

Bodh I. Jugdutt
Editor

Aging and Heart Failure

Mechanisms and
Management

 Springer

Aging and Heart Failure

Bodh I. Jugdutt
Editor

Aging and Heart Failure

Mechanisms and Management

 Springer

Editor

Bodh I. Jugdutt, MD, MSc, DM, FRCPC, FACC, FACP, FAHA, FESC, FIACS
Division of Cardiology
Department of Medicine
Mazankowski Alberta Heart Institute
University of Alberta and Hospitals
Edmonton, AB, Canada

ISBN 978-1-4939-0267-5 ISBN 978-1-4939-0268-2 (eBook)
DOI 10.1007/978-1-4939-0268-2
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2014931487

© Springer Science+Business Media New York 2014

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed. Exempted from this legal reservation are brief excerpts in connection with reviews or scholarly analysis or material supplied specifically for the purpose of being entered and executed on a computer system, for exclusive use by the purchaser of the work. Duplication of this publication or parts thereof is permitted only under the provisions of the Copyright Law of the Publisher's location, in its current version, and permission for use must always be obtained from Springer. Permissions for use may be obtained through RightsLink at the Copyright Clearance Center. Violations are liable to prosecution under the respective Copyright Law.

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

While the advice and information in this book are believed to be true and accurate at the date of publication, neither the authors nor the editors nor the publisher can accept any legal responsibility for any errors or omissions that may be made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

This book is dedicated to:

Catherine Elizabeth Jugdutt (1947–2012)

who as my friend and wife selflessly supported me, through many trials and tribulations, in a lifelong pursuit of knowledge and hidden truths that may be applied to improve cardiovascular health and benefit mankind

and

Dr. Myron L. Weisfeldt

who, as leader and mentor during my fellowship at the Johns Hopkins Hospital, provided me with the inspiration and stimulation to continue on my search for hidden truths and knowledge and undertake this project on aging and heart failure.

Biosketch



Dr. Myron Weisfeldt graduated from Johns Hopkins Medical School and took postdoctoral training at Columbia Presbyterian, the National Institute on Aging of the NIH, and finally cardiology fellowship at the Massachusetts General Hospital. Soon after assuming a faculty position at Johns Hopkins, he was named an Established Investigator of the American Heart Association.

One of his areas of research interest has been heart function, particularly with aging. He developed with James Weiss the time constant of isovolumic pressure fall as an independent index of left ventricular relaxation. This index Tau is used to this day as the gold standard index for ventricular relaxation. His research interests have also included treatment and management of acute myocardial infarction. He was the senior author of the first paper to establish the clinical value of TPA in acute myocardial infarction and also the senior author of the first paper describing successful implantation of a defibrillator in human beings. He is perhaps best known for his discovery of the mechanism of movement of blood during CPR. The major mechanism is, as a consequence of the rise in general intrathoracic pressure, not direct compression of the heart. He currently heads the Resuscitation Outcomes Consortium, an international network of EMS systems in ten major cities or regions sponsored by NHLBI, the Department of Defense, and Canadian Health Agencies. This is the first major effort to conduct large-scale clinical trials in cardiac arrest victims to improve survival.

From 1975 to 1991 he headed the Division of Cardiology at Johns Hopkins.

From 1991 to 2001 he was chair of medicine at Columbia Presbyterian in New York and was the Samuel Bard professor of medicine. Since 2001 he has served as chair of medicine and William Osler professor at Johns Hopkins.

Dr. Weisfeldt received the AHA Award of Merit in 1992 and the AHA Gold Heart in 1998. He received the Dickinson Richards Award of the Council on Cardiopulmonary and Critical Care Medicine in 2001 and the James B. Herrick Award of the Council on Clinical Cardiology in 2004. He was recognized for “outstanding leadership in resuscitation research” by the American Heart Association in 2003. From 1989 to 1990, he was president of the American Heart Association (AHA). During his presidency with the AHA, a successful program was begun to provide the first nutritional food labels on all packaged food products. Also, an AHA Task Force endorsed the manufacture of automatic external defibrillators for public use. During his tenure as president, there was a continuation of programs focusing on Heart Disease in Women, which was begun by Dr. Bernadine Healy who preceded him.

Dr. Weisfeldt is a member of the Institute of Medicine, the American Society for Clinical Investigation, the Association of American Physicians, and the Association of Professors of Medicine.

He received the Diversity Award from the Association of Professors of Medicine in 2008.

Preface

The concept for this book on aging and heart failure (HF) was born in the 1980s with the publication of the book entitled *The Aging Heart: Its Function and Responses to Stress*, edited by Dr. Myron L. Weisfeldt, MD. It was later fueled along in the early 1990s by the monograph entitled *Inclusion of Elderly Individuals in Clinical Trials: Cardiovascular Disease and Cardiovascular Therapy as a Model* by Dr. Nanette K. Wenger, MD. Concurrently, observations in population studies and large randomized clinical trials (RCTs) suggesting that the elderly patient after myocardial infarction was at higher risk for cardiovascular (CV) complications and adverse left ventricular remodeling leading to HF added fuel to the burning fire.

The concept of cardiac remodeling as a mechanism of heart disease leading to HF has evolved since the mid-1970s following extensive bench-to bedside and bedside-to-bench research studies. Since the mid-1980s, the initial emphasis on HF related to pressure and volume overload led to theories on adaptive and maladaptive structural and functional remodeling after insults such as myocardial infarction (MI) and hypertension (HTN) and later expanded to pure and mixed pressure/volume overload states and a wide range of cardiomyopathies.

The concept of adverse left ventricular remodeling during acute and subacute phases of MI established that adverse cardiac remodeling is a major mechanism for progressive left ventricular enlargement, deterioration of ventricular function, increased suffering, and deaths from chronic HF. Concurrently, over the last four decades, expanding knowledge about the biology of aging and the effects of aging on the response to insults by prevalent CV diseases such as MI and HTN has identified several potential molecular pathways and targets that may lead to drug discovery and development and improved therapies for the ravages of these diseases in the elderly patient. A major payoff of the research studies has been the appreciation that lifelong exposure to CV risk factors and cardiotoxic agents from childhood through adulthood and old age fuels the march to HF. This has clearly opened up a new area of research into the biology of CV aging and its impact on cardiac remodeling throughout life.

Despite the advances, a sobering finding has been that hearts continue to enlarge and the HF burden continues to increase, especially after ST-segment elevation MI (STEMI). Vast knowledge gaps exist. With the expanded spectrum of diseases that result in adverse cardiac remodeling, improved

understanding of the underlying molecular mechanisms through research is crucial. Improvements in medicine, public health, Medicare, and socioeconomic conditions in Western countries have extended life span, but the increased longevity is sadly associated with a parallel increase in morbidity due to HF. During the last 20 years, attention has turned to aging-related physiological as well as cellular, subcellular, molecular, and biochemical remodeling that influence responses to CV diseases and therapy. An explosion in knowledge of molecular and cellular mechanisms, importance of oxidative stress, metabolic pathways, extracellular and intracellular matrix remodeling, and the far-reaching effects of infarct and non-infarct zone fibrosis in the progression to HF has occurred. The profusion of original scientific and review papers dealing with several aspects of molecular mechanisms of adverse cardiac remodeling that impact therapy of HF in the elderly and clinical studies on novel therapies and strategies that may benefit the elderly suggested the need to synthesize the main ideas into one book.

In 2008, two special symposium issues of *Heart Failure Reviews* on aging and HF for which I served as guest editor generated a great deal of interest. The first issue published in 2010 drew attention to the arbitrary nature of the chronological definition of elderly in the context of progressive biological aging and the importance of the changing demographics with respect to the growing population of elderly people with major aging-related CV changes and diseases that lead to HF such as HTN and MI. The second issue published in 2012 focused on important aging-related issues pertinent to HF therapy in the elderly. In September 2010, I had the opportunity to drive those points home in an invited lecture on “The Biology of Aging in the Cardiac Patient” for a symposium on “Biology of Aging and HF Management” during the 14th Annual Scientific Meeting of the Heart Failure Society of America in San Diego.

As the American pop singers Sonny and Cher put it, “*the beat goes on...*” And the beat must go on. In this book, a group of invited clinician-scientists discuss pertinent aspects of aging and HF. The book is organized into two sections. Chapters 1–20 discuss clinical issues, and Chapters 21–32 explore molecular mechanisms. In the chapters in the first section, I deal with the changing demographics in the aging population with HF and the pertinent aspects of the biology of aging in therapy of HF. I address HF prevention strategies in the context of the aging continuum and chronological versus biological aging and discuss promotion of healthy aging through education on CV risk factors and prevention through aggressive CV risk management. There is increasing need for development and discovery of novel targets and therapies pertinent to the growing elderly population in order to ensure that they enjoy the extended life span and continue to contribute meaningfully to society if they so choose. Since the changes with aging are progressive and a host of risk factors damage the CV system during aging, improving the lot of the older, elderly, and oldest elderly segments depends to some extent on the success of preventative measures in the young, beginning in early childhood.

Chapter 3 presents a masterful discussion of HTN and prevention of diastolic HF in the aging population. Chapter 4 discusses therapy of systolic HF. Atrial fibrillation in the aging population is explored in Chapter 5. Chapter 6 discusses optimizing therapy with monitoring in HF clinics. Chapter 7

addresses cardiac remodeling in aging, HTN, and diastolic HF. Polypharmacy and adverse drug reactions with HF pharmacotherapy in the elderly are highlighted in Chapter 8. Chapter 9 presents vascular remodeling with aging and HF. Chapter 10 discusses biomarkers in optimal management of HF in the aging population. Benefits of exercise in the elderly and a review of the RAAS in HF are described in Chapters 11 and 12. Chapter 13 addresses aging and diastolic dysfunction and the interplay with inflammation and extracellular matrix regulation. We address improving outcome with reperfusion and vasodilator therapy in elderly patients with STEMI and HF in Chapter 14. Erythropoietin therapy and the role of resistin in HF are reviewed in Chapters 15 and 16. Chapter 17 discusses the role of coronary artery calcium in CV risk stratification. We address the remodeling of the RAS, RAAS, and related pathways with aging and implications for therapy in Chapter 18. The utility of mineralocorticoid receptor antagonists (MRAs) in the very old patient, in whom the age-related decrease in aldosterone levels is balanced by a novel pathway involving decreased 11β HSD-2 levels and cortisol-induced stimulation of the mineralocorticoid receptor, is discussed in Chapter 18. Chapter 19 aging and right ventricular remodeling and failure secondary to pulmonary artery remodeling and pulmonary hypertension. Biomarkers of CV aging are discussed in Chapter 20.

In the section on molecular mechanisms, the chapters focus on important translational research areas. Chapter 21 discusses the changes in the heart that accompany aging, from humans to molecules. Cell death and cell survival pathways are explored in Chapter 22, and Chapter 23 addresses telomeres and telomerases. Chapter 24 discusses changes in inflammation and fibrosis with aging. Alterations in extracellular matrix and ventricular remodeling after MI and calcium signaling and cardiac function in the aging heart are explored in Chapters 25 and 26, respectively. Chapter 27 examines integrins and HF failure therapy with aging, and Chapter 28 discusses adipokines as novel biomarkers in aging and HF. Aging-related changes in cellular and molecular mechanisms of post-MI remodeling is addressed in Chapter 29. Chapter 30 presents aging-related changes in mitochondrial function and implications for HF therapy. Finally, Chapters 31 and 32, respectively, discuss regulation of SERCA and implications in diastolic dysfunction in the aging heart and SMP-30 and aging-related cardiac remodeling and HF.

These chapters should give the readers an appreciation of the need for more research on the biology of CV aging, more evidence-based clinical trial data on the “older-elderly” HF patients, and new therapies for HF with preserved ejection fraction (HF-PEF) as well as for HF with low ejection fraction (HF-low EF). Together, they point out that while longer life comes at a price, there is still hope and potential for novel targets and therapies in the near future.

In summary, this book provides a high profile and valuable resource on the major clinical issues facing HF therapy in the elderly and molecular mechanisms of the changes with CV aging for both the present and future generations of healthcare professionals including physicians, clinician-scientists, researchers, teachers, fellows, trainees, and students. It also provides a valuable resource on pertinent aspects of age-related changes in physiology, biochemistry, and pathophysiology that impact HF management in the elderly and important

clinical issues in the care of the elderly HF patient. It is hoped that the book will stimulate future translational research targeted towards discovery and development for preventing, limiting, and reversing changes in pathways leading to the growing HF burden with aging and in the elderly. The invited leaders and established investigators in the field have generously contributed 32 chapters on key topics. The reference lists are comprehensive and include key papers that are currently not easily accessed from PubMed or other search engines. The chapters suggest potential novel strategies that should receive attention in terms of translating basic research knowledge to application in patients at the bedside. I hope that the book will also prove useful for scientists and clinicians, students and teachers, and the industries interested in drug discovery research. While the list of topics is by no means comprehensive, the chapters address some major areas needing attention. To our knowledge, there is no other book on this topic to date.

Edmonton, AB, Canada

Bodh I. Jugdutt, MD, MSc, DM,
FRCPC, FACC, FACP, FAHA, FESC, FIACS

Acknowledgments

We would like to thank all the contributors for their excellent chapters. We would also like to express our deepest appreciation for the preparation and editorial help provided by Catherine E. Jugdutt and especially Michael D. Sova at Springer.

