# Ihor Gussak Charles Antzelevitch Editors

Arthur A. M. Wilde, Paul A. Friedman, Michael J. Ackerman, and Win-Kuang Shen *Co-Editors* 

# Electrical Diseases of the Heart

Genetics, Mechanisms, Treatment, Prevention



Ihor Gussak and Charles Antzelevitch (Eds)

Arthur A.M. Wilde, Paul A. Friedman, Michael J. Ackerman, and Win-Kuang Shen (Co-Eds)

# **Electrical Diseases**of the Heart

Genetics, Mechanisms, Treatment, Prevention



Editors
Ihor Gussak MD, PhD, FACC
Deputy Therapeutic Area Head
Cardiovascular
Boehringer Ingelheim Pharmaceuticals
Ridgefield, CT, USA
Clinical Professor of Medicine
University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School
Bridgewater, NJ, USA

Co-Editors
Arthur A.M. Wilde, MD, PhD, FESC, FAHA
Professor
Heart Failure Research Center
Department of Clinical and Experimental Cardiology
Academic Medical Center
Amsterdam, The Netherlands

Michael J. Ackerman, MD, PhD, FACC
Professor of Medicine, Pediatrics and Pharmacology
Consultant
Cardiovascular Disease and Pediatric Cardiology
Director
Long QT Syndrome Clinic and the Mayo Clinic
Windland Smith Rice Sudden Death Genomics
Laboratory
President
Sudden Arrhythmia Death Syndromes (SADS)
Foundation
Mayo Clinic College of Medicine
Rochester, MN, USA

Charles Antzelevitch PhD, FACC,
FAHA, FHRS
Executive Director and Director
of Research
Gordon K. Moe Scholar
Masonic Medical Research Laboratory
Utica, NY, USA
Professor of Pharmacology
Upstate Medical University
Syracuse, NY, USA

Paul A. Friedman, MD Professor of Medicine Mayo Clinic College of Medicine Rochester, MN, USA

Win-Kuang Shen, MD
Consultant
Division of Cardiovascular Diseases
Professor of Medicine
Mayo Clinic College of Medicine
Rochester, MN, USA

British Library Cataloguing in Publication Data

Electrical diseases of the heart: genetics, mechanisms, treatment, prevention

1. Arrhythmia

I. Gussak, Ihor II. Antzelevitch, Charles III. Wilde, Arthur 616.1'28

ISBN-13: 9781846288531

Library of Congress Control Number: 2007923776

ISBN: 978-1-84628-853-1 e-ISBN: 978-1-84628-854-8

Printed on acid-free paper

© Springer-Verlag London Limited 2008

Apart from any fair dealing for the purposes of research or private study, or criticism or review, as permitted under the Copyright, Designs and Patents Act 1988, this publication may only be reproduced, stored or transmitted, in any form or by any means, with the prior permission in writing of the publishers, or in the case of reprographic reproduction in accordance with the terms of licences issued by the Copyright Licensing Agency. Enquiries concerning reproduction outside those terms should be sent to the publishers.

The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant laws and regulations and therefore free for general use.

Product liability: The publisher can give no guarantee for information about drug dosage and application thereof contained in this book. In every individual case the respective user must check its accuracy by consulting other pharmaceutical literature.

9 8 7 6 5 4 3 2 1

Springer Science+Business Media springer.com

To the pioneers of cardiac electrophysiology whose seminal contributions are depicted in the historical perspectives included in many of the chapters. Our mentors, collaborators, and fellows who have assisted us in advancing the field,

last, but not least, to our families, whose understanding and support have permitted us to dedicate the time and effort needed to formulate this text.

I.G. C.A.

### **Foreword**

She was about 35 years old when she first became my patient in 1975. She had suffered from bouts of a supraventricular tachycardia (SVT) as far back as she could remember. "In the early days," she recalled, "when I was a kid, they would give me something in the emergency room that elevated my blood pressure and damn near tore my head off. What a headache I would get! But a lot of times it didn't work. Then they stuck my head in a bucket of cold water and told me to 'bear down.' Finally, they would give me more digitalis in my vein until I started vomiting. That usually stopped the SVT." But nothing seemed to prevent recurrences. She was on a full dose of digitoxin and was one of the first to try a  $\beta$  blocker (propranolol) in the late 1960s. Her episodes were fast, around 220/min, and frightened her terribly, so much so that she would ride the tractor alongside her farmer-husband all day long just to be near him in case she had a recurrence.

Then came one of the first breakthroughs. Gordon Moe had published a "case report" of a dog with probable atrioventricular node reentry (AVNRT), showing that such a tachycardia could be started and stopped by external stimuli. Clinical studies followed (though somewhat belatedly) and replicated such responses in humans. Medtronic developed an implantable pacemaker (5998 RF unit) that was triggered by an external battery-driven stimulator held over the passive receiver to deliver a burst of rapid stimuli to the epicardial electrodes implanted on her right atrium. Magic! She terminated her own SVT with unerring reliability and never precipitated atrial fibrillation. Now a free woman, she no longer needed tractor rides. But she never left her house without the RF generator and always carried a spare battery in her pocket.

Over time she stopped her medications and gradually stopped coming back for return visits because she had complete control of her SVT. About 15 years later she showed up unannounced because one of the wires in her handheld unit had fractured and she no longer could stop the SVT. Could I get her a replacement or send the broken unit for repairs, she asked. The next day she was in the EP laboratory, had a slow pathway ablation, cure of the AVNRT, and removal of the implanted unit.

My, what a ride the last 30-plus years has provided! From a group of half dozen or so arguing at the American Heart Association Scientific Sessions as to what was the true duration of the H-V interval, to the keynote lecture

viii Foreword

on pacing I was privileged to give at the very first North American Society of Pacing and Electrophysiology (NASPE) meeting in 1980 attended by maybe 27 people, to the most recent Heart Rhythm Society (HRS) meeting with over 12,500 attendees, there has been excitement at all levels, molecular, ionic, genetic, in vitro, in vivo, and clinical. We have mined the riches offered by the study of cardiac electrical phenomena and that is what this book captures. It offers a true bridge between the basic and clinical, with insights that few texts can claim. To all for whom the squiggles of the electrocardiogram tantalize with further insights into the electrophysiology of the heart, this book offers a wonderful guide—a searchlight—into the incredible electricity that makes us tick. I compliment the editors and the authors for a wonderful job. We've come a long way, baby, and it is awesome to read about it between the covers of this book!

Douglas P. Zipes, MD Indiana University School of Medicine Krannert Institute of Cardiology Indianapolis, IN, USA

## **Contents**

eword by Douglas P. Zipes	XV
t I Basic Foundations of Normal and Abnormal Cardiac etrical Activity ted by Charles Antzelevitch and Arthur A.M.Wilde	
Past and Promise of Basic Cardiac Electrophysiology	3
Basic Physiology of Ion Channel Function	11
Developmental Aspects of the Electrophysiology of the Heart: Function Follows Form	24
Anatomic and Histopathological Characteristics of the Conductive Tissues of the Heart	37
Neural Regulation of the Heart in Health and Disease	52
Mechanisms of Cardiac Arrhythmia	65
Mechanisms of Action of Antiarrhythmic Drugs	133
Mechanoelectrical Interactions and Their Role in Electrical Function of the Heart	145
	trical Activity  eed by Charles Antzelevitch and Arthur A.M.Wilde  Past and Promise of Basic Cardiac Electrophysiology

<sup>†</sup>Deceased.

x Contents

8	The Role of Cellular Sodium and Calcium Loading in Cardiac Energetics and Arrhythmogeneis: Contribution of the Late Sodium Current	161
9	Sodium Ion Channelopathies	170
10	L-Type Calcium Channel Disease	187
11	$K^+$ Channelopathies ( $I_{Ks}$ and $I_{Kr}$ )	194
12	Channelopathies of Cardiac Inwardly Rectifying Potassium Channels	207
13	Calcium Release Channels (Ryanodine Receptors) and Arrhythmogenesis	218
14	Caveolae and Arrhythmogenesis	232
15	Senescence and Arrhythmogenesis	247
16	Comparisons of Substrates Responsible for Atrial Versus Ventricular Fibrillation	261
17	Single Nucleotide Polymorphisms in Health and Cardiac Disease	281
18	Electrophysiological Remodeling in Dilated Cardiomyopathy and Heart Failure	290
19	Ventricular Electrical Remodeling in Compensated Cardiac Hypertrophy	305
20	Physiological and Other Biological Pacemakers	316

Contents

Edi	t II Clinical Rhythmology: Diagnostic Methods and Tools ted by Win-Kuang Shen, Michael J. Ackerman, Paul A. Friedman, hur A.M. Wilde, and Ihor Gussak	
21	Diagnostic Electrocardiography	331
22	Ambulatory Monitoring (Holter, Event Recorders, External, and Implantable Loop Recorders and Wireless Technology) Rajesh N. Subbiah, Lorne J. Gula, George J. Klein, Allan C. Skanes, Raymond Yee, and Andrew D. Krahn	344
23	Signal Averaged Electrocardiogram	353
24	Heart Rate Variability: Measurements and Risk Stratification Yi Gang and Marek Malik	365
25	Surface Mapping and Magnetoelectrocardiography	379
26	Microvolt T Wave Alternans: Mechanisms and Implications for Prediction of Sudden Cardiac Death	394
27	Invasive Electrophysiologic Testing: Role in Sudden  Death Prediction	409
28	Provocative Testing in Inherited Arrhythmias	424
29	Novel Predictors of Sudden Cardiac Death	434
30	Genetic Testing  David J. Tester and Michael J. Ackerman	444
Dis Edi	t III Heritable Cardiac Channelopathies, Primary Electrical eases, and Clinical Syndromes ted by Arthur A.M. Wilde, Ihor Gussak, Michael J. Ackerman, 1-Kuang Shen, and Charles Antzelevitch	
	ebrating the Challenge of Cardiac Arrhythmias	461
31	Congenital Long QT Syndrome	462

xii Contents

	Paola G. Meregalli, Hanno L. Tan, and Arthur A.M. Wilde	
33	Brugada Syndrome: Cellular Mechanisms and Approaches to Therapy	500
	Charles Antzelevitch and Sami Viskin	
34	Catecholaminergic Polymorphic Ventricular Tachycardia  Nian Liu, Carlo Napolitano, and Silvia G. Priori	536
35	Andersen–Tawil and Timothy Syndromes	545
36	Short QT Syndrome	554
37	Progressive Cardiac Conduction Disease	564
38	Familial Atrial Fibrillation and Standstill	577
39	Idiopathic Ventricular Fibrillation	588
	t IV Secondary Hereditary Electrical Diseases and nical Syndromes	
Lul	ted by Arthur A.M. Wilde, Michael J. Ackerman, and Ihor Gussak	
Car	diac Remodelingrey E. Saffitz	607
Car	diac Remodeling rey E. Saffitz	607
Car Jeffi	diac Remodeling	610
Car Jeffi	diac Remodeling  rey E. Saffitz  Arrhythmogenic Malignancies in Hypertrophic Cardiomyopathy Shaji C. Menon, J. Martijn Bos, Steve R. Ommen, and Michael J. Ackerman	
Car Jeffi 40	diac Remodeling	
Car Jeffi 40	diac Remodeling	610

Contents

Sud	t V latrongenic (Drug-Induced) Cardiac Channelopathies and Iden Cardiac Death ted by Ihor Gussak, Arthur A.M. Wilde, and Charles Antzelevitch	
Dea Dru	ng-Induced Enhanced Risk for Sudden Cardiac ath in Clinical Practice, Clinical Research, and ng Development	673
44	Pharmacogenomics in Drug Development and Clinical Research Richard Judson	677
45	Mechanisms of Drug-Induced Cardiac Toxicity	691
46	Acquired (Drug-Induced) Long QT Syndrome  Jeffrey S. Litwin, Robert B. Kleiman, and Ihor Gussak	705
47	Acquired Form of Brugada Syndrome	719
	t VI Treatment Modalities ted by Paul A. Friedman, Win-Kuang Shen, and Michael J. Ackerma	an
	atment Modalitiesrk E. Josephson	731
48	Clinical Role of Antiarrhythmic Drugs in the Prevention of Sudden Death	733
49	Nonantiarrhythmic Drugs in Sudden Death Prevention  Alan Kadish and Vikram Reddy	760
50	The Implantable Cardioverter Defibrillator: Technical and Clinical Considerations	772
51	Beyond Sudden Death Prevention: Minimizing Implantable Cardioverter Defibrillator Shocks and Morbidity and Optimizing Efficacy	781
52	Pacing and Cardiac Resynchronization	801
53	Device Therapy for Remote Patient Management  Dwight W. Reynolds, Christina M. Murray, and Robin E. Germany	809

xiv Contents

54	Catheter Ablation of Ventricular Tachycardia and Fibrillation	826
55	Surgical Treatment of Atrial Fibrillation	839
Dea Edit	t VII Risk Stratification and Prevention of Sudden Cardiac th in Acquired Clinical Conditions ted by Michael J. Ackerman, Paul A. Friedman, Arthur A.M. Wilde, te-Kuang Shen, and Ihor Gussak	
	eening for Risk of Sudden Cardiac Death	851
56	Clinical Trials in Sudden Cardiac Death Prevention: Principles and Endpoints	853
57	Risk Stratification for Sudden Death in Patients with Coronary Artery Disease	858
58	Heart Failure and Sudden Death	873
59	Neurological Conditions and Sudden Death	888
60	Obstructive Sleep Apnea and Sudden Death	898
61	Sudden Cardiac Death in Athletes	911
62	Sudden Cardiac Death in Infancy: Focus on Prolonged Repolarization	924
63	Sudden Cardiac Death in Kidney Diseases	934
Inde	ex	943

### **Contributors**

Raushan Abdula, MD
Research Attending
Department of Medicine
New York Methodist Hospital
Brooklyn, NY, USA

Michael J. Ackerman, MD, PhD, FACC
Professor of Medicine, Pediatrics and
Pharmacology
Consultant
Cardiovascular Disease and Pediatric Cardiology
Director
Long QT Syndrome Clinic and the Mayo
Clinic Windland Smith Rice Sudden Death
Genomics Laboratory
President
Sudden Arrhythmia Death Syndromes
(SADS) Foundation
Mayo Clinic College of Medicine

Fadi G. Akar, PhD
Assistant Professor of Medicine
Department of Cardiology
The Johns Hopkins University School
of Medicine
Baltimore, MD, USA

Rochester, MN, USA

Alexey E. Alekseev, PhD
Assistant Professor of Medicine and Pharmacology
Division of Cardiovascular Diseases
Departments of Medicine, Molecular Pharmacology and Therapeutics
Mayo Clinic College of Medicine
Rochester, MN, USA

Charles Antzelevitch, PhD, FACC, FAHA, FHRS Executive Director and Director of Research Gordon K. Moe Scholar Masonic Medical Research Laboratory Utica, NY Professor of Pharmacology Upstate Medical University Syracuse, NY, USA

Isabelle Baró, PhD
CNRS Senior Research Scientist
Leader of the Team "Cell and Molecular
Physiology"
INSERM U533
Nantes France
Université de Nantes
Faculté de médecine
L'institut du thorax
Nantes, France
CHU Nantes
L'institut du thorax
Nantes, France

Cristina Basso, MD, PhD
Professor of Pathological Anatomy
Department of Medico-Diagnostic Sciences and
Special Therapies
Pathological Anatomy-Cardiovascular
Pathology
University of Padua Medical School
Padua, Italy

xvi Contributors

Luiz Belardinelli, MD

Senior Vice-President of Pharmacology and Translational Biomedical Research

CV Therapeutics, Inc.

Palo Alto, CA, USA

Bernard Belhassen, MD

Professor Director

Cardiac Electrophysiology Unit Department of Cardiology

Tel-Aviv Sourasky Medical Center

Tel-Aviv, Israel

David Benson, MD

Attending Electrophysiologist

Department of Medicine

New York Methodist Hospital

Brooklyn, NY, USA

David H. Birnie, MD, MB, FRCP

Staff Cardiac Electrophysiologist

Division of Cardiology

Department of Medicine

University of Ottawa Heart Institute

Ottawa, ON, Canada

Preben Bjerregaard, MD, DMSc

Professor of Medicine

Director

Electrophysiology and Pacemaker Service

VA Medical Center

Saint Louis, MO, USA

Raffaella Bloise, MD

Medical Genetic Counselor

Molecular Cardiology Laboratories

**IRCCS Salvatore Maugeri Foundation** 

Pavia, Italy

Pierre Bordachar, MD

Hôpital Cardiologique du Haut-Lévêque

Bordeaux-Pessac, France

J. Martijn Bos, MD

Postdoctoral Research Fellow

Department of Medicine

Division of Cardiovascular Diseases

Mayo Clinic College of Medicine

Rochester, MN, USA

Peter R. Brink, PhD

Professor and Chair

Department of Physiology and Biophysics

Stony Brook University

State University of New York

Stony Brook, NY, USA

Alexander Burashnikov, PhD

Research Scientist I

Masonic Medical Research Laboratory

Utica, NY, USA

Brett Burstein, BSc

MD/PhD Student

Pharmacology and Therapeutics

Montreal Heart Institute and McGill University

Montreal, QC, Canada

Alfred E. Buxton, MD

Ruth and Paul Levinger Professor of Medicine

Director

Division of Cardiology

Director

Arrhythmia Services and Electrophysiology

Laboratory

The Warren Alpert Medical School of Brown

University

Providence, RI, USA

Hugh Calkins, MD

Professor of Medicine

Director of Electrophysiology

Department of Medicine

The Johns Hopkins University School of Medicine

Baltimore, MD, USA

Simona Casini, MSc

PhD Student

Heart Failure Research Center

Department of Clinical and Experimental

Cardiology

Academic Medical Center

Amsterdam, The Netherlands

Yong-Mei Cha, MD

Assistant Professor

Consultant

Division of Cardiovascular Diseases

Mayo Clinic College of Medicine

Rochester, MN, USA

Contributors xvii

Flavien Charpentier, PhD Researcher Inserm U533 L'institut du thorax Nantes, France

Vincent M. Christoffels, PhD
Assistant Professor
Heart Failure Research Center
Department of Anatomy and Embryology
Academic Medical Center
Amsterdam, The Netherlands

Sumeet S. Chugh, MD
Section Chief
Clinical Cardiac Electrophysiology
Associate Professor of Medicine
Oregon Health & Science University
Portland, OR, USA

Jacques Clémenty, MD Professor Université Bordeaux II Hôpital Cardiologique du Haut-Lévêque Bordeaux-Pessac, France

Ira S. Cohen, MD, PhD
Leading Professor of Physiology and
Biophysics
Professor of Medicine
Director
Institute of Molecular Cardiology
Department of Physiology and Biophysics
Stony Brook University
State University of New York
Stony Brook, NY, USA

Philippe Comtois, PhD Postdoctoral Fellow Research Center Montreal Heart Institute Montreal, QC, Canada

Domenico Corrado, MD
Professor of Medicine
Department of Cardiac, Thoracic and Vascular
Science
University of Padua, Italy

Ottorino Costantini, MD
Director
Clinical Trials Program
Heart and Vascular Research Center
MetroHealth Campus
Case Western Reserve University
Cleveland, OH, USA

Lia Crotti, MD
Assistant Professor
Department of Cardiology
Policlinico San Matteo
University of Pavia
Pavia, Italy

Antoine Deplagne, MD Hôpital Cardiologique du Haut-Lévêque Bordeaux-Pessac, France

*Nicolas Derval, MD* Hôpital Cardiologique du Haut-Lévêque Bordeaux-Pessac, France

José M. Di Diego, MD Research Scientist I Masonic Medical Research Laboratory Utica, NY, USA

Nabil El-Sherif, MD
Chief
Cardiology Division
Department of Medicine
New York Harbor VA Health Care System
Brooklyn Campus
Brooklyn, NY, USA

Denis Escande, MD, PhD<sup>†</sup>
Director of "L'institut du thorax"
Head of the INSERM U533 Department
Head of the Clinical Physiology Laboratory
Cardiologist
Professor of Physiology and Medicine
University of Nantes, Medical School
INSERM U533
L'institut du thorax
UMR de Médecine
Nantes, France

<sup>†</sup>Deceased.

xviii Contributors

Tania Ferrer, PhD
Postdoctoral Fellow
Nora Eccles Harrison Cardiovascular Research
Institute
University of Utah School of Medicine
Salt Lake City, UT, USA

David M. Ficker, MD
Associate Professor of Neurology
Director
Epilepsy Monitoring Unit and EEG Lab
University Hospital
University of Cincinnati Academic Health
Center
Cincinnati, OH, USA

Harry A. Fozzard, MD
Otho SA Sprague Distinguished Service
Professor Emeritus
Department of Medicine
The University of Chicago
Chicago, IL, USA

Paul A. Friedman, MD
Professor of Medicine
Mayo Clinic College of Medicine
Rochester, MN, USA

Apoor S. Gami, MD Assistant Professor of Medicine Division of Cardiovascular Diseases Mayo Clinic College of Medicine Rochester, MN, USA

Yi Gang, MD, PhD
Research Fellow
Department of Cardiac and Vascular
Sciences
St George's, University of London
London, UK

Robin E. Germany, MD
Assistant Professor
Cardiovascular Section
Department of Medicine
University of Oklahoma Health Sciences
Center
Oklahoma City, OK, USA

Michael Glikson, MD, FACC, FESC
Clinical Professor of Cardiology
Director of Pacing and Electrophysiology Heart
Institute
Sheba Medical Center
Tel Aviv University
Tel Hashomer, Israel
Ramat Gan, Israel

Michael H. Gollob, MD, FRCP
Director
Staff Cardiac Electrophysiologist
Arrhythmia Research Laboratory and Division
of Cardiology
University of Ottawa Heart Institute
Ottawa, ON, Canada

Robert M. Gow, MD, FRCP Staff Cardiac Electrophysiologist Division of Cardiology Department of Medicine Children's Hospital of Eastern Ontario University of Ottawa Heart Institute Ottawa, ON, Canada

Martin S. Green, MD, FRCP Staff Cardiac Electrophysiologist Division of Cardiology Department of Medicine University of Ottawa Heart Institute Ottawa, ON, Canada

Lorne J. Gula, MD, MSc, FRCPC
Assistant Professor of Medicine
University of Western Ontario
Clinical Cardiac Electrophysiologist
Cardiology
Arrhythmia Service
Department of Medicine
Division of Cardiology
London Health Sciences Center
London, ON, Canada

Osnat Gurevitz, MD
Pacing and Electrophysiology Unit
The Heart Institute
Sheba Medical Center and Tel Aviv
University
Tel Hashomer, Israel

Contributors xix

Hiie M. Gussak, MD
Assistant Professor of Medicine
University of Medicine and Dentistry of
New Jersey
Hackensack University Medical Center
Nephrologist
Internal Medicine
Nephrology Associates
Teaneck, NJ, USA

Ihor Gussak, MD, PhD, FACC
Deputy Therapeutic Area Head
Cardiovascular
Boehringer Ingelheim Pharmaceuticals
Ridgefield, CT, USA
Clinical Professor of Medicine
University of Medicine and Dentistry of
New Jersey
Robert Wood Johnson Medical School
Bridgewater, NJ, USA

Michel Haïssaguerre, MD Professor Université Bordeaux II Hôpital Cardiologique du Haut-Lévêque Bordeaux-Pessac, France

Masayasu Hiraoka, MD, PhD
Professor Emeritus
Tokyo Medical and Dental University and
Commissioner
Labor Insurance Appeal Committee
Ministry of Health, Labor and Welfare
Shibakouen, Minato-ku, Tokyo, Japan

Siew Yen Ho, PhD
Honorary Consultant Cardiac Morphologist
Cardiac Morphology
Royal Brompton Hospital and National Heart
and Lung Institute
London, UK

Mélèze Hocini, MD Hôpital Cardiologique du Haut-Lévêque Bordeaux-Pessac, France Arshad Jahangir, MD
Professor of Medicine
Director
CardioGerontology Research Laboratory
Division of Cardiovascular Diseases
Department of Internal Medicine
Mayo Clinic College of Medicine
Rochester, MN, USA

Pierre Jaïs, MD Hôpital Cardiologique du Haut-Lévêque Bordeaux-Pessac, France

Anders Jönsson, MD Hôpital Cardiologique du Haut-Lévêque Bordeaux-Pessac, France

Mark E. Josephson, MD Chief Cardiovascular Division Clinical Professor of Medicine Beth Israel Deaconess Medical Center Boston, MA, USA

Lilian Joventino, MD
Assistant Professor of Medicine
The Warren Alpert Medical School of Brown
University
Department of Medicine
Rhode Island and Miriam Hospitals
Providence, RI, USA

Richard Judson, PhD
National Center for Computational Toxicology
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC, USA

Alan Kadish, MD Northwestern University Feinberg School of Medicine Chicago, IL, USA

Robert S. Kass, PhD
Columbia University Alumnus and David
Hoasack Professor and Chairman
Department of Pharmacology
College of Physicians and Surgeons of Columbia
University
New York, NY, USA

xx Contributors

Anant Khositseth, MD
Department of Pediatrics
Division of Pediatric Cardiology
Faculty of Medicine Ramathibodi Hospital
Mahidol University
Bangkok, Thailand

Robert B. Kleiman, MD Senior Director International Cardiology eResearchTechnology, Inc. Philadelphia, PA, USA

George J. Klein, MD
Electrophysiology Training Program Director
Professor of Medicine
University of Western Ontario
London, ON, Canada

Peter Kohl, MD, PhD
Senior Fellow
Department of Physiology, Anatomy and Genetics
University of Oxford
Oxford, UK

Andrzej S. Kosinski, PhD
Associate Professor
Department of Biostatistics and Bioinformatics
Duke University
Duke Clinical Research Institute
Durham, NC, USA

John B. Kostis, MD
Chairman
Department of Medicine
Professor of Medicine and Pharmacology
John G. Detwiler Professor of Cardiology
University of Medicine and Dentistry of
New Jersey
Robert Wood Johnson Medical School
Chief of Medical Service
Robert Wood Johnson University Hospital
New Brunswick, NJ, USA

Andrew D. Krahn MD, FACC, FRCPC
Electrophysiology Training Program Director
Professor
Division of Cardiology
University of Western Ontario
London, ON, Canada

Yoshihisa Kurachi, MD, PhD
Professor and Chairman
Department of Pharmacology
Osaka University Graduate School of Medicine
Suita, Osaka, Japan

Julien Laborderie, MD Université Bordeaux II Hôpital Cardiologique du Haut-Lévêque Bordeaux-Pessac, France

Dominique Lacroix, MD, PhD Professor Hôpital Cardiologique CHRU De Lille Lille, France

Hon-Chi Lee, MD, PhD
Professor of Medicine
Mayo Medical School
Consultant
Division of Cardiovascular Diseases
Department of Internal Medicine
Mayo Clinic College of Medicine
Rochester, MN, USA

Hervé Le Marec, MD, PhD
Professor
Head of Cardiovascular Department
Nantes Hospital
L'institut du thorax
Saint-Herblain, France

Nicolas Lindegger, PhD
Postdoctoral Fellow
Department of Pharmacology
Columbia University
New York, NY, USA

Jeffrey S. Litwin, MD
Senior Vice President and Chief Medical
Officer
eResearchTechnology, Inc.
Philadelphia, PA, USA

Nian Liu, MD
Research Fellow
Department of Molecular Cardiology
IRCCS Salvatore Maugeri Foundation
Maugeri, Pavia, Italy

Contributors xxi

David Luria, MD
Senior Cardiologist
Pacing and Electrophysiology Unit
Heart Institute
Sheba Medical Center
Tel Hashomer, Israel

Marek Malik, MD, PhD, DSc (Med), FACC, FESC, FHRS
Professor of Cardiac Electrophysiology
Department of Cardiac and Vascular Sciences
St. George's, University of London
London, UK

Frank I. Marcus, MD
Professor Emeritus
Department of Cardiology
University of Arizona
Sarver Heart Center
Tucson, AZ, USA

Barry J. Maron, MD
Hypertrophic Cardiomyopathy Center
Minneapolis Heart Foundation
Minneapolis, MN, USA

Shaji C. Menon, MD
Fellow
Pediatric Cardiology
Mayo Clinic College of Medicine
Rochester, MN, USA

Paola G. Meregalli, MD
Cardiologist
Heart Failure Research Center
Department of Clinical and Experimental
Cardiology
Academic Medical Center
Amsterdam, The Netherlands

Antoon F.M. Moorman, PhD
Professor
Heart Failure Research Center
Department of Anatomy and Embryology
Academic Medical Center
Amsterdam, The Netherlands

Christophe Moreau, PhD
Career Scientist
Biophysique Moléculaire and Cellulaire
CNRS UMR5090
CEA/DRDC
Grenoble, France

Joel Morganroth, MD
Chief Scientist
eResearchTechnology, Inc.
Clinical Professor of Medicine
University of Pennsylvania
Philadelphia, PA, USA

Shingo Murakami, PhD Assistant Professor Department of Pharmacology Osaka University Graduate School of Medicine Osaka, Japan

Christina M. Murray, MD
Fellow in Cardiovascular Medicine
Department of Medicine
University of Oklahoma Health Sciences
Center
Oklahoma City, OK, USA

Carlo Napolitano, MD, PhD
Adjunct Professor
School of Cardiology
University of Pavia
Research Coordinator
Molecular Cardiology Laboratories
Pavia, Italy

Stanley Nattel, MD
Professor
Cardiovascular Electrophysiology
Department of Medicine
Montreal Heart Institute Research Center and
Université de Montréal
Montreal, QC, Canada

Jan Nemec, MD, FACC
Assistant Professor of Medicine
Department of Cardiac Electrophysiology
Cardiovascular Institute
University of Pittsburgh Medical Center
Pittsburgh, PA, USA

xxii Contributors

Timothy M. Olson, MD
Associate Professor of Medicine and
Pediatrics
Director
Cardiovascular Genetics
Division of Cardiovascular Diseases
Departments of Medicine, Pediatrics
and Adolescent Medicine and Medical
Genetics
Mayo Clinic College of Medicine

Steve R. Ommen, MD Associate Professor of Medicine Cardiovascular Diseases Mayo Clinic College of Medicine Rochester, MN, USA

Rochester, MN, USA

Mark D. O'Neill, MB, BCh, DPhil Hôpital Cardiologique du Haut-Lévêque Bordeaux-Pessac, France

Ganiyu O. Oshodi, MD
Heart and Vascular Research Center
MetroHealth Campus
Case Western Reserve University
Cleveland, OH, USA

Mai Ots, MD, ScD (med)
Associate Professor of Medicine
Division of Nephrology
Department of Internal Medicine
Tartu University Clinic
Tartu, Estonia

Antonio Pelliccia, MD Center of Sports Sciences Rome, Italy

Yigal M. Pinto, MD, PhD
Professor
Cardiologist
Department of Cardiology
University Hospital Maastricht
Maastricht, The Netherlands

Alex V. Postma, PhD
Department of Anatomy and Embryology
Academic Medical Center
Amsterdam, The Netherlands

Silvia G. Priori, MD, PhD
Professor of Cardiology
University of Pavia
Director of Molecular Cardiology
Department of Molecular Cardiology
IRCCS Salvatore Maugeri Foundation
Pavia, Italy

Sridharan Rajamani, PhD Scientist Department of Pharmacology CV Therapeutics, Inc. Palo Alto, CA, USA

Robert F. Rea, MD
Associate Professor of Medicine
Cardiovascular Division
Department of Medicine
Mayo Clinic College of Medicine
Rochester, MN, USA

Vikram Reddy, MD Northwestern University Feinberg School of Medicine Chicago, IL, USA

Dwight W. Reynolds, MD
Professor and Chief
Cardiovascular Section
Department of Medicine
University of Oklahoma Health Sciences
Center
Oklahoma City, OK, USA

John Jeremy Rice, PhD, MS, BS
Research Staff Member
Department of Functional Genomics and
Systems Biology
IBM T.J Watson Research Center
Yorktown Heights, NY, USA

Richard B. Robinson, PhD Professor of Pharmacology Associate Dean of Graduate Affairs Columbia University New York, NY, USA Contributors xxiii

Michael R. Rosen, MD
Gustavus A. Pfeiffer Professor of
Pharmacology
Professor of Pediatrics
Director, Center for Molecular Therapeutics
Department of Pharmacology
Columbia University
New York, NY, USA

David S. Rosenbaum, MD

Director

Heart and Vascular Center for the MetroHealth System

Professor of Medicine and Biomedical Engineering MetroHealth Campus Case Western Reserve University Cleveland, OH, USA

Yanfei Ruan, MD
Research Fellow
Molecular Cardiology Laboratories
IRCCS Salvatore Maugeri Foundation
Pavia, Italy

Frédéric Sacher, MD Université Bordeaux II Hôpital Cardiologique du Haut-Lévêque Bordeaux-Pessac, France

Jeffrey E. Saffitz, MD, PhD
Mallinckrodt Professor of Pathology
Harvard Medical School Chief
Department of Pathology
Beth Israel Medical Center
Boston, MA, USA

Rafeeq Samie, MD
Fellow
Clinical Electrophysiology
Division of Cardiology
Department of Medicine
University of Ottawa Heart Institute
Ottawa, ON, Canada

Srinivasan Sattiraju, MD
Department of Molecular Pharmacology and
Experimental Therapeutics
Mayo Clinic College of Medicine
Rochester, MN, USA

Hartzell V. Schaff, MD
Chair
Division of Cardiovascular Surgery
Stuart W. Harrington Professor of Surgery
Department of Surgery
Mayo Clinic College of Medicine
Rochester, MN, USA

Bas A. Schoonderwoerd, MD, PhD
Department of Cardiology
Thoraxcenter
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

Jean-Jacques Schott, PhD
Researcher
INSERM U533
L'institut du thorax
Nantes, France

Eric Schulze-Bahr, MD
Professor
Department of Cardiology and Angiology
Molecular Genetics
Hospital of the University of Münster
Münster, Germany

Peter J. Schwartz, MD
Professor of Cardiology
Department of Cardiology
University of Pavia and IRCCS Policlinico San
Matteo
Pavia, Italy

Win-Kuang Shen, MD
Consultant
Division of Cardiovascular Diseases
Professor of Medicine
Mayo Clinic College of Medicine
Rochester, MN, USA

Wataru Shimizu, MD, PhD
Senior Staff
Co-Director of Clinical Cardiac
Electrophysiology Laboratory
Division of Cardiology
Department of Internal Medicine
National Cardiovascular Center
Suita, Osaka, Japan

xxiv Contributors

John C. Shryock, PhD
Senior Director
Department of Pharmacology
CV Therapeutics, Inc.
Palo Alto, CA, USA

Allan C. Skanes, MD
Director of Electrophysiology Laboratory
University Hospital
University of Western Ontario
London, ON, Canada

Elson L. So, MD
Professor of Neurology
Director
Section of Electroencephalography
Mayo Clinic College of Medicine
Rochester, MN, USA

Virend K. Somers, MD, DPhil Professor of Medicine Division of Cardiovascular Diseases Mayo Clinic College of Medicine Rochester, MN, USA

Subeena Sood, PhD
Postdoctoral Associate
Department of Molecular Physiology and
Biophysics
Baylor College of Medicine
Houston, TX, USA

Marco Stramba-Badiale, MD, PhD Head Pediatric Arrhythmias Center IRCCS Istituto Auxologico Italiano Milan, Italy

Rajesh N. Subbiah, BSc(Med), MBBS, PhD, FRACP Electrophysiology Fellow University of Western Ontario London, ON, Canada Yoshihide Takahashi, MD Hôpital Cardiologique du Haut-Lévêque Bordeaux-Pessac, France

Hanno L. Tan, MD, PhD
Cardiologist
Heart Failure Research Center
Department of Clinical and Experimental
Cardiology
Academic Medical Center
Amsterdam, The Netherlands

Andre Terzic, MD, PhD Marriott Family Endowed Professor of Cardiovascular Research Professor of Medicine, Molecular Pharmacology and Experimental Therapeutics Director Marriott Heart Disease Research **Program** Mayo Clinic Associate Director of Research Division of Cardiovascular Diseases Departments of Medicine, Molecular Pharmacology and Experimental Therapeutics, and Medical Genetics Mayo Clinic College of Medicine Rochester, MN, USA

David J. Tester, BS
Senior Research Technologist II
Departments of Medicine, Pediatrics, and
Molecular Pharmacology and Experimental
Therapeutics
Divisions of Cardiovascular Diseases and
Pediatric Cardiology
Mayo Clinic College of Medicine
Rochester, MN, USA

Sergio G. Thal, MD Staff of Cardiac Electrophysiology South Arizona VA Health Care System Assistant Professor of Clinical Medicine University of Arizona Tucson, AZ, USA Contributors

Gaetano Thiene, MD, FRCPHon
Professor of Pathological Anatomy
Department of Medico-Diagnostic Sciences and
Special Therapies
Pathological Anatomy-Cardiovascular Pathology
University of Padua Medical School
Padua, Italy

Gordon F. Tomaselli, MD
David J. Carver Professor of Medicine
The Johns Hopkins University School of Medicine
Baltimore, MD, USA

Jeffrey A. Towbin, MD
Professor of Medicine
Chief
Pediatric Cardiology
Texas Children's Hospital
Baylor College of Medicine
Houston, TX, USA

Martin Tristani-Firouzi, MD
Associate Professor of Pediatrics
Pediatric Cardiology
Nora Eccles Harrison Cardiovascular Research
Institute
University of Utah School of Medicine
Salt Lake City, UT, USA

Gioia Turitto, MD
Director
Cardiac Electrophysiology Services
Department of Medicine
New York Methodist Hospital
Brooklyn, NY, USA

Jop H. van Berlo, MD, PhDDepartment of Molecular CardiovascularBiologyCincinnati Children's Hospital Medical CenterCincinnati, OH, USA

Isabelle C. van Gelder, MD, PhD
Cardiologist
Department of Cardiology
Thoraxcenter
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

J. Peter van Tintelen, MD
Clinical Geneticist
Department of Clinical Genetics
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

Matteo Vatta, PhD
Assistant Professor
Department of Pediatrics
(in Cardiology)
Baylor College of Medicine and Texas Children's
Hospital
Houston, TX, USA

Richard L. Verrier, MD, PhD, FACC
Associate Professor of Medicine
Harvard Medical School
Beth Israel Deaconess Medical Center
Harvard-Thorndike Electrophysiology
Institute
Harvard Institutes of Medicine
Boston, MA, USA

Sami Viskin, MD
Director
Cardiac Hospitalization
Tel Aviv Sourasky Medical Center
Sackler School of Medicine
Tel Aviv University
Tel Aviv, Israel

Michel Vivaudou, PhD
Director of Research
Biophysique Moléculaire and Cellulaire
CNRS UMR5090
CEA/DRDC
Grenoble, France

Marc A. Vos, PhD
Professor
Head of Department
Medical Physiology
Heart and Lung Center Utrecht
University Medical Center Utrecht
Utrecht, The Netherlands

xxvi Contributors

Xander H.T. Wehrens, MD, PhD
Assistant Professor
Department of Molecular Physiology and
Biophysics
Department of Medicine (in Cardiology)
Baylor College of Medicine
Houston, TX, USA

Ans C.P. Wiesfeld, MD, PhD
Department of Cardiology
Thoraxcenter
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

Arthur A.M. Wilde, MD, PhD, FESC, FAHA
Professor
Heart Failure Research Center
Department of Clinical and Experimental
Cardiology
Academic Medical Center
Amsterdam, The Netherlands

Bruce L. Wilkoff, MD
Professor of Medicine
Director of Cardiac Pacing and Tachyarrhythmia
Devices
Department of Cardiovascular Medicine
Cleveland Clinic Lerner College of
Medicine of Case Western Reserve
University
Cleveland, OH, USA

Lance D. Wilson, MD
Assistant Professor of Emergency Medicine
Staff Physician
Heart and Vascular Research Center
MetroHealth Campus
Case Western Reserve University
Cleveland, OH, USA

Stephan K.G. Winckels, MD
PhD Student
Medical Physiology
Heart and Lung Center Utrecht
University Medical Center Utrecht
Utrecht, The Netherlands

Satsuki Yamada, MD, PhD
Senior Research Fellow
Division of Cardiovascular Diseases
Department of Medicine, Molecular
Pharmacology and Experimental Therapeutics
Mayo Clinic College of Medicine
Rochester, MN, USA

Raymond Yee, MD
Professor of Medicine
Director
Arrhythmia Service
Staff Cardiac Electrophysiologist
London HSC-University Hospital and University
of Western Ontario
London, ON, Canada

Leonid V. Zingman, PhD
Assistant Professor of Medicine and Pharmacology
Division of Cardiovascular Diseases
Departments of Medicine, Molecular Pharmacology and Therapeutics
Mayo Clinic College of Medicine
Rochester, MN, USA

Douglas P. Zipes, MD
Distinguished Professor
Professor Emeritus of Medicine, Pharmacology
and Toxicology
Director Emeritus
Division of Cardiology and the Krannert
Institute of Cardiology
Indiana University School of Medicine
Indianapolis, IN, USA