia**Jacob S. Koruth, MD**

Assistant Professor, Helmsley Electrophysiology Center, Mount Sinai Medical Center, New York, NY, United States

Chapter 138: Renal Sympathetic Denervation**Andrew D. Krahn, MD**

Professor and Head, Division of Cardiology, University of British Columbia, Vancouver, BC, Canada

Chapter 66: Cardiac Monitoring: Short- and Long-Term Recording**Chapter 97: Idiopathic Ventricular Fibrillation****Trine Krogh-Madsen, PhD**

Assistant Research Professor, Department of Medicine, Division of Cardiology, Weill Cornell Medicine, New York, NY, United States

Chapter 32: Global Optimization Approaches to Generate Dynamically Robust Electrophysiological Models**Karl Heinz Kuck, MD**

Professor and Chief, Department of Cardiology, Asklepios Klinik St. Georg, Hamburg, Germany

Chapter 126: Ablation of Supraventricular Tachyarrhythmias**Saurabh Kumar, MBBS, PhD**

Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, United States

Chapter 75: Typical and Atypical Atrial Flutter: Mapping and Ablation**Chapter 76: Atrial Fibrillation: Mechanisms, Clinical Features, and Management****Alexander Kushnir, MD, PhD**

Fellow, Division of Cardiology, New York–Presbyterian Hospital/Columbia University College of Physicians and Surgeons, New York, NY, United States

Chapter 2: Voltage-Gated Calcium Channels**Neal K. Lakdawala, MD, MSc**

Instructor of Medicine, Harvard Medical School; Associate Physician, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, United States

Chapter 89: Ventricular Arrhythmias in Heart Failure**Zachary W.M. Laksman, MD**

Clinical Assistant Professor; The University of British Columbia, Vancouver, British Columbia, Canada

Chapter 97: Idiopathic Ventricular Fibrillation**Rakesh Latchamsetty, MD**

Assistant Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, United States

Chapter 80: Premature Ventricular Complexes**Dennis H. Lau, MBBS, PhD**

Robert J. Craig Research Fellow and Staff Specialist, Centre for Heart Rhythm Disorders, South Australian Health and Medical Research Institute, University of Adelaide, Royal Adelaide Hospital, Adelaide, SA, Australia

Chapter 72: Sinus Node Abnormalities**Bruce B. Lerman, MD**

H. Altschul Master Professor of Medicine, Chief, Division of Cardiology, Director, Cardiac Electrophysiology Laboratory, Department of Medicine, Division of Cardiology, Cornell University Medical Center, New York–Presbyterian Hospital, New York, NY, United States

Chapter 79: Junctional Tachycardia

Richard Z. Lin, MD

Professor, Department of Physiology and Biophysics, Stony Brook University Medical Center, Stony Brook, NY, United States

Chapter 11: Inhibition of Phosphoinositide 3-Kinase and Acquired Long QT Syndrome

Shien-Fong Lin, PhD, MBA

Professor and Director, Institute of Biomedical Engineering, National Chiao-Tung University, Hsinchu, Taiwan; Professor, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, United States

Chapter 40: Neural Activity and Atrial Tachyarrhythmias

Mark S. Link, MD

Professor of Medicine, Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, United States

Chapter 108: Sudden Cardiac Deaths in Athletes, Including Commotio Cordis

Bin Liu, PhD

Research Scientist, The Ohio State University, Columbus, OH, United States

Chapter 6: Structural and Molecular Bases of Sarcoplasmic Reticulum Ion Channel Function

Christopher F. Liu, MD

Assistant Professor of Medicine, Division of Cardiology, Weill Cornell Medicine, Cornell University, New York, NY, United States

Chapter 79: Junctional Tachycardia

Deborah J. Lockwood, MB, BCH

Associate Professor of Medicine, Medicine/Cardiovascular, Heart Rhythm Institute, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States

Chapter 78: Electrophysiological Characteristics of Atrioventricular Nodal Reentrant Tachycardia: Implications for the Reentrant Circuits

Anatoli N. Lopatin, PhD

Associate Professor, Department of Physiology, University of Michigan, Ann Arbor, MI, United States

Chapter 4: Structural and Molecular Bases of Cardiac Inward Rectifier Potassium Channel Function

Steven A. Lubitz, MD, MPH

Assistant Professor of Medicine, Harvard Medical School; Cardiac Arrhythmia Service, Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, United States

Chapter 49: Genetics of Atrial Fibrillation

Rajiv Mahajan, MD, PhD

Leo J. Mahar Lecturer and Clinical Associate, Centre for Heart Rhythm Disorders, South Australian Health and Medical Research Institute, University of Adelaide, Royal Adelaide Hospital, Adelaide, SA, Australia

Chapter 72: Sinus Node Abnormalities

Jonathan C. Makielski, MD

Professor, Department of Medicine, University of Wisconsin, Madison, WI, United States

Chapter 98: Sudden Infant Death Syndrome

Marek Malik, PhD, MD, DSc

Professor and Senior Clinical Investigator, National Heart and Lung Institute, Imperial College London, London, England, United Kingdom

Chapter 68: Autonomic Regulation and Cardiac Risk

Francis E. Marchlinski, MD, FACC, FHRS

Professor of Medicine, Director of Cardiac Electrophysiology Program, Cardiovascular Division, Electrophysiology Section, Hospital of the University of Pennsylvania, Philadelphia, PA, United States

Chapter 84: Ischemic Heart Disease

Steven M. Markowitz, MD

Professor of Medicine, Weill Cornell Medicine, New York, NY, United States

Chapter 79: Junctional Tachycardia

Barry J. Maron, MD

Hypertrophic Cardiomyopathy Institute, Tufts Medical Center, Professor of Medicine, Tufts University School of Medicine, Boston, MA, United States

Chapter 86: Ventricular Arrhythmias in Hypertrophic Cardiomyopathy: Sudden Death, Risk Stratification, and Prevention With Implantable Defibrillators

Martin S. Maron, MD

Director of the Hypertrophic Cardiomyopathy Center, Tufts Medical Center; Assistant Professor, Tufts University School of Medicine, Boston, MA, United States

Chapter 86: Ventricular Arrhythmias in Hypertrophic Cardiomyopathy: Sudden Death, Risk Stratification, and Prevention With Implantable Defibrillators

Steven O. Marx, MD

Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, NY, United States

Chapter 2: Voltage-Gated Calcium Channels

Stéphane Massé, MASc

Biomedical Engineer, Cardiology, University Health Network, Toronto, Ontario, Canada

Chapter 48: Mechanisms of Human Ventricular Tachycardia and Human Ventricular Fibrillation

Andrew D. McCulloch, PhD

Professor and Jacobs School Distinguished Scholar, Director, Cardiac Biomedical Science and Engineering Center, Departments of Bioengineering and Medicine, University of California San Diego, La Jolla, California

Chapter 33: Calcium Signaling in Cardiomyocyte Models With Realistic Geometries

Pippa McKelvie-Sebileau, PhD

Centre Hospitalier Universitaire de Bordeaux, Hopital Cardiologique du Haut Leveque, L'institut de Rythmologie et Modélisation Cardiaque, Bordeaux, France

Chapter 129: Ventricular Fibrillation

Spencer J. Melby, MD

Associate Professor of Surgery, Division of Cardiothoracic Surgery, Washington University School of Medicine, St. Louis, MO, United States

Chapter 133: Surgery for Atrial Fibrillation and Other Supraventricular Tachycardias

Andreas Metzner, MD

Department of Cardiology, Asklepios Klinik St. Georg,
Hamburg, Germany

Chapter 126: Ablation of Supraventricular Tachyarrhythmias**Anushka P. Michailova, PhD[†]**

Associate Research Scientist, Department of Bioengineering,
University of California San Diego, La Jolla, CA, United States

Chapter 33: Calcium Signaling in Cardiomyocyte Models With Realistic Geometries**Gregory F. Michaud, MD**

Associate Professor of Medicine, Division of Cardiology,
Harvard Medical School, Brigham and Women's Hospital,
Boston, MA, United States

Chapter 76: Atrial Fibrillation: Mechanisms, Clinical Features, and Management**John M. Miller, MD**

Professor of Medicine, Department of Medicine, Indiana
University School of Medicine; Director, Cardiac
Electrophysiology Services, Indiana University Health,
Indianapolis, IN, United States

Chapter 60: Differential Diagnosis of Narrow and Wide Complex Tachycardias**Jyotsna Mishra, PhD**

Postdoctoral Fellow, Center for Translational Medicine,
Department of Medicine, Jefferson Medical College,
Thomas Jefferson University, Philadelphia, PA, United States

Chapter 7: Organellar Ion Channels and Transporters**Raul D. Mitrani, MD**

Division of Cardiology, University of Miami Miller School of
Medicine, Miami, FL, United States

Chapter 114: Impact of Nontraditional Antiarrhythmic Drugs on Sudden Cardiac Death**Peter J. Mohler, PhD**

Professor and Director, Dorothy M. Davis Heart and Lung
Research Institute, Departments of Physiology & Cell
Biology and Internal Medicine, The Ohio State University
Medical Center, Columbus, OH, United States

Chapter 23: Function and Dysfunction of Ion Channel Membrane Trafficking and Posttranslational Modification**Fred Morady, MD**

McKay Professor of Cardiovascular Disease and Professor of
Internal Medicine, University of Michigan Medical School,
Ann Arbor, MI, United States

Chapter 77: Preexcitation, Atrioventricular Reentry, and Variants**Robert J. Myerburg, MD**

Professor of Medicine and Physiology, American Heart
Association Chair in Cardiovascular Research, Department
of Medicine, University of Miami Miller School of Medicine,
Miami, FL, United States

Chapter 99: Sudden Cardiac Death in Adults**Hiroshi Nakagawa, MD, PhD**

Professor of Medicine, Heart Rhythm Institute, University of
Oklahoma Health Sciences Center, Oklahoma City, OK,
United States

Chapter 78: Electrophysiological Characteristics of Atrioventricular Nodal Reentrant Tachycardia: Implications for the Reentrant Circuits**Chrisan Joseph Nalliah, MBBS, BSc**

Department of Cardiology and Department of Medicine, Royal
Melbourne Hospital, University of Melbourne, Melbourne,
VIC, Australia

Chapter 75: Typical and Atypical Atrial Flutter: Mapping and Ablation**Kumaraswamy Nanthakumar, MD**

Electrophysiologist, Cardiology, University Health Network;
Professor of Medicine, Department of Medicine, University
of Toronto, Toronto, Ontario, Canada

Chapter 48: Mechanisms of Human Ventricular Tachycardia and Human Ventricular Fibrillation**Carlo Napolitano, MD, PhD, FHRS**

Senior Scientist, Molecular Cardiology Laboratories, ICS
Maugeri IRCCS, Pavia, Italy

**Chapter 56: Gene Therapy to Treat Cardiac Arrhythmias
Chapter 95: Timothy Syndrome****Sanjiv M. Narayan, MD, PhD**

Professor of Medicine, Division of Cardiovascular Medicine,
Stanford University School of Medicine, Stanford, CA,
United States

Chapter 45: Rotors in Human Atrial Fibrillation**Andrea Natale, MD, FACC, FHRS, FESC**

Executive Medical Director, Texas Cardiac Arrhythmia Institute
at St. David's Medical Center, Austin, TX, United States

Chapter 124: Catheter Ablation: Clinical Aspects**Stanley Nattel, MD**

Professor of Medicine and Paul-David Chair in Cardiovascular
Electrophysiology, Medicine, Montreal Heart Institute and
University of Montreal, Montreal, Quebec, Canada

Chapter 42: The Molecular Pathophysiology of Atrial Fibrillation**Saman Nazarian, MD, PhD**

Associate Professor of Medicine, Section for Cardiac Electro-
physiology, The University of Pennsylvania Perelman School
of Medicine, Philadelphia, PA, United States

**Chapter 63: Computed Tomography and Magnetic Resonance Imaging for Electrophysiology
Chapter 100: Arrhythmia in Neurological Disease****Thao P. Nguyen, MD, PhD**

UCLA Cardiovascular Research Laboratory, Division of
Cardiology, Department of Medicine, David Geffen School
of Medicine, University of California Los Angeles, Los
Angeles, United States

Chapter 50: Mechanisms in Heritable Sodium Channel Diseases

[†]Deceased.

Akihiko Nogami, MD, PhD

Professor, Cardiovascular Division, University of Tsukuba,
Tsukuba, Ibaraki, Japan

Chapter 83: Bundle Branch Reentry Tachycardia

Sami F. Noujaim, PhD

Assistant Professor, Director of Cardiac Electrophysiology
Research, Department of Molecular Pharmacology and
Physiology, University of South Florida Morsani College of
Medicine, Tampa, FL, United States

**Chapter 13: Molecular Regulation of Cardiac Inward Rectifier
Potassium Channels by Pharmacological Agents**

**Chapter 39: Pulmonary Vein Ganglia and the Neural
Regulation of the Heart Rate**

Karine Nubret Le Coniat, MD

Anesthesiology Department, Centre Hospitalier Universitaire
de Bordeaux, Bordeaux, France

**Chapter 111: Ventricular Assist Devices and Cardiac
Transplantation Recipients**

Brian Olshansky, MD

Professor Emeritus, Department of Internal Medicine, University
of Iowa Hospitals and Clinics, Iowa City, IA, United States

Chapter 83: Bundle Branch Reentry Tachycardia

Jin O-Uchi, MD, PhD

Assistant Professor of Medicine, Cardiovascular Research
Center, Rhode Island Hospital; Department of Medicine,
The Warren Alpert Medical School of Brown University,
Providence, RI, United States

Chapter 7: Organellar Ion Channels and Transporters

Gavin Y. Oudit, MD, PhD, FRCPC

Division of Cardiology, University of Alberta, Edmonton, AB,
Canada

Chapter 3: Voltage-Gated Potassium Channels

Feifan Ouyang, MD

Department of Cardiology, Asklepios Klinik St. Georg,
Hamburg, Germany

**Chapter 126: Ablation of Supraventricular
Tachyarrhythmias**

Cevher Ozcan, MD

Assistant Professor of Medicine, Department of Medicine,
Section of Cardiology, University of Chicago, Chicago, IL,
United States

Chapter 107: Sex Differences in Arrhythmias

Douglas L. Packer, MD

Division of Cardiology, Mayo Clinic College of Medicine,
Rochester, MN, United States

Chapter 139: Left Atrial Appendage Closure

Sandeep V. Pandit, PhD

Adjunct Associate Research Scientist, Internal Medicine-
Cardiology, University of Michigan, Ann Arbor, MI,
United States

Chapter 31: Ionic Mechanisms of Atrial Action Potentials

Alexander V. Panfilov, PhD

Professor, Department of Physics and Astronomy, Ghent
University, Ghent, Belgium

Chapter 34: Theory of Rotors and Arrhythmias

David S. Park, MD, PhD

Assistant Professor of Medicine, Cardiac Electrophysiology,
New York University School of Medicine, New York, NY,
United States

**Chapter 29: Cell Biology of the Specialized Cardiac
Conduction System**

Bence Patocskaï, MD, PhD

Intern, Universitätsmedizin Mannheim, Heidelberg University,
Heidelberg, Germany

**Chapter 51: Genetic, Ionic, and Cellular Mechanisms
Underlying the J Wave Syndromes**

Dainius H. Pauza, PhD

Professor, Institute of Anatomy, Lithuanian University of
Health Sciences, Kaunas, Lithuania

Chapter 37: Innervation of the Sinoatrial Node

Neringa Pauziene, PhD

Professor, Institute of Anatomy, Lithuanian University of
Health Sciences, Kaunas, Lithuania

Chapter 37: Innervation of the Sinoatrial Node

Jonathan P. Piccini, MD, MHS

Associate Professor of Medicine, Division of Cardiology Duke
University Hospital; Duke Clinical Research Institute,
Durham, NC, United States

**Chapter 122: Remote Monitoring of Cardiac Implantable
Electronic Devices**

Geoffrey S. Pitt, MD, PhD

Ida and Theo Rossi Distinguished Professor of Medicine,
Director, Cardiovascular Research Institute, Weill Cornell
Medicine, New York, NY, United States

**Chapter 19: Fibroblast Growth Factor Homologous Factors
Modulate Cardiac Sodium and Calcium Channels**

Sunny S. Po, MD, PhD

Professor of Medicine, Heart Rhythm Institute, University of
Oklahoma Health Sciences Center, Oklahoma City, OK,
United States

**Chapter 44: Role of the Autonomic Nervous System in
Atrial Fibrillation**

Abhiram Prasad, MD, FRCP, FACC

Professor of Medicine, Department of Cardiovascular Diseases,
Mayo Clinic, Rochester, MN, United States

**Chapter 91: Ventricular Arrhythmias in Takotsubo
Cardiomyopathy**

Silvia G. Priori, MD, PhD

Professor of Cardiology, ICS Maugeri, IRCCS and Department
of Molecular Medicine, University of Pavia, Pavia, Italy

**Chapter 56: Gene Therapy to Treat Cardiac Arrhythmias
Chapter 95: Timothy Syndrome**

Przemysław B. Radwański, PharmD, PhD

Research Assistant Professor, Pharmacy Practice and Science,
The Ohio State University College of Pharmacy, Columbus,
OH, United States

**Chapter 6: Structural and Molecular Bases of
Sarcoplasmic Reticulum Ion Channel Function**

Wouter-Jan Rappel, PhD

Principal Investigator, Rappel Laboratory at the Department of Physics, UC San Diego, La Jolla, CA, United States

Chapter 45: Rotors in Human Atrial Fibrillation

Michelle Reiser, MS

Research Specialist, Department of Molecular Pharmacology and Physiology, Morsani College of Medicine, University of South Florida, Tampa, FL, United States

Chapter 13: Molecular Regulation of Cardiac Inward Rectifier Potassium Channels by Pharmacological Agents

Alejandro Jimenez Restrepo, MD

Clinical Assistant Professor of Medicine, Case Western Reserve University, Cleveland, OH, United States; Consultant Electrophysiologist, Cleveland Clinic Abu Dhabi, United Arab Emirates

Chapter 62: Computed Tomography for Electrophysiology

Richard B. Robinson, PhD

Professor of Pharmacology in the Center for Molecular Therapeutics, Professor, Department of Pharmacology, Columbia University Medical Center, New York, NY, United States

Chapter 25: Stem Cell-Derived Sinoatrial-Like Cardiomyocytes as a Novel Pharmacological Tool
Chapter 26: Gene Therapy and Biological Pacing

Dan M. Roden, MD

Professor, Departments of Medicine, Pharmacology, and Biomedical Informatics; Senior Vice President for Personalized Medicine, Vanderbilt University Medical Center, Nashville, TN, United States

Chapter 55: Pharmacogenomics of Cardiac Arrhythmias

Michael R. Rosen, MD

Gustavus A. Pfeiffer Professor of Pharmacology and Professor of Pediatrics, Columbia University, New York; Adjunct Professor, Department of Physiology and Biophysics, Stony Brook University, Stony Brook, NY, United States

Chapter 26: Gene Therapy and Biological Pacing

Raphael Rosso, MD

Head of the Atrial Fibrillation Service, Cardiology, Tel Aviv Sourasky Medical Center; Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Chapter 96: J-Wave Syndromes

Yoram Rudy, PhD

Fred Saigh Distinguished Professor, Professor of Biomedical Engineering, Cell Biology and Physiology, Medicine, Radiology, and Pediatrics; Director, Cardiac Bioelectricity and Arrhythmia Center (CBAC); Washington University in St. Louis, St. Louis, MO, United States

Chapter 70: Noninvasive Electrocardiographic Imaging of Arrhythmogenic Substrates and Ventricular Arrhythmias in Patients

Kristina Rysevaite-Kyguoliene, PhD

Assistant Professor, Institute of Anatomy, Lithuanian University of Health Sciences, Kaunas, Lithuania

Chapter 37: Innervation of the Sinoatrial Node

Hani N. Sabbah, PhD, FACC, FCCP, FHRS

Professor of Medicine, Wayne State University; Director of Cardiovascular Research, Henry Ford Health System, Detroit, MI, United States

Chapter 135: Vagus Nerve Stimulation for the Treatment of Heart Failure

Frederic Sacher, MD, PhD

Arrhythmia Department, Centre Hospitalier Universitaire de Bordeaux, L'institut de Rythmologie et Modélisation Cardiaque, Bordeaux, France

Chapter 111: Ventricular Assist Devices and Cardiac Transplantation Recipients
Chapter 128: Epicardial Approach in Electrophysiology

Frank B. Sachse, PhD

Associate Professor, Department of Bioengineering, Nora Eccles Harrison Cardiovascular Research and Training Institute, University of Utah, Salt Lake City, UT, United States

Chapter 12: Structural Determinants and Biophysical Properties of hERG1 Channel Gating

Ardan M. Saguner, MD

Department of Cardiology, University Hospital Zürich, Zürich, Switzerland

Chapter 126: Ablation of Supraventricular Tachyarrhythmias

Prashanthan Sanders, MBBS, PhD

Knapman Chair of Cardiology Research and Director of Cardiac Electrophysiology, Centre for Heart Rhythm Disorders, South Australian Health and Medical Research Institute, University of Adelaide, Royal Adelaide Hospital, Adelaide, SA, Australia

Chapter 72: Sinus Node Abnormalities
Chapter 75: Typical and Atypical Atrial Flutter: Mapping and Ablation

Michael C. Sanguinetti, PhD

Professor, Department of Medicine, Nora Eccles Harrison Cardiovascular Research and Training Institute, University of Utah, Salt Lake City, UT, United States

Chapter 12: Structural Determinants and Biophysical Properties of hERG1 Channel Gating

Pasquale Santangeli, MD, PhD

Assistant Professor of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, United States

Chapter 124: Catheter Ablation: Clinical Aspects

Mohammad Sarraf, MD

Director of Structural Heart Disease, Assistant Professor, University of Alabama, Birmingham, AL, United States

Chapter 139: Left Atrial Appendage Closure

Jonathan Satin, PhD

Professor, Department of Physiology, University of Kentucky College of Medicine, Lexington, KY, United States

Chapter 10: Regulation of Cardiac Calcium Channels

Martin Jan Schalij, MD, PhD

Professor of Cardiology, Chief of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

Chapter 102: Ventricular Arrhythmias in Congenital Heart Disease

Benjamin J. Scherlag, MA, PhD

Heart Rhythm Institute, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States

Chapter 44: Role of the Autonomic Nervous System in Atrial Fibrillation

Matthew R. Schill, MD

Research Fellow, Department of Surgery, Washington University in St. Louis, St. Louis, MO, United States

Chapter 133: Surgery for Atrial Fibrillation and Other Supraventricular Tachycardias

J. William Schleifer, MD

Division of Cardiovascular Diseases, Mayo Clinic Arizona, Scottsdale, AZ, United States

Chapter 103: Syncope

Richard B. Schuessler, PhD

Professor of Surgery and Biomedical Engineering, Washington University School of Medicine, St. Louis, MO, United States

Chapter 133: Surgery for Atrial Fibrillation and Other Supraventricular Tachycardias

Peter J. Schwartz, MD

Director, Center for Cardiac Arrhythmias of Genetic Origin, IRCCS Istituto Auxologico Italiano, Milano, Italy

Chapter 93: Long and Short QT Syndromes

Timon Seeger, MD

Stanford Cardiovascular Institute, School of Medicine, Stanford University, Stanford, CA, United States

Chapter 30: Cardiac Remodeling and Regeneration

Christopher Semsarian, MBBS, PhD, MPH

Head, Molecular Cardiology Program, Centenary Institute; Professor of Medicine, University of Sydney; Cardiologist, Royal Prince Alfred Hospital; NHMRC Practitioner Fellow; Sydney, NSW, Australia

Chapter 71: Genetic Testing

Prof. Gino Seravalle

Cardiology, S. Luca Hospital, Istituto Auxologico Italiano, Milan, Italy

Chapter 136: Baroreceptor Stimulation

Ashok J. Shah, MBBS, MD, DM, CCDS

CHU Bordeaux, University of Bordeaux, LIRYC, Bordeaux, France

Chapter 47: Panoramic Mapping of Atrial Fibrillation From the Body Surface

Chapter 129: Ventricular Fibrillation

Robin M. Shaw, MD, PhD

Wasserman Endowed Chair in Cardiology, Heart Institute and Department of Medicine, Cedars-Sinai Medical Center and UCLA, Los Angeles, CA, United States

Chapter 17: Ion Channel Trafficking in the Heart

Mark J. Shen, MD

Cardiology Fellow, Department of Medicine, Krannert Institute of Cardiology, Indiana University, Indianapolis, IN, United States

Chapter 40: Neural Activity and Atrial Tachyarrhythmias

Chapter 137: Spinal Cord Stimulation for Heart Failure and Arrhythmias

Win-Kuang Shen, MD

Professor and Chair, Cardiovascular Diseases, Mayo Clinic Arizona, Phoenix, AZ, United States

Chapter 103: Syncope

Shey-Shing Sheu, PhD

Professor and Associate Director, Center for Translational Medicine, Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, United States

Chapter 7: Organellar Ion Channels and Transporters

Kalyanam Shivkumar, MD, PhD, FHRS

UCLA Cardiac Arrhythmia Center, David Geffen School of Medicine, UCLA Health System, Los Angeles, CA, United States

Chapter 123: Catheter Ablation: Technical Aspects

Jennifer N.A. Silva, MD

Director, Pediatric Electrophysiology, Division of Pediatric Cardiology, Washington University School of Medicine, St. Louis, MO, United States

Chapter 130: Ablation in Pediatrics

Allan C. Skanes, MD

Professor, Arrhythmia Service, Western University; Director of Electrophysiology Laboratory, London Heart Rhythm Program, London, ON, Canada

Chapter 66: Cardiac Monitoring: Short- and Long-Term Recording

Kyoko Soejima, MD

Professor, Department of Cardiology, Kyorin University School of Medicine, Tokyo, Japan

Chapter 82: Fascicular Ventricular Arrhythmias

Virend K. Somers, MD, PhD

Department of Internal Medicine, Divisions of Hypertension and Cardiovascular Diseases, Rochester, MN, United States

Chapter 110: Sleep-Disordered Breathing and Arrhythmias

Dan Sorajja, MD

Assistant Professor of Medicine, Cardiovascular Diseases/Electrophysiology, Mayo Clinic Arizona, Phoenix, AZ, United States

Chapter 103: Syncope

Stavros Stavrakis, MD, PhD

Heart Rhythm Institute, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States

Chapter 44: Role of the Autonomic Nervous System in Atrial Fibrillation

Christian Steinberg, MD

Division of Cardiology, Quebec Heart and Lung Institute, Quebec, Quebec, Canada

Chapter 97: Idiopathic Ventricular Fibrillation

Lynne Warner Stevenson, MD

Professor of Medicine, Harvard Medical School; Director of Cardiomyopathy and Heart Failure, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, United States

Chapter 89: Ventricular Arrhythmias in Heart Failure

William G. Stevenson, MD

Director, Cardiac Arrhythmia Program, Cardiovascular Division, Brigham and Women's Hospital; Professor of Medicine, Harvard Medical School, Boston, MA, United States

- Chapter 127: Catheter Ablation for Ventricular Tachycardia With or Without Structural Heart Disease**
Chapter 132: Anesthesiology Considerations for the Electrophysiology Laboratory

Michael O. Sweeney, MD

Associate Professor of Medicine, Cardiovascular Division, Harvard Medical School; Cardiac Pacing and Heart Failure Device Therapy, Brigham and Women's Hospital, Boston, MA, United States

- Chapter 120: Use of QRS Fusion Complex Analysis in Cardiac Resynchronization Therapy**

Charles Swerdlow, MD

Cedars Sinai Heart Institute, Clinical Professor of Medicine, University of California Los Angeles and Cedars Sinai Medical Center, Los Angeles, CA, United States

- Chapter 117: Implantable Cardioverter Defibrillator: Clinical Aspects**

Masateru Takigawa, MD

Department of Cardiovascular Medicine, Tokyo Medical and Dental University; Cardiovascular Center, Yokosuka Kyosai Hospital, Tokyo, Japan

- Chapter 125: Ablation for Atrial Fibrillation**

Juan Tamargo, MD, PhD, FESC

Professor of Pharmacology, Department of Pharmacology, School of Medicine, Universidad Complutense, CIBERCV, Madrid, Spain

- Chapter 54: Pharmacological Bases of Antiarrhythmic Therapy**

Harikrishna Tandri, MBBS, MD

Department of Medicine, Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD, United States

- Chapter 87: Ventricular Tachycardias in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy**

Usha B. Tedrow, MD, MSH

Director, Clinical Cardiac Electrophysiology Program, Department of Medicine, Cardiovascular Division, Brigham and Women's Hospital; Assistant Professor of Medicine, Harvard Medical School, Boston, MA, United States

- Chapter 127: Catheter Ablation for Ventricular Tachycardia With or Without Structural Heart Disease**

Nathaniel Thompson, MD

Centre Hospitalier Universitaire de Bordeaux, Hôpital Cardiologique du Haut Lévêque, Bordeaux, France

- Chapter 125: Ablation for Atrial Fibrillation**

Paul D. Thompson, MD

Chief of Cardiology, Division of Cardiology, Hartford Hospital, Hartford, CT, United States

- Chapter 65: Exercise-Induced Arrhythmias**

Gordon F. Tomaselli, MD

Michel Mirowski MD Professor of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, United States

- Chapter 38: Mechanisms for Altered Autonomic and Oxidant Regulation of Cardiac Sodium Currents**

Jeffrey A. Towbin, MD, MS

Executive Co-Director and Chief, Pediatric Cardiology, Heart Institute, Le Bonheur Children's Hospital; Professor, Pediatric Cardiology, University of Tennessee Health Science Center; Chief, Pediatric Cardiology, Pediatrics, St. Jude Children's Research Hospital; Vice Chair of Pediatrics for Strategy Advancement, Pediatrics, University of Tennessee Health Science Center, Memphis, TN, United States

- Chapter 90: Arrhythmias and Conduction Disturbances in Noncompaction Cardiomyopathy**

Natalia A. Trayanova, PhD

Murray B. Sachs Endowed Chair, Professor of Biomedical Engineering and Medicine, Johns Hopkins University, Baltimore, MD, United States

- Chapter 36: Modeling the Aging Heart**

Martin Tristani-Firouzi, MD

Professor, Division of Pediatric Cardiology, University of Utah School of Medicine; Associate Director, Nora Eccles Harrison Cardiovascular Research and Training Institute, Salt Lake City, UT, United States

- Chapter 94: Andersen-Tawil Syndrome**

Zian H. Tseng, MD, MAS

Associate Professor of Medicine in Residence, Section of Cardiac Electrophysiology, Division of Cardiology, Department of Medicine, University of California San Francisco, San Francisco, CA, United States

- Chapter 81: Outflow Tract Ventricular Tachyarrhythmias: Mechanisms, Clinical Features, and Management**

Akiko Ueda, MD

Assistant Professor, Department of Cardiology, Kyorin University School of Medicine, Tokyo, Japan

- Chapter 82: Fascicular Ventricular Arrhythmias**

Héctor H. Valdivia, MD, PhD

Frank N. Wilson Professor of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, United States

- Chapter 53: Inheritable Phenotypes Associated With Altered Intracellular Calcium Regulation**

Virginijus Valiunas, PhD

Research Associate Professor, Department of Physiology and Biophysics, Stony Brook University, Stony Brook, NY, United States

- Chapter 15: Biophysical Properties of Gap Junctions**

Christian van der Werf, MD, PhD

Department of Clinical and Experimental Cardiology, AMC Heart Center, Academic Medical Center, Amsterdam, The Netherlands

- Chapter 88: Ventricular Tachycardias in Catecholaminergic Cardiomyopathy (Catecholaminergic Polymorphic Ventricular Tachycardia)**

George F. Van Hare, MD

Professor, Department of Pediatrics, Washington University School of Medicine; Director, Pediatric Cardiology, St. Louis Children's Hospital, St. Louis, MO, United States

Chapter 130: Ablation in Pediatrics

David Vidmar, MSc

Graduate Student, Rappel Laboratory at the Department of Physics, UC San Diego, La Jolla, CA, United States

Chapter 45: Rotors in Human Atrial Fibrillation

Sami Viskin, MD

Director, Cardiac Hospitalization, Tel Aviv Medical Center; Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Chapter 96: J-Wave Syndromes

Niels Voigt, MD

Professor of Molecular Pharmacology, Institute of Pharmacology and Toxicology, University Medical Center Göttingen, Georg-August University, Göttingen, Germany

Chapter 42: The Molecular Pathophysiology of Atrial Fibrillation

Edward P. Walsh, MD

Chief, Cardiac Electrophysiology Division, Department of Cardiology, Boston Children's Hospital, Boston, MA, United States

Chapter 109: Arrhythmias in the Pediatric Population
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Paul J. Wang, MD

Professor of Medicine and Bioengineering (by courtesy), Director, Arrhythmia Service, Department of Medicine, Stanford University, Stanford, CA, United States

Chapter 119: Implantable Pacemakers

Xander H.T. Wehrens, MD, PhD

Director, Cardiovascular Research Institute, Baylor College of Medicine, Houston, TX, United States

Chapter 42: The Molecular Pathophysiology of Atrial Fibrillation

Mark S. Weiss, MD

Assistant Professor, Department of Anesthesiology and Critical Care, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States

Chapter 132: Anesthesiology Considerations for the Electrophysiology Laboratory

Arthur A.M. Wilde, MD, PhD

Professor of Cardiology, Department of Clinical and Experimental Cardiology, AMC Heart Center, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Chapter 52: Inheritable Potassium Channel Diseases
Chapter 88: Ventricular Tachycardias in Catecholaminergic Cardiomyopathy (Catecholaminergic Polymorphic Ventricular Tachycardia)

Bruce L. Wilkoff, MD

Professor of Medicine, Cleveland Clinic Lerner College of Medicine at Case Western Reserve University; Director, Cardiac Pacing and Tachyarrhythmia Devices, Associate Section Head, Pacing and Electrophysiology Section, Robert and Suzanne Tomsich Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH, United States

Chapter 116: Implantable Cardioverter Defibrillators: Technical Aspects

Y. Joseph Woo, MD

Norman E. Shumway Professor and Chair, Department of Cardiothoracic Surgery, Professor of Bioengineering (by courtesy), Stanford University, Stanford, CA, United States

Chapter 134: Surgery for Ventricular Arrhythmias

Joseph C. Wu, MD, PhD

Stanford Cardiovascular Institute and Department of Medicine, Division of Cardiology, School of Medicine, Stanford University, Stanford, CA, United States

Chapter 30: Cardiac Remodeling and Regeneration

Raymond Yee, B.MD.Sc, MD

Professor of Medicine, Department of Medicine, Western University; Director, London Heart Rhythm Program, University Hospital, London, ON, Canada

Chapter 66: Cardiac Monitoring: Short- and Long-Term Recording

Junaid A.B. Zaman, MA, BMBCh, MRCP

Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA, United States

Chapter 45: Rotors in Human Atrial Fibrillation

Manuel Zarzoso, PhD

Assistant Professor, Department of Physiotherapy, University of Valencia, Valencia, Spain

Chapter 13: Molecular Regulation of Cardiac Inward Rectifier Potassium Channels by Pharmacological Agents
Chapter 39: Pulmonary Vein Ganglia and the Neural Regulation of the Heart Rate

Emily P. Zeitler, MD, MHS

Fellow in Clinical Cardiac Electrophysiology, Division of Cardiology, Duke University School of Medicine, Durham, NC, United States

Chapter 122: Remote Monitoring of Cardiac Implantable Electronic Devices

Katja Zeppenfeld, MD, PhD

Professor of Cardiology, Director of Clinical Electrophysiology, Leiden University Medical Center, Leiden, The Netherlands

Chapter 102: Ventricular Arrhythmias in Congenital Heart Disease

Tarek Zghaib, MD

Post-Doctoral Research Fellow, Johns Hopkins University School of Medicine, Baltimore, MD, United States

Chapter 100: Arrhythmia in Neurological Disease

Xiao-Dong Zhang, MS, PhD

Assistant Researcher, Department of Internal Medicine, University of California Davis, Davis, CA, United States

Chapter 24: Feedback Mechanisms for Cardiac-Specific MicroRNAs and cAMP Signaling in Electrical Remodeling

Douglas P. Zipes, MD

Distinguished Professor, Emeritus Professor of Medicine, Pharmacology, and Toxicology, Emeritus Director, Division of Cardiology and the Krannert Institute of Cardiology, Indiana University School of Medicine; Editor-in-Chief, Practice-Update/Cardiology, Editor-in-Chief, Trends in Cardiovascular Medicine, Indianapolis, IN, United States

Chapter 59: Assessment of the Patient With a Cardiac Arrhythmia
Chapter 137: Spinal Cord Stimulation for Heart Failure and Arrhythmias

PREFACE

Cardiac electrophysiology, both basic and clinical, continues to advance rapidly with new observations almost daily. Multiple electrophysiologic journals now publish so many articles, it is hard to stay abreast of new information vitally useful at the bench and bedside. While the sixth edition of *Cardiac Electrophysiology: From Cell to Bedside* was published in 2014, this rapid pace of new discovery compelled us to create the seventh edition in record time.

Not only have we advanced the publishing date, we have also added to the total number of chapters—from 132 to 139. In addition to all chapters being totally revised by international authorities who are experts in their fields, we have provided 19 totally new chapters in basic and clinical arenas. We have continued the full color display and the electronic version inaugurated with the sixth edition. Each chapter is crammed full with the latest information in that particular area, while the website provides space for overflow information, figures, tables, and videos.

We hope *Cardiac Electrophysiology: From Cell to Bedside* continues to be the go-to reference source for all levels of learners, from basic scientists to clinicians, for those early in their careers to those well advanced. We—the editors—have strived in our careers to blend basic with clinical in a bidirectional effort and have patterned this book with that in mind.

As before, the first half provides the foundation of basic electrophysiology, including sections on Structural and Molecular Bases of Ion Channel Function, Biophysics of Cardiac Ion Channel Function, Intermolecular Interactions and Cardiomyocyte Electrical Function, Cell Biology of Cardiac Impulse Initiation

and Propagation, Models of Cardiac Excitation, Neural Control of Cardiac Electrical Activity, Arrhythmia Mechanisms, Molecular Genetics and Pharmacogenomics, and Pharmacologic, Genetic, and Cell Therapy of Ion Channel Dysfunction.

The second half is devoted to clinical cardiac electrophysiology, including sections on Diagnostic Evaluation, Supraventricular Tachyarrhythmias, Ventricular Tachyarrhythmias, Syncope and Bradyarrhythmias, Arrhythmias in Special Populations, Pharmacologic Therapy, Cardiac Implantable Electronic Devices, Catheter Ablation, Surgery for Arrhythmias, and New Approaches.

New for this edition is the addition of William G. Stevenson as an editor. Bill is well known to the electrophysiology community and joined us in preparation to take over the role of Doug Zipes for the eighth edition.

We would like to thank our spouses, Joan Zipes, Paloma Jalife, and Lynne Stevenson, for their love and support, and for putting up with the countless hours demanded of such a project.

We would also like to thank all of our colleagues who generously contributed their time, talents, and efforts to this book, and Lucia Gunzel, Dolores Meloni, and Kristine Feeherty at Elsevier for help with the publication.

Finally, we thank the readers who use our book as their learning manual and source for fact checking. We hope this edition continues the tradition of the past and meets your standards.

Douglas P. Zipes
José Jalife
William G. Stevenson

1

Voltage-Gated Sodium Channels and Electrical Excitability of the Heart

William A. Catterall

CHAPTER OUTLINE

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Voltage-gated sodium channels initiate action potentials in nerves, cardiac myocytes, and other excitable cells.^{1,2} They are responsible for the propagation of action potentials through the atria, the conduction system, and the ventricles of the heart. As shown in Fig. 1.1, action potentials in atrial and ventricular muscle fibers rise rapidly from a resting potential of about -80 mV and reach their peak within 1 ms. During this brief interval, cardiac sodium channels respond to the change in pacemaker potential as it reaches a threshold and open to allow the rapid entry of sodium ions (Na^+). Sodium channels begin to inactivate as soon as they open and are inactivated to 98% or 99% completion within a few milliseconds. The plateau phase of the cardiac action potential is generated by the opening of voltage-gated calcium channels (see Chapter 2), and the cell is finally repolarized by slower opening of voltage-gated potassium channels (see Chapter 3). The rate of conduction of the action potential through the cardiac tissue depends directly on the rate of rise of the cardiac action potential and therefore on the density of active sodium channels and their rate of activation.

Much is now known about the molecular mechanisms of activation, inactivation, and ion conduction by the sodium channel protein, as is summarized in this chapter. Multiple genes encode sodium channel subunits, and the distinct sodium channel subtypes exhibit subtle differences in functional properties and differential distribution in subcellular compartments of cardiac myocytes. These differences in the function and localization of sodium channels may contribute to their specialized functional roles in cardiac physiology and pharmacology.

Subunit Structure of Sodium Channels

Sodium channel proteins purified from excitable cells are complexes composed of an ~ 260 -kDa α -subunit in association with one or two auxiliary β -subunits of ~ 33 to ~ 39 kDa in size.³ Purified sodium channel complexes of α - and β -subunits are sufficient for voltage-dependent gating and ion conduction in artificial lipid membranes, and expression of the α -subunit alone is sufficient for physiological function in recipient nonexcitable cells; this indicates that the α -subunit has all of the structural

elements required for voltage-dependent gating and ion conduction.⁴⁻⁶ The primary sequence predicts that the sodium channel α -subunit folds into four internally repeated domains (I to IV), each of which contains six α -helical transmembrane segments (S1 to S6; Fig. 1.2).^{3,6-8} In each domain, segments S1 through S4 serve as the voltage-sensing module, and segments S5 and S6 and the reentrant P-loop between them serve as the pore-forming module. One large extracellular loop connects either the S5 or S6 transmembrane segment to the P-loop in each domain, whereas the other extracellular loops are small. Large intracellular loops link the four homologous domains, and the large N-terminal and C-terminal domains also contribute substantially to the mass of the intracellular face of the sodium channels. This view of sodium channel architecture, originally derived from hydrophobicity analysis of the amino acid sequence,⁷ has largely been confirmed by biochemical, electrophysiological, and structural experiments.^{3,9}

Initial purification studies of sodium channels identified auxiliary $\beta 1$ - and $\beta 2$ -subunits.⁴ These subunits have a single transmembrane segment, a large N-terminal extracellular domain, and a short C-terminal intracellular segment (see Fig. 1.2).^{10,11} The β -subunits interact with α -subunit extracellular domains, modulating α -subunit function and enhancing their cell surface expression.¹⁰⁻¹³ They also serve as cell adhesion molecules by interacting with extracellular matrix proteins, other cell adhesion molecules, signaling proteins, and cytoskeletal linker proteins.¹⁴⁻²⁰ These interactions are thought to localize and stabilize sodium channels in specific subcellular compartments and to bring crucial signaling molecules to the sodium channel to regulate it. Deletion of the genes encoding β -subunits causes alterations in sodium channel function; reduced action potential conduction and abnormal development of myelin folds in axons; hyperexcitability and epilepsy in the brain; and arrhythmias in the heart.²¹⁻²³

Three-Dimensional Structure of Sodium Channels

Sodium channel architecture has been revealed in three-dimensions through determination of the crystal structure of the bacterial sodium channels at high resolution (2.7 Å) (Fig. 1.3).^{9,24} This ancient sodium channel has a simple structure: four identical subunits, each similar to one homologous domain of a mammalian sodium channel but without the large intracellular and extracellular loops of the mammalian protein.⁹ Knowledge of the structure has revealed a wealth of new information about the structural basis for sodium selectivity and conductance, the mechanism for blockage of the channel by therapeutically important drugs, and the mechanism of voltage-dependent gating. As viewed from the top, NavAb has a central pore surrounded by four pore-forming modules composed of S5 and S6 segments and the intervening

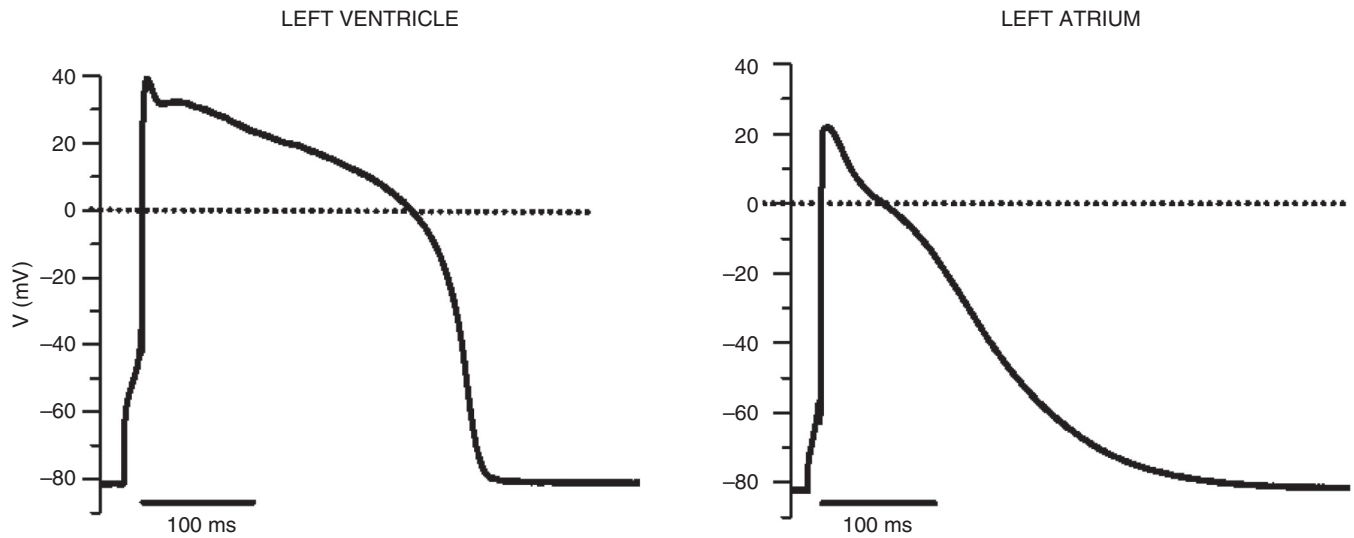


FIGURE 1.1 Cardiac action potential in sheep heart. Cardiac myocytes in the left ventricle or left atrium were impaled with a microelectrode, and the cardiac action potential was recorded. *ms*, Millisecond; *mV*, millivolt; *V*, voltage. (Courtesy J. Jalife.)

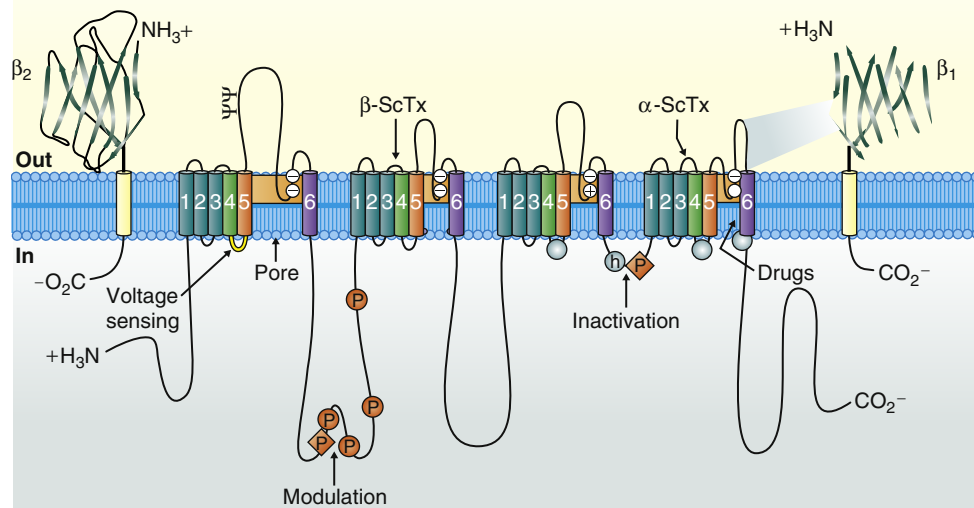


FIGURE 1.2 Transmembrane organization of sodium channel subunits. The primary structures of the subunits of the voltage-gated ion channels are illustrated as transmembrane folding diagrams. Cylinders represent probable alpha helical segments: S1 to S3, blue; S4, green; S5, yellow; and S6, red. The outer pore loop is the shaded orange area, and the intracellular S4-S5 helix is shown in purple. Bold lines represent the polypeptide chains of each subunit, with lengths approximately proportional to the number of amino acid residues in the brain sodium channel subtypes. The extracellular domains of the β_1 - and β_2 -subunits are shown as immunoglobulin-like folds. Ψ , sites of probable N-linked glycosylation. P, sites of demonstrated protein phosphorylation by protein kinase A (circles) and protein kinase C (diamonds). White circles, the outer (EEDD) and inner (DEKA) rings of amino residues that form the ion selectivity filter and the tetrodotoxin binding site. ++, S4 voltage sensors. h (in the shaded circle), inactivation particle in the inactivation gate loop. Open shaded circles, sites implicated in forming the inactivation gate receptor. The structure of the extracellular domain of the β -subunits is illustrated as an immunoglobulin-like fold based on amino acid sequence homology to the myelin P0 protein. Also shown are binding sites of α - and β -scorpion toxins and a site of interaction between α - and β_1 -subunits. (Modified from Catterall WA. From ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. *Neuron*. 2000;26:13-25.)

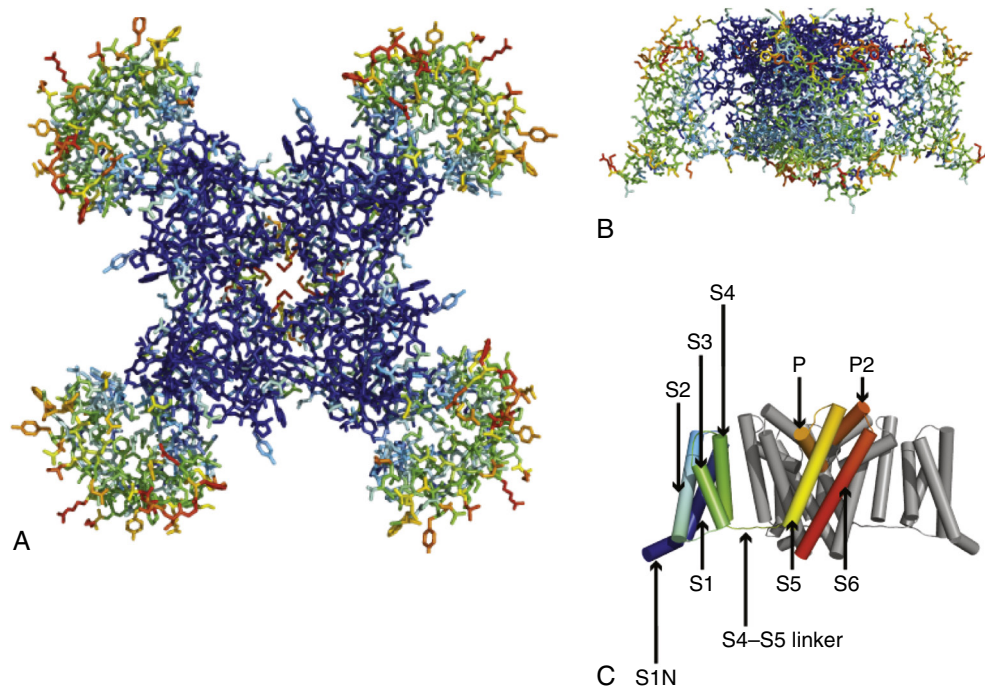


FIGURE 1.3 Three-dimensional structure of sodium channels. (A) Top view of NavAb channels colored according to crystallographic temperature factors of the main chain (blue <math>< 50 \text{ \AA}^2</math> to red > 150 Nature. 2011;475:353-358.)

P-loop (see Fig. 1.3A, blue). Four voltage-sensing modules composed of segments S1 to S4 are symmetrically located around the outer rim of the pore module (see Fig. 1.3A and B, red and green). The transmembrane architecture of NavAb shows that the adjacent subunits have swapped their functional domains such that each voltage-sensing module is most closely associated with the pore-forming module of its neighbor (see Fig. 1.3C). It is likely that this arrangement enforces concerted gating of the four subunits or domains of the sodium channels.

A comparison of the primary structures of the isoforms of auxiliary β -subunits to those of other proteins has revealed a close structural relationship to the family of proteins that contain immunoglobulin-like folds, which includes many cell adhesion molecules.^{10,11,25,26} The extracellular domains of these type-I single-membrane-spanning proteins have been predicted to fold in a similar manner to that of myelin protein P0, whose immunoglobulin-like fold is formed by a sandwich of two beta sheets held together by hydrophobic interactions (see Fig. 1.2).²⁷ Three-dimensional structures of the extracellular domains of the $\beta 3$ - and $\beta 4$ -subunits confirm these expectations.^{28,29} As would be expected from having structures that resemble cell adhesion molecules, Nav β -subunits interact with extracellular matrix molecules, other cell adhesion molecules, and intracellular cytoskeletal and signaling proteins.¹⁴⁻¹⁸ In addition, homophilic and heterophilic interactions of β -subunits have been demonstrated at both cellular and structural levels.^{20,30}

Sodium Channel Structure and Function

The three key functions of sodium channels were defined in a classic study¹ as (1) voltage-dependent activation, (2) fast inactivation, and (3) selective ion conductance. Building on this foundation, detailed biophysical studies have revealed the ion selectivity of the channel pore, detected the movement of the

voltage sensors as a capacitive gating current, and developed mechanistic models for these essential channel functions.^{2,31} Recent structure-function studies that employed molecular, biochemical, structural, and electrophysiological techniques have resulted in a clear understanding of the molecular and structural basis for these sodium channel functions.

Outer Pore and Selectivity Filter

Voltage clamp studies showed that sodium channels are highly selective for sodium versus potassium and other monovalent cations.^{2,32} Because of the high energy of hydration of Na^+ , theoretical considerations predicted there would be an outer, high-field-strength site that would partially dehydrate the permeating ion, and two inner sites that would conduct and rehydrate the permeant Na^+ ion.³³ Analysis of ion selectivity and blocking by tetrodotoxin and saxitoxin led to a model in which these toxins can plug the selectivity filter in the outer pore of sodium channels.³⁴ Mutational analysis identified a key glutamate residue in the membrane-reentrant loop in domain I as a crucial residue for tetrodotoxin and saxitoxin binding.³⁵ Further studies revealed a pair of important amino acid residues, mostly negatively charged, in analogous positions in all four domains (see Fig. 1.2, small white circles).³⁶⁻³⁸ The mutation to glutamates of a set of four residues in analogous positions in each domain (aspartate in domain I, glutamate in domain II, lysine in domain III, and alanine in domain IV, DEKA) confers calcium selectivity³⁹; this indicates that the side chains of these amino acid residues are likely to interact with sodium ions as they are conducted through the ion selectivity filter of the pore, thus conferring sodium selectivity. Mutations in this ring of four amino acid residues have strong effects on selectivity for organic and inorganic monovalent cations, which is in agreement with the idea that they form the selectivity filter, and structure-function studies suggest specific

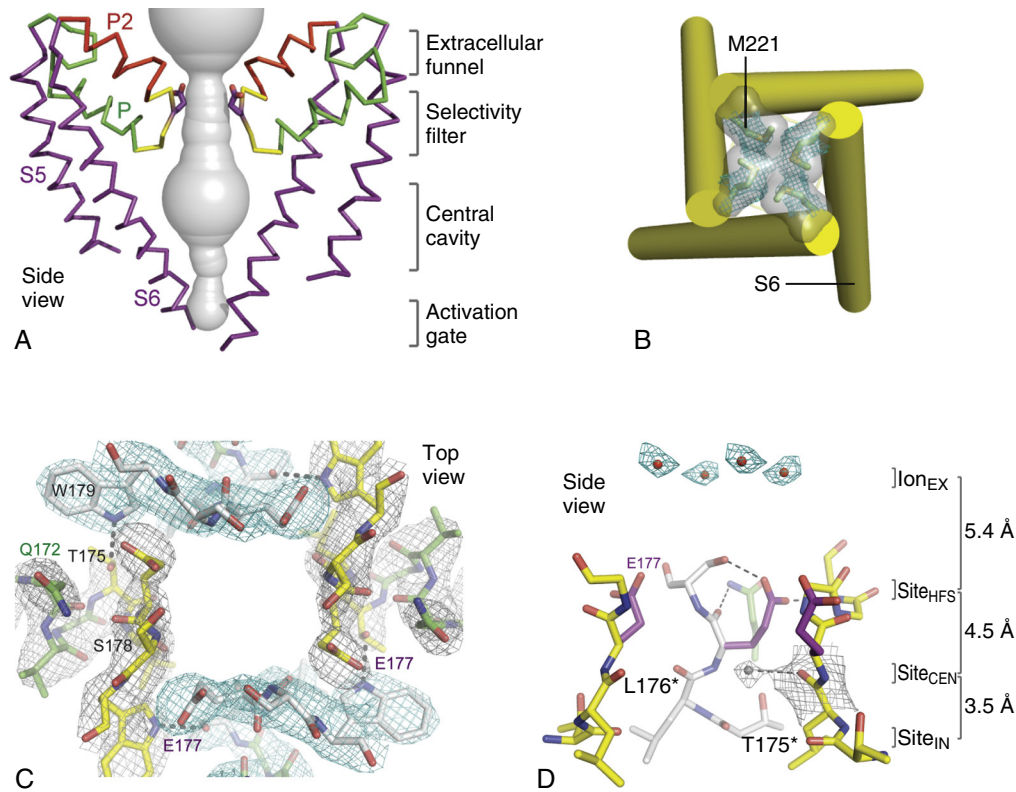


FIGURE 1.4 NavAb pore and selectivity filter. (A) Architecture of the NavAb pore. Glu177 side-chains, *purple*; pore volume, *gray*. (B) The closed activation gate at the intracellular end of the pore illustrating the close interaction of Met221 residues in closing the pore. (C) Top view of the ion selectivity filter. Symmetry-related molecules are colored *white* and *yellow*; P-helix residues are colored *green*. Hydrogen bonds between Thr175 and Trp179 are indicated by *gray dashes*. Electron-densities from $F_o - F_c$ omit maps are contoured at 4.0σ (*blue* and *gray*), and subtle differences can be appreciated (*small arrows*). (D) Side view of the selectivity filter. Glu177 (*purple*) interactions with Gln172, Ser178 and the backbone of Ser180 are shown in the far subunit. $F_o - F_c$ omit map, 4.75σ (*blue*); putative cations or water molecules (*red spheres*, Ion_{EX}). Electron-density around Leu176 (*gray*; $F_o - F_c$ omit map at 1.75σ) and a putative water molecule is shown (*gray sphere*). Na^+ -coordination sites: Site_{HFS}, Site_{CEN}, and Site_{IN}. (Modified from Payandeh J, Scheuer T, Zheng N, Catterall WA. The crystal structure of a voltage-gated sodium channel. *Nature*. 2011;475:353-358.)

structural interactions and functional roles for the P-loops from the four domains.^{40–43}

The overall pore architecture in the bacterial sodium channel NavAb includes the following component structures: a large external vestibule; a narrow ion selectivity filter that contains the amino acid residues shown to determine ion selectivity in vertebrate sodium and calcium channels; a large central cavity filled with water and lined by the S6 segments; and an intracellular activation gate formed at the crossing of the S6 segments at the intracellular surface of the membrane (Fig. 1.4A).^{9,24} The activation gate in the NavAb structure is tightly closed (Fig. 1.4B), and there is no space for ions or water to move through it. This general architecture resembles voltage-gated potassium channels (see Chapter 3). However, although the overall pore architecture of sodium and potassium channels is similar, the structures of their ion selectivity filters and their mechanisms of ion selectivity and conductance are completely different. Potassium channels select the potassium ion (K^+) through interacting directly with a series of four ion coordination sites formed by the backbone carbonyls of the amino acid residues that comprise the ion selectivity filter (see Chapter 3). No charged amino acid residues are involved, and no water molecules intervene between K^+ ions and the interacting backbone carbonyls in the ion selectivity filter of the potassium channels. In contrast, the NavAb ion selectivity filter has a high field strength site at its extracellular end (Fig. 1.4C), which is formed by amino acid residues that are highly conserved and are

key determinants of ion selectivity in vertebrate sodium and calcium channels (see Fig. 1.2). This high field strength site's dimensions of approximately 4.6 \AA square would allow Na^+ with two to four planar waters of hydration to fit within it. This outer site is followed by two ion coordination sites formed by backbone carbonyls (Fig. 1.4D). These two carbonyl sites are perfectly designed to bind Na^+ with four planar waters of hydration but would be much too large to bind Na^+ directly. Thus the chemistry of Na^+ selectivity and conductance is opposite to that of K^+ : negatively charged residues interact with Na^+ to remove most (but not all) of its waters of hydration, and Na^+ is conducted as a hydrated ion, interacting with the pore through its inner shell of bound waters.

Molecular dynamics simulations have revealed additional details of the mechanism of the ion conduction process. Remarkably, the negatively charged glutamate side chains at the high field strength site coordinate an approaching Na^+ ion and move with it into the selectivity filter in a “dunking” motion that involves rotation at a single torsion angle in the glutamate side chain.^{24,44} Different numbers of glutamate side chains move with the individual Na^+ ions, and the displacement of waters of hydration is proportional to these interactions with the glutamate side chains. Thus, in contrast to classical views of a static selectivity filter, molecular dynamics simulations of sodium conduction in the structure of the NavAb selectivity filter reveal the direct catalytic participation of glutamate side chain motions in each ion-conducting event.

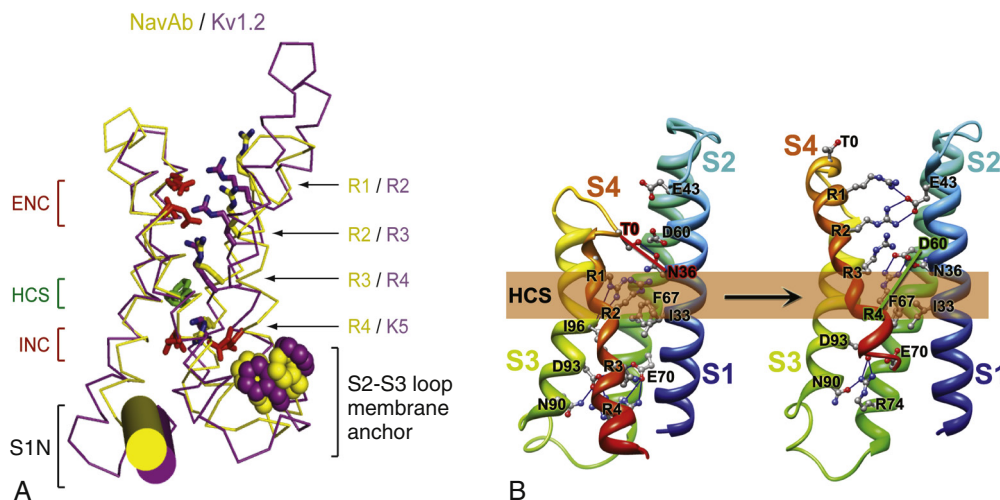


FIGURE 1.5 The voltage sensing domain (VSD). (A) Side view of the VSD illustrating the extracellular negative charge-cluster (red, ENC), the intracellular negative charge-cluster (red, INC), hydrophobic constriction site (green, HCS), residues of the S1N helix (cyan) and phenylalanines of the S2-S3 loop (purple). S4 segment and gating charges (R1-R4) are in yellow. (B) Transmembrane view of the lowest-energy Rosetta models of the VSD of NaChBac in Resting State 1 (left) and Activated State 3 (right). Side chains of the gating-charge-carrying arginines in S4 and key residues in S1, S2, and S3 segments are shown in stick representation and labeled. Gray, blue, and red atoms C, N, and O. The HCS is highlighted by orange bars. The majority of the lowest-energy models of Resting State 1 predict that R1 forms hydrogen bonds with the backbone carbonyl of I96 (in S3) at the extracellular edge of the HCS. On the intracellular side of the HCS, R3 makes ionic interactions with the amino acid residues of the intracellular negatively charged cluster, including E70 (in S2) and D93 (in S3), and R4 forms an ion pair with D93 (in S3). The lowest energy models for Activated State 3 predict that R1 forms an ion pair with E43 (in S1), R2 forms an ion pair with E43 (in S1), R3 forms hydrogen bond with Y156 (in S5) and makes ionic interactions with D60 (in S2) and E43 (in S1), and R4 forms an ion pair with D60 (in S2). (Modified from Payandeh J, Scheuer T, Zheng N, Catterall WA. The crystal structure of a voltage-gated sodium channel. *Nature*. 2011;475:353-358; and Yarov-Yarovoy V, DeCaen PG, Westenbroek RE, et al. Structural basis for gating charge movement in the voltage sensor of a sodium channel. *Proc Natl Acad Sci U S A*. 2012;109:E93-102.)

Voltage-Dependent Activation

The voltage dependence of the activation of sodium channels derives from outward movement of approximately 12 gating charges as a consequence of depolarization of the membrane and reduction of the membrane electrical field.^{31,45} The S4 segments of each homologous domain serve as the primary voltage sensors for activation.^{7,8} These contain repeated motifs of a positively charged amino acid residue followed by two hydrophobic residues, which creates a transmembrane spiral of positive charges. Upon depolarization, outward movement and rotation of S4 are thought to initiate a conformational change that opens the sodium channel pore.^{7,8} This “sliding helix” or “helical screw” model is supported by strong evidence. For example, neutralization of the positively charged residues in S4 reduces the voltage-dependence of the gating.⁴⁶ The outward and rotational gating movement of the S4 segment has been detected directly by the reaction of substituted cysteine residues in S4 segments with extracellular sulfhydryl reagents following channel activation, and by analysis of the movement of fluorescent probes incorporated into these substituted cysteine residues.^{47,48} Further support for this mechanism derives from a wide range of structure-function studies,⁴⁹ including extensive disulfide crosslinking studies of substituted cysteine residues that have charted the exchange of ion pair partners during activation.^{50–53} In four-domain mammalian sodium channels, there is a hierarchy of activation of the four voltage sensors. Studies of fluorescently labeled S4 segments show that the voltage sensors of domains I to III activate rapidly, whereas the S4 segment of domain IV activates much more slowly.⁵⁴

In the structure of the bacterial sodium channel NavAb, the S4 segment is in a transmembrane position in its activated state

and its positive charges are neutralized by negative charges in the nearby S1, S2, and S3 segments⁹ (Fig. 1.5A). This conformation is nearly identical to that of the voltage sensor of potassium channels (see Fig. 1.5A). In this snapshot of an activated voltage sensor, three gating charges (R1 to R3 in NavAb) interact with the extracellular negative charge cluster and are located on the extracellular side of the hydrophobic constriction site, which seals the structure to prevent leak of water and ions. At the resting membrane potential, the force of the electrical field (which is negative inside the cell) would pull the positive charges inward such that gating charges R2 to R4 interact with the intracellular negative cluster.⁵³ Depolarization would abolish this force and allow an outward movement of the S4 helix and its gating charges, catalyzed by the exchange of ion pair partners (see Fig. 1.5B; Video 1.1).⁵³ After conformational changes have occurred in all four domains, the transmembrane pore can open and conduct ions (see Video 1.1).⁵³ This structural model shows that the S4 segment and its gating charges move through a gating pore that narrows the transmembrane electrical field to a distance of N5Å allowing a short transit through the channel protein (see Video 1.1).⁵³

Pore Opening

These structural models allow the steps in the gating of a voltage-gated ion channel to be visualized.^{24,53} In the closed state, the negative internal membrane potential of -70 mV to -90 mV pulls the S4 gating charges inward by electrostatic force. The inward position of the S4 segment exerts a force on the S4–S5 linker, straightens the S6 segment, and closes the pore at its inner mouth. Depolarization of the cell relieves the electrostatic force

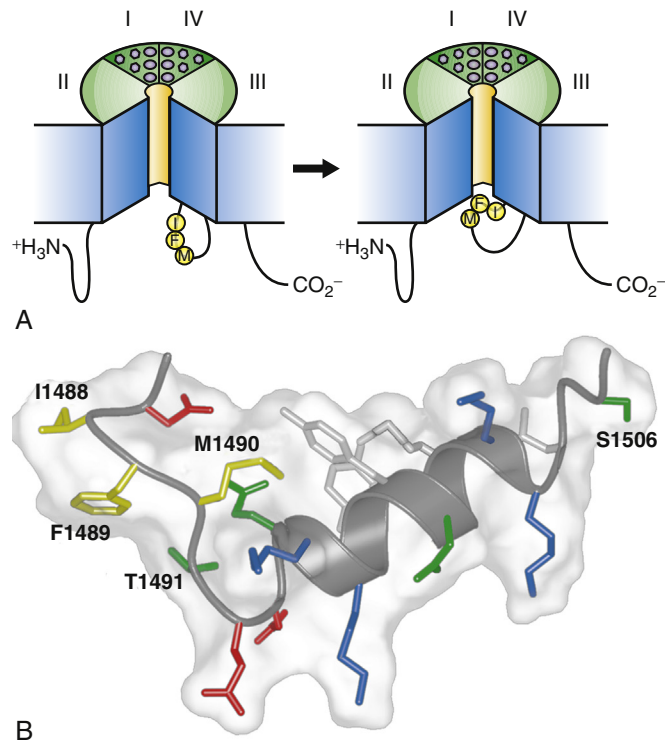


FIGURE 1.6 The molecular mechanism of fast sodium channel inactivation. (A) The hinged-lid mechanism. The intracellular loop connecting domains III and IV of the sodium channel is depicted as forming a hinged lid with the critical phenylalanine (Phe1489) within the isoleucine, phenylalanine, and methionine (IFM) motif shown occluding the mouth of the pore during the inactivation process. The *circles* represent the transmembrane helices. (B) Three-dimensional structure of the central segment of the inactivation gate as determined by multidimensional nuclear magnetic resonance. Isoleucine 1488, phenylalanine 1489, and methionine 1490 (IFM) are illustrated in *yellow*, which is important for inactivation, and serine 1506, which is a site of phosphorylation and modulation by protein kinase C, are also indicated. (Modified from Catterall WA. From ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. *Neuron*. 2000;26:13-25.)

pulling the S4 segment inward. In response to the change in electrostatic force, the S4 segment moves outward, with each positive gating charge interacting with the charged amino acid side chains in turn to ease their movement through the voltage-sensing module. When the R3 and R4 gating charges pass the hydrophobic constriction site in the center of the voltage sensor module, the outward force on the S4–S5 linker is sufficient to exert a torque on the pore-forming module and bend the S6 segment, resulting in the pore opening at its intracellular end. During activation of the voltage sensors of the sodium channels, the S4–S5 intracellular linkers in each domain (see Fig. 1.2) exert a force on the adjacent S6 segments, and the pore opens by bending and twisting the S6 segment (see Fig. 1.2). In bacterial voltage-gated potassium channels and sodium channels, bending of the S6 segment occurs at a critical hinge glycine residue about one-third down the length of the S6 segment^{55–57}; this bending motion allows the inner mouth of the pore to open (Videos 1.1 and 1.2)⁵³ and allow rapid movement of the ions across the membrane.

Fast Inactivation

Fast inactivation of the sodium channel is a critical process that occurs within milliseconds of the channel opening. The generally accepted model of this process involves a conserved inactivation gate formed by the intracellular loop connecting domains

III and IV (see Fig. 1.2), which serves as a hinged lid that binds to the intracellular end of the pore and blocks it (Fig. 1.6).³ The intracellular perfusion of proteases prevents fast inactivation.³¹ Site-directed antipeptide antibodies against the short, highly conserved intracellular loop that connects domains III and IV of the sodium channel α -subunit (see Fig. 1.2) were found to prevent fast sodium channel inactivation, but this was not the case for antibodies directed to other intracellular domains.^{58,59} Furthermore, the accessibility of this site for antibody binding was reduced when the membrane was depolarized to induce inactivation, which suggests that the loop connecting domains III and IV forms an inactivation gate that folds into the channel structure during inactivation.^{58,59} Cutting the loop between domains III and IV by expression of the sodium channel in two pieces greatly slows inactivation.⁴⁶ Mutagenesis studies of this region revealed a hydrophobic triad of isoleucine, phenylalanine, and methionine (IFM) that is critical for fast inactivation (see Fig. 1.2, *blue circle with “b”*),⁶⁰ and peptides containing this motif can serve as pore blockers and can restore inactivation to sodium channels that have a mutated inactivation gate.⁶¹ The latch of this fast inactivation gate is formed by the three key hydrophobic residues, IFM, and adjacent threonine (T). These results support a model in which the IFM motif serves as a tethered pore blocker that binds to a receptor in the intracellular mouth of the pore. Inactivation is impaired in proportion to the hydrophilicity of the amino acid