

CONTEMPORARY CARDIOLOGY

Cardiac Repolarization

Bridging Basic and Clinical Science

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HUMANA PRESS

CARDIAC REPOLARIZATION

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CHRISTOPHER P. CANNON, MD

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HUMANA PRESS
TOTOWA, NEW JERSEY

© 2003 Humana Press Inc.
999 Riverview Drive, Suite 208
Totowa, New Jersey 07512
www.humanapr.com

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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.

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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

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.



Douglas P. Zipes, MD
*Indiana University
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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
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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.

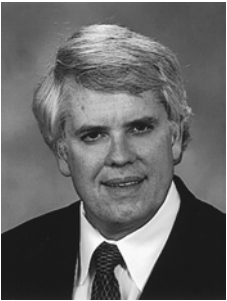
The editors of *Cardiac Repolarization: Bridging Basic and Clinical Science* wish to recognize the significant contribution made by all of the authors. The book is the result of a collaboration that has brought together the skills and perspectives of researchers, scientists, and clinicians. We also wish 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



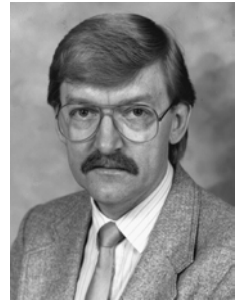
Charles Antzelevitch, PhD



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CONTENTS

Dedication	v
Foreword	vii
Preface	ix
Contributors	xv

Part I. Introduction

Chapter 1. Ventricular Repolarization and the Identification of the Sudden Death Candidate: Hype or Hope?	3
<i>Hein J. Wellens and Douglas P. Zipes</i>	
Chapter 2. Historical Milestones of Electrical Signal Recording and Analysis	7
<i>Thorsten Lewalter and Berndt Lüderitz</i>	

Part II. Basic Electrophysiology, Pharmacology, and Molecular Biology of Ventricular Repolarization

Edited by Charles Antzelevitch

Chapter 3. Physiology and Molecular Biology of Ion Channels Contributing to Ventricular Repolarization	25
<i>Jeanne M. Nerbonne and Robert S. Kass</i>	
Chapter 4. Electrophysiology and Pharmacology of Ventricular Repolarization	63
<i>Charles Antzelevitch, Andrew C. Zygmunt, and Robert Dumaine</i>	
Chapter 5. How Do We Measure Repolarization Inside the Heart?	91
<i>Charles Antzelevitch, Andrew C. Zygmunt, Jeffrey Fish, Guillermo Perez, and Fabiana Scornik</i>	
Chapter 6. Contribution of Electrical Heterogeneity of Repolarization to the ECG	111
<i>Charles Antzelevitch and Vladislav V. Nesterenko</i>	
Chapter 7. Electrical and Structural Remodeling of the Ventricular Myocardium in Disease	127
<i>Antonis A. Armoundas and Gordon F. Tomaselli</i>	
Chapter 8. Ischemia-Related Changes in Repolarization	153
<i>André G. Kléber and Michiel J. Janse</i>	

- Chapter 9. The Long QT Syndrome: Molecular and Genetic Aspects 169
Carlo Napolitano and Silvia G. Priori
- Chapter 10. Ion Channel Disease as a Cause of the Brugada Syndrome:
Molecular and Genetic Aspects 187
Connie R. Bezzina and Arthur A. M. Wilde
- Chapter 11. Cellular and Ionic Mechanisms Underlying Arrhythmogenesis .. 201
Charles Antzelevitch, Alexander Burashnikov, and Jose M. Di Diego

Part III. Clinical Physiology and Pathophysiology of Ventricular Repolarization: Theory and Practice

Edited by Stephen C. Hammill, Win-Kuang Shen, and Ihor Gussak

- Chapter 12. Evaluation of Ventricular Repolarization:
The Clinician's Perspective 255
Jan Nemeč, Stephen C. Hammill, and Win-Kuang Shen
- Chapter 13. Human Cardiac Repolarization 291
Philip T. Sager
- Chapter 14. QT Interval and Its Drug-Induced Prolongation 311
Wojciech Zareba and Arthur J. Moss
- Chapter 15. Neuro-Mediated Repolarization Abnormalities 329
Philippe Coumel and Pierre Maison-Blanche
- Chapter 16. The Electrophysiologic Matrix: Equilibrium
and Arnsdorf's Paradox 351
Morton F. Arnsdorf
- Chapter 17. Antiarrhythmic Drugs and Future Direction 387
Arshad Jahangir, Andre Terzic, and Win-Kuang Shen

Part IV. Specific Electrocardiographic Phenomena and Clinical Syndromes of Ventricular Repolarization

Edited by Ihor Gussak, Charles Antzelevitch, and Preben Bjerregaard

- Chapter 18. ECG Phenomena of the Early Ventricular Repolarization:
Early Repolarization Syndrome 407
Ihor Gussak, Charles Antzelevitch, and Preben Bjerregaard
- Chapter 19. The Brugada Syndrome 427
*Pedro Brugada, Ramon Brugada, Charles Antzelevitch,
Koonlawee Nademanee, Jeffrey Towbin, and Josep Brugada*
- Chapter 20. Clinical Evaluation, Risk Stratification, and Management
of Congenital Long QT Syndrome 447
Anant Khositseth and Michael J. Ackerman

Chapter 21.	Prolonged Repolarization and Sudden Infant Death Syndrome	481
	<i>Peter J. Schwartz</i>	
Chapter 22.	Short QT Interval: ECG Phenomenon and Clinical Syndrome	497
	<i>Ihor Gussak, Charles Antzelevitch, Daniel Goodman, and Preben Bjerregaard</i>	
Chapter 23.	T-Wave Alternans: Mechanisms, Relevance, and Clinical Implications	507
	<i>Etienne Pruvot and David S. Rosenbaum</i>	
Index		531

