Neural Mechanisms in Cardiac Arrhythmias

Perspectives in Cardiovascular Research Volume 2

Editors

Peter J. Schwartz, M.D.
Associate Professor of Medicine
Institute of Cardiovascular Research
University of Milan
Milan, Italy
and
Adjunct Associate Professor
Department of Physiology and Biophysics
University of Texas Medical Branch
Galveston, Texas

Arthur M. Brown, M.D., Ph.D.
Professor and Chairman
Department of Physiology and Biophysics
University of Texas Medical Branch
Galveston, Texas

Alberto Malliani, M.D.
Professor of Medicine
Institute of Cardiovascular Research
University of Milan
Milan, Italy

Alberto Zanchetti, M.D.
Professor of Medicine
Institute of Cardiovascular Research
University of Milan
Milan, Italy

Raven Press ▪ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

Made in the United States of America

Library of Congress Cataloging in Publication Data

Main entry under title:

Neural mechanisms in cardiac arrhythmias.

(Perspectives in cardiovascular research; v. 2)
Includes bibliographical references and index.
1. Arrhythmia—Congresses. 2. Heart—Innervation—Congresses. I. Schwartz, Peter J.
[DNLM: 1. Arrhythmia—Physiopathology. 2. Neurophysiology. W1 PE871AL v. 2 / WG330 N494]
RC685.A65N46 616.1'28 77–77962
ISBN 0–89004–209–8

Preface

In the past few years it has become increasingly evident that the nervous system is a primary factor in the genesis of lethal arrhythmias whether or not they are associated with acute myocardial ischemia. However, the mechanism whereby the nervous system exerts its actions is unknown and the methods of treating this component remain empirical. The significance of the problem lies in the overwhelming importance of cardiac arrhythmias as a cause of death.

The problem involves both practical considerations of therapy for the physician and hypotheses about control of the heart's function for the experimental scientist. In fact this is one setting in which the physician has the opportunity to act also as an experimental scientist. The problem is extremely complex and the most rewarding approach initially seems likely to be a multidisciplinary attack. The present volume contains reviews by outstanding clinicians and researchers working in the areas of clinical cardiology, cardiac electrophysiology, cardiac pharmacology, and neurocirculatory control. In order to explore questions of fundamental significance with regard to the neural mechanisms involved in the genesis of cardiac arrhythmias, a variety of innovative techniques have been developed, ranging from experiments on isolated cardiac cells to studies in conscious animals, from penetrating clinical observations to controlled clinical trials. This volume does not solve the problem of neural involvement in arrhythmias; rather it focuses attention upon the problem, outlines its current status, and suggests new lines of research.

The first section of this volume is devoted to the definition and discussion of the clinical problem. This is followed by an analysis of the roles played by the vagal and sympathetic cardiac nerves in the genesis of arrhythmias, a review of cardiac and baroreceptor reflexes and their participation in the control of cardiac rhythm, cardiac autonomic pharmacology, and ongoing studies on various aspects of neural involvement in cardiac arrhythmias.

Peter J. Schwartz
Arthur M. Brown
Alberto Malliani
Alberto Zanchetti

Acknowledgments

The symposium on which this volume is based was chaired by Professor Cesare Bartorelli, Director of the Istituto di Ricerche Cardiovascolari, "G. Sisini," Università di Milano, and would not have been possible without the enthusiastic cooperation and financial support provided by the Fondazione Internazionale Menarini, Firenze, and by the National Institutes of Health, Bethesda, Maryland. The symposium was held in Florence, and was an official Satellite Symposium of the XXVII Congress of the Union of Physiological Sciences.

It is a pleasure to acknowledge and express our thanks to Dr. Sergio Gorini, President of Fondazione Menarini, and Dr. Angela Perrone of the Fondazione Menarini, for the superb manner in which they handled all organizational problems and local arrangements. We also thank Miss Kathleen Fagan, Mrs. Grazia Soriani, Miss Alessandra Franceschini, and Mrs. Marina Enrico for excellent secretarial assistance.

The Editors

Contributors

F. M. Abboud
Cardiovascular Division
Department of Medicine
Department of Physiology
Cardiovascular Center
University of Iowa
Iowa City, Iowa 52240

John C. Bailey
The Krannert Institute of Cardiology
Indiana University School of Medicine
Indianapolis, Indiana 46202

Mario Bergamaschi
Department of Pharmacology and Toxicology
De Angeli Institute
Milan, Italy

H. R. Besch, Jr.
Department of Pharmacology
Indiana University School of Medicine
Indianapolis, Indiana 46202

Oscar Bonazzi
Institute of Cardiovascular Research
University of Milan
Milan, Italy

M. Bossi
A. De Gasperis Center
Cardiology Division
Maggiore Hospital
Milan, Italy

Arthur M. Brown
Department of Physiology and Biophysics
University of Texas Medical Branch
Galveston, Texas 77550

G. E. Burch
Department of Medicine
Tulane University School of Medicine
Charity Hospital of Louisiana
and
Veterans Administration Hospital
New Orleans, Louisiana 70112

Chia-Maou Chen
Cardiovascular Division
Department of Medicine
University of Kentucky Medical Center
Lexington, Kentucky 40506

Richard S. Crampton
Cardiology Division
158 Medical Center
University of Virginia
Charlottesville, Virginia 22901

Peter Danilo, Jr.
Departments of Pharmacology and Pediatrics
Columbia University College of Physicians and Surgeons
New York, New York 10032

Albert K. Dawson
Cardiovascular Research
Medtronic, Inc.
3055 Old Highway Eight
P. O. Box 1453
Minneapolis, Minnesota 55440

Matteo Di Biase
Department of Cardiology
University of Bari
70124 Bari, Italy

Russell T. Dowell
Marine Biomedical Institute
and
University of Texas Medical Branch
Galveston, Texas 77550

Dwain L. Eckberg
Veterans Administration
Department of Medicine
Medical College of Virginia
Richmond, Virginia 23298

Ella Elazar
The Heart Institute
Chaim Sheba Medical Center
Tel Hashomer, Israel

M. Eldar
The Heart Institute
Chaim Sheba Medical Center
Tel Hashomer, Isreal
and
Sackler Medical School
Tel Aviv University
Tel Aviv, Israel

David E. Euler
Department of Physiology
Loyola University
Stritch School of Medicine
Maywood, Illinois 60153

Alberto Ferrari
Institute of Cardiovascular Research
University of Milan
Milan, Italy

Robert D. Foreman
Department of Physiology and Biophysics
University of Texas Medical Branch
and
Marine Biomedical Institute
Galveston, Texas 77550

Dean Franklin
Cardiology Division
University of California, San Diego
School of Medicine
La Jolla, California 92093

Kevin D. Gerhart
University of Texas Medical Branch
Department of Physiology and Biophysics
Galveston, Texas 77550

Leonard S. Gettes
Cardiovascular Division
Department of Medicine
University of Kentucky Medical Center
Lexington, Kentucky 40506

Leslie G. Goulding
Cardiac Department
The Radcliffe Infirmary
University of Oxford
Oxford, England

Maria Gardumi
Institute of Cardiovascular Research
University of Milan
Milan, Italy

Luisa Gregorini
Institute of Cardiovascular Research
University of Milan
Milan, Italy

Michael Guberek
University of California at San Diego
School of Medicine
La Jolla, California 92093

Gilbert R. Hageman
Department of Physiology
University of Alabama Medical Center
Birmingham, Alabama 35294

David M. Hasson
Department of Physiology and Biophysics
University of Kentucky Medical Center
Lexington, Kentucky 40506

L. A. J. Higginson
Department of Medicine
University of Ottawa
Ottawa, Ontario, Canada K1Y 4E9

Brian F. Hoffman
Department of Pharmacology

Columbia University College of Physicians and Surgeons
New York, New York 10032

A. J. Honour
Department of Cardiovascular Medicine
The Radcliffe Infirmary
University of Oxford
Oxford, England

Allan J. Hordof
Departments of Pharmacology and Pediatrics
Columbia University College of Physicians and Surgeons
New York, New York 10032

James H. Isobe
Cardiovascular Research and Training Center
University of Alabama School of Medicine
Birmingham, Alabama 35294

José Jalife
Masonic Medical Research Laboratory
Utica, New York 13503

Thomas N. James
Department of Medicine
University of Alabama Medical Center
Birmingham, Alabama 35294

J. Johnston
Department of Cardiovascular Medicine
Radcliffe Infirmary
University of Oxford
Oxford, England

Scott Kemper
University of California at San Diego
School of Medicine
La Jolla, California 92093

Kenneth M. Kent
Section on Cardiovascular Diagnosis
Cardiology Branch
National Heart, Lung, and Blood Institute
Bethesda, Maryland 20014

Diana L. Kunze
Department of Physiology and Biophysics
University of Texas Medical Branch
Galveston, Texas 77550

David A. Lathrop
Department of Medicine
Division of Cardiology
University of Chicago
Chicago, Illinois 60637

Arthur S. Leon
Department of Medicine
University of Minnesota
Minneapolis, Minnesota 55440

Matthew N. Levy
The Mt. Sinai Hospital of Cleveland
Cleveland, Ohio 44106

Federico Lombardi
Institute of Cardiovascular Research
University of Milan
Milan, Italy

Bernard Lown
Cardiovascular Laboratory
Department of Nutrition
Harvard School of Public Health
Boston, Massachusetts 02115

John Ludbrook
Department of Surgery
School of Medicine
University of Adelaide
Adelaide, South Australia

Alberto Malliani
Institute of Cardiovascular Research
University of Milan
Milan, Italy

Giuseppe Mancia
Institute of Cardiovascular Research
University of Milan
and
Milan, Italy

A. L. Mark
Cardiovascular Division
Department of Medicine

Department of Physiology
Cardiovascular Center
University of Iowa
Iowa City, Iowa 52240

Luc Mary-Rabine
University of Liege
Liege, Belgium

F. Mauri
A. De Gasperis Center
Cardiology Division
Maggiore Hospital
Milan, Italy

Gordon K. Moe
Masonic Medical Research Laboratory
Utica, New York 13503

Dan McKown
University of California at San Diego
School of Medicine
La Jolla, California 92093

E. Neil Moore
Schools of Veterinary Medicine and Medicine
University of Pennsylvania
Philadelphia, Pennsylvania 19104

H. N. Neufeld
The Heart Institute
Chaim Sheba Medical Center
Tel Hashomer, Israel
and
Sackler Medical School
Tel Aviv University
Tel Aviv, Israel

Carl A. Ohata
University of Texas Medical Branch
Department of Physiology and Biophysics
and
Marine Biomedical Institute
Galveston, Texas 77550

Arie Orenstein
Department of Surgery
Chaim Sheba Medical Center
Tel Hashomer, Israel

J. F. Pantridge
Cardiac Department
Royal Victoria Hospital
Belfast, BT12 6BA, Ireland

Rodolfo Perondi
Institute of Cardiovascular Research
University of Milan
Milan, Italy

Thomas G. Pickering
Department of Hypertension and Cardiology
New York Hospital–Cornell Medical Center
New York, New York 10021

Luigi Pozzoni
Institute of Cardiovascular Research
University of Milan
Milan, Italy

Babeth Rabinowitz
The Heart Institute
Chaim Sheba Medical Center
Tel Hashomer, Isreal
and
Sackler Medical School
Tel Aviv University
Tel Aviv, Israel

David Clark Randall
Department of Physiology and Biophysics
College of Medicine
University of Kentucky
Lexington, Kentucky 40506

Walter C. Randall
Department of Physiology
Loyola University
Stritch School of Medicine
Maywood, Illinois 60153

Jane C. Reed
Department of Physiology
Baylor College of Medicine
Houston, Texas 77030

Paolo Rizzon
Department of Cardiology
University of Bari
Medical Clinic I
Polyclinic
70124 Bari, Italy

Michael R. Rosen
Department of Pharmacology
Columbia University College of Physicians and Surgeons
New York, New York 10032

John Ross, Jr.
Cardiovascular Division
University of California, San Diego
School of Medicine
La Jolla, California 92093

George J. Rozanski
Department of Physiology
Loyola University
Stritch School of Medicine
Maywood, Illinois 60153

G. P. Sanna
A. De Gasperis Center
Cardiology Division
Maggiore Hospital
Milan, Italy

Peter J. Schwartz
University of Milan
Institute of Cardiovascular Research
Milan, Italy
and
Department of Physiology and Biophysics
University of Texas Medical Branch
Galveston, Texas 77550

James E. Skinner
Department of Physiology
Baylor College of Medicine
Houston, Texas 77030

Peter Sleight
Cardiac Department
The Radcliffe Infirmary
University of Oxford
Oxford, England

L. A. Sordahl
Division of Biochemistry
University of Texas Medical Branch
Galveston, Texas 77550

Joseph F. Spear
Schools of Veterinary Medicine and Medicine
University of Pennsylvania
Philadelphia, Pennsylvania 19104

H. Lowell Stone
Department of Physiology and Biophysics
and
Cardiovascular Control Section
Marine Biomedical Institute
University of Texas Medical Branch
Galveston, Texas 77550

John X. Thomas
Department of Physiology
Loyola University
Stritch School of Medicine
Maywood, Illinois 60153

Peter Thorén
Department of Physiology
University of Goteborg
Fack, S–400 33 Goteborg 33, Sweden

Hitonobu Tomoike
University of California at San Diego
School of Medicine
La Jolla, California 92093

Ferdinand Urthaler
Cardiovascular Research and Training Center
University of Alabama School of Medicine
Birmingham, Alabama 35294

Stephen F. Vatner
New England Regional Primate Research Center
Southboro, Massachusetts 01772

Richard L. Verrier
Department of Nutrition
Harvard School of Public Health
Boston, Massachusetts 02115

J. L. Walker
Cardiovascular Division
Departments of Medicine and Physiology
Cardiovascular Center
University of Iowa
Iowa City, Iowa 52240

August M. Watanabe
The Krannert Institute of Cardiology
Indiana University School of Medicine
Indianapolis, Indiana 46202

Stewart G. Wolf
Department of Medicine
Temple University
and
St. Luke's Hospital,
Bethlehem, Pennsylvania
and
The Totts Gap Institute
Bangor, Pennsylvania 18013

Alberto Zanchetti
Institute of Cardiovascular Research
University of Milan
Milan, Italy

Z. Zivner
The Heart Institute
Chaim Sheba Medical Center
Tel Hashomer
and
Sackler Medical School
Tel Aviv University
Tel Aviv, Israel

CARDIAC ARRHYTHMIAS: THE CLINICAL PROBLEM

Contents

CARDIAC ARRHYTHMIAS: THE CLINICAL PROBLEM

ELECTROPHYSIOLOGY OF CARDIAC ARRHYTHMIAS: SYMPATHETIC AND VAGAL INFLUENCES

BARORECEPTOR CONTROL OF CARDIAC RHYTHM

CARDIAC AND AUTONOMIC PHARMACOLOGY

Neural Mechanisms in Cardiac Arrhythmias, edited by P. J. Schwartz, A. M. Brown, A. Malliani, and A. Zanchetti. Raven Press, New York © 1978.

Some Aspects of Sudden Cardiac Death

Richard S. Crampton and Peter J. Schwartz

Cardiology Division, University of Virginia, Charlottesville, Virginia 22908 and Institute of Cardiovascular Research, University of Milan, Milan, Italy 20122

Among the many noncoronary conditions precipitating abrupt cardiac death are dysrhythmias or conduction blocks in idiopathic scarring of the conduction system and in sinus node dysfunction, in acquired and congenital valvular lesions and other malformations, in hypertrophic obstructive and other cardiomyopathies, in Wolff-Parkinson-White syndrome, in mitral valve prolapse, in metabolic and electrolyte disturbances, in cardiac sensitivity to drugs such as quinidine, digitalis, phenothiazines, and amitriptyline, and in the long QT syndrome. The last is the most provocative example of neurally mediated, noncoronary sudden cardiac death. Episodes of ventricular fibrillation in individuals with the long QT syndrome often occur with emotional or physical stress. A congenital imbalance in cardiac sympathetic innervation has been postulated as the pathogenetic mechanism (25). The two most successful ways to prevent ventricular fibrillation in this disorder are treatment with β-adrenergic blocking agents and surgical interruption of the left sympathetic pathways to the heart (25,26; Schwartz and Stone, *this volume*).

Coronary disease is the principal cause of death in the Western world, and the majority of afflicted patients die suddenly outside the hospital from cardiac arrest. Two points are paramount in sudden coronary death. First, death is almost always due to ventricular fibrillation. Second, acute or chronic myocardial ischemia seems responsible for initiating the sequence of events that leads to ventricular fibrillation. Myocardial ischemia creates biochemical, metabolic, and hormonal disturbances that result in electrophysiologic and hemodynamic aberrations (5,28). Although many of these pathophysiologic responses to ischemia may be viewed as not neural, the link with deranged autonomic activity is strong. Sympathetic overactivity early in acute myocardial infarction is a well-defined clinical syndrome that may lead directly to ventricular fibrillation as it enlarges the threatened myocardium (21). If vagal overactivity produces bradycardia, the attendant temporal dispersion of the refractory periods of injured and normal ventricular myocardial cells (13) exposes the heart to greater danger from ectopic beats (11), particularly if sympathetic activity increases suddenly (12).