CONTEMPORARY CARDIOLOGY

# Cardiac Repolarization

## Bridging Basic and Clinical Science


Edited by

Ihor Gussak, MD, PhD

Charles Antzelevitch, PhD

Co-Edited by

Stephen C. Hammill, MD

Win-Kuang Shen, MD

Preben Bjerregaard, MD, DMSc



HUMANA PRESS

# Cardiac Repolarization

# CONTEMPORARY CARDIOLOGY

## CHRISTOPHER P. CANNON, MD

*SERIES EDITOR*

***Cardiac Repolarization:*** *Bridging Basic and Clinical Science,* edited by *Ihor Gussak, MD, PhD, Charles Antzelevitch, PhD,* Co-Edited by *Stephen C. Hammill, MD, Win-Kuang Shen, MD, and Preben Bjerregaard, MD, DMSc, 2003*

***Nuclear Cardiology Basics:*** *How to Set Up and Maintain a Laboratory,* by *Frans J. Th. Wackers, MD, Wendy Bruni, CNMT, and Barry L. Zaret, MD, 2003*

***Minimally Invasive Cardiac Surgery, Second Edition,*** edited by *Mehmet C. Oz, MD and Daniel J. Goldstein, MD, 2003*

***Cardiovascular Health Care Economics,*** edited by *William S. Weintraub, MD, 2003*

***Platelet Glycoprotein IIb/IIIa Inhibitors in Cardiovascular Disease, Second Edition,*** edited by *A. Michael Lincoff, MD, 2003*

***Heart Failure:*** *A Clinician's Guide to Ambulatory Diagnosis and Treatment,* edited by *Mariell L. Jessup, MD and Evan Loh, MD, 2003*

***Management of Acute Coronary Syndromes, Second Edition,*** edited by *Christopher P. Cannon, MD, 2003*

***Aging, Heart Disease, and Its Management:*** *Facts and Controversies,* edited by *Niloo M. Edwards, MD, Mathew S. Maurer, MD, and Rachel B. Wellner, MPH, 2003*

***Peripheral Arterial Disease:*** *Diagnosis and Treatment,* edited by *Jay D. Coffman, MD and Robert T. Eberhardt, MD, 2003*

***Essentials of Bedside Cardiology:*** *With a Complete Course in Heart Sounds and Murmurs on CD, Second Edition,* by *Jules Constant, MD, FACC, 2003*

***Primary Angioplasty in Acute Myocardial Infarction,*** edited by *James E. Tcheng, MD, 2002*

***Cardiogenic Shock:*** *Diagnosis and Treatment,* edited by *David Hasdai, MD, Peter B. Berger, MD, Alexander Battler, MD, and David R. Holmes, Jr., MD, 2002*

***Management of Cardiac Arrhythmias,*** edited by *Leonard I. Ganz, MD, 2002*

***Diabetes and Cardiovascular Disease,*** edited by *Michael T. Johnstone, MD and Aristidis Veves, MD, DSC, 2001*

***Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics,*** edited by *William B. White, MD, 2001*

***Vascular Disease and Injury:*** *Preclinical Research,* edited by *Daniel I. Simon, MD, and Campbell Rogers, MD 2001*

***Preventive Cardiology:*** *Strategies for the Prevention and Treatment of Coronary Artery Disease,* edited by *JoAnne Micale Foody, MD, 2001*

***Nitric Oxide and the Cardiovascular System,*** edited by *Joseph Loscalzo, MD, PhD and Joseph A. Vita, MD, 2000*

***Annotated Atlas of Electrocardiography:*** *A Guide to Confident Interpretation,* by *Thomas M. Blake, MD, 1999*

***Platelet Glycoprotein IIb/IIIa Inhibitors in Cardiovascular Disease,*** edited by *A. Michael Lincoff, MD, and Eric J. Topol, MD, 1999*

***Minimally Invasive Cardiac Surgery,*** edited by *Mehmet C. Oz, MD and Daniel J. Goldstein, MD, 1999*

***Management of Acute Coronary Syndromes,*** edited by *Christopher P. Cannon, MD, 1999*

# Cardiac Repolarization

## *Bridging Basic and Clinical Science*


*Edited by*

**Ihor Gussak, MD, PhD**

*eResearchTechnology Inc., Bridgewater, NJ*

**Charles Antzelevitch, PhD**

*Masonic Medical Research Laboratory, Utica, NY*

*Co-Edited by*

**Stephen C. Hammill, MD**

*Mayo Clinic, Rochester, MN*

**Win-Kuang Shen, MD**

*Mayo Clinic, Rochester, MN*

**Preben Bjerregaard, MD, DMSc**

*St. Louis University Health Sciences Center, St. Louis, MO*

*Foreword by*

**Douglas P. Zipes, MD**

*Indiana University School of Medicine, Indianapolis, IN*



Humana Press
Totowa, New Jersey

999 Riverview Drive, Suite 208
Totowa, New Jersey 07512
**www.humanapr.com**

For additional copies, pricing for bulk purchases, and/or information about other Humana titles, contact Humana at the above address or at any of the following numbers: Tel.: 973-256-1699; Fax: 973-256-8341, E-mail: humana@humanapr.com; or visit our website.



Production Editor: Mark J. Breaugh.

Cover design by Patricia F. Cleary.

This publication is printed on acid-free paper. ∞
ANSI Z39.48-1984 (American National Standards Institute) Permanence of Paper for Printed Library Materials.



Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

Library of Congress Cataloging-in-Publication Data

# Dedication

*To my family:*
*wife, Hiie, children Maria and Georg,*
*my parents Bohdan and Maria,*
*and to my mentors:*
*Drs. Charles Antzelevitch, Preben Bjerregaard,*
*Mary Osbakken, and Ronald Selvester.*

**-IG**

*This book is dedicated to my wife Brenda,*
*whose love and understanding have been a constant source of inspiration,*
*to my children Daniel and Lisa, whose shining existence light my every day and night, and to my parents,*
*Frieda and Chaim, for their unconditional love and support.*

**-CA**

# FOREWORD

**Douglas P. Zipes,** MD
***Indiana University School of Medicine, Indianapolis, IN***

I once wrote, paraphrasing Churchill's description of Stalin, that "The AV node is an enigma in an island of whimsy surrounded by a sea of uncertainty." I could easily substitute the T wave for the AV node in that statement. Despite intense study for 100 years, unanswered questions about the T wave abound. Some of these important questions are relatively pedestrian and include how to accurately measure the QT interval when the end of the T wave is blurred or merged with the U wave, or the T wave contour is distorted; how to correct for rate changes (Bazett's formula is most commonly used despite its under correction at slow rates and over correction at fast rates and the fact that Bazett applied it only in normal, relatively young, drug-free individuals); the relation of the T wave to the U wave, what causes the U wave, and what the importance of the QU interval is; the meaning of T wave lability (for the clinician: just what does "nonspecific T wave change" really mean?); the mechanism of broad negative T waves in non-Q-wave myocardial infarction and CNS injury; how to measure T wave dispersion accurately and what does it mean; the impact of autonomic and hormonal alterations; and the true upper limit of normal for the QT and QTc intervals for men and women.

Then, probing deeper, what is the relationship of the long QT syndrome (LQTS) to the sudden infant death syndrome; do all patients who develop drug-induced LQTS start with a congenital abnormality; do early after-depolarizations precipitate or maintain *torsades de pointes*; can *torsades de pointes* occur in the atria; and do patients who prolong ventricular repolarization after cardiac remodeling from heart failure or ventricular hypertrophy really die from *torsades de pointes*?

And then, at a basic level, how relevant are data from models such as the left ventricular wedge, isolated myocytes and membrane patches, and computer simulations? What is the role of M cells in repolarization, the U wave, and *torsades de pointes*? How do the intracellular $Ca^{2+}$/calmodulin-dependent processes regulate the development of *torsades de pointes*?

While it seems we have more questions than answers—and indeed the questions I have asked are only a partial list—*Cardiac Repolarization: Bridging Basic and Clinical Science* attempts to answer some of those questions. From basic electrophysiology, pharmacology, and molecular biology to clinical physiology and pathophysiology and a consideration of specific electrocardiographic phenomena and syndromes, world-class experts give their views on these and related topics.

The study of cardiac repolarization is an area of intense interest, but an evolving field. As new knowledge accumulates, our concepts are certain to change, but that is the challenge and fun of what we do. Hopefully, in several years, we will be reading a much updated second edition.

***Douglas P. Zipes,*** *MD*
*Indianapolis, IN*

# PREFACE

There are a number of excellent books on molecular biology, single-channel electrophysiology, animal experimentation, and clinical electrophysiology. However, the past decade has seen an explosion of knowledge and radical changes in our understanding of ventricular repolarization as an integral part of the cardiac electrophysiologic matrix; a topic which, until now, has not been covered in depth. *Cardiac Repolarization: Bridging Basic and Clinical Science* presents comprehensively the latest developments in the field of cardiac electrophysiology with a focus on the clinical and experimental aspects of ventricular repolarization, newly discovered clinical repolarization syndromes, electrocardiographic phenomena, and their correlation with the most recent advances in basic science.

Repolarization has distinct adaptive mechanisms that are responsible for maintenance of electrophysiological equilibrium and electrical stability of the heart under normal and pathophysiological conditions. Both congenital and acquired abnormalities of ventricular repolarization have recently received significant recognition because these are major contributors of life-threatening cardiac arrhythmias and are an important target for antiarrhythmic drugs and interventions. We have aimed to provide unique prospective views on ventricular repolarization by emphasizing the clinical and basic aspects of physiology and pathophysiology in conjunction with new clinical findings and research discoveries. The authors have provided a thought-provoking and enlightening review of the latest research and clinical accomplishments in their areas of expertise. Each chapter is outlined with objectives, key points, current perspectives, and recommendations for future investigations. Each chapter includes established and evidence-based knowledge, the authors' personal opinions, areas of controversy, and future trends. We aimed to provide a contemporary and succinct distillation of the current status of cardiac repolarization. Although some of the areas are highly subspecialized, this book has been designed for a broad audience ranging from medical and graduate students to clinicians and scientists.

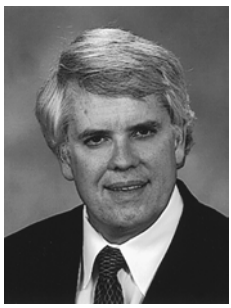
*Cardiac Repolarization: Bridging Basic and Clinical Science* is organized so as to make the large volume of rapidly evolving information understandable and easy to assimilate, with each section focusing on a theme of cardiac repolarization. The spectrum of ventricular repolarization, historical milestones of electrical signal recording, and their relevance to clinical arrhythmias and sudden cardiac death syndromes are presented as an introduction. Part II focuses on the theme of basic mechanisms underlying ventricular repolarization. In addition to an overview of electrophysiology, pharmacology, and molecular biology underlying ventricular repolarization, basic mechanisms have been integrated with specific disease conditions, including heart failure, ischemia, long QT syndrome, and Brugada syndrome. The theme of Part III includes clinical physiology and pathophysiology of ventricular repolarization; state-of-the-art information on human cardiac repolarization with an emphasis on clinical application; challenges and clinical relevance of the dynamic interactions of neurohumeral and pharmacological factors; and

a peek into the future of antiarrhythmic drug development based on molecular and electrophysiological properties. Part IV of the book provides a comprehensive review of the clinical presentation and management of specific cardiac repolarization conditions, including early repolarization and short QT interval, Brugada syndrome, long QT syndrome, and sudden infant death syndrome.

The editors of *Cardiac Repolarization: Bridging Basic and Clinical Science* wish to recognize the significant contribution made by all of the authors. The book is the result of a collaboration that has brought together the skills and perspectives of researchers, scientists, and clinicians. We also wish to thank all of our mentors, without whom the work presented in the book would not have been realized. Finally, we are grateful to our colleagues, trainees, and students for stimulating interactions that have served as the basis for many innovative ideas and investigations.

Ihor Gussak, MD, PhD

Charles Antzelevitch, PhD



Stephen C. Hammill, MD

Win-Kuang Shen, MD

Preben Bjerregaard, MD, DMSc

# CONTENTS