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Editor

Aging and Heart Failure

Mechanisms and Management

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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

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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 11βHSD-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

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Contents

Contributors

Seraj Abualnaja, MDDS, FRCPC Division of Cardiology, Department of Medicine, University of Alberta, Edmonton, AB, Canada

Adriana Adameova, PharmD, PhD Department of Pharmacology and Toxicology, Comenius University, Bratislava, Slovak Republic

Ali Ahmed, MD, MPH Department of Medicine, University of Alabama School of Medicine at Birmingham, Birmingham, AL, USA

Department of Medicine, Veterans Affairs Medical Center, Birmingham, AL, USA

Ezra A. Amsterdam, MD Department of Internal Medicine, University of California, Davis, Sacramento, CA, USA

Wilbert S. Aronow, MD Department of Medicine, Westchester Medical Center/New York Medical College, Valhalla, NY, USA

Cardiology Division, New York Medical College, Macy Pavilion, Valhalla, NY, USA

Maciej Banach, MD, FAHA, FESC Department of Hypertension, Medical University of Lodz, Lodz, Poland

Peter Moritz Becher, MD Department of General and Interventional Cardiology, University Heart Center Hamburg Eppendorf, Hamburg, Germany

Margarita Borovka, BA University at Buffalo School of Medicine, Staten Island, NY, USA

Andrew J. Boyle, MBBS, PhD Department of Cardiology, University of Newcastle, John Hunter Hospital, Newcastle, NSW, Australia

Craig R. Butler, MSc, MD Division of Cardiology, Mazankowski Alberta Heart Institute, Edmonton, AB, Canada

Richard A. Cohen, MD Department of Medicine, Boston University School of Medicine, Boston, MA, USA

Wilson S. Colucci, MD Boston University Medical Center, Boston, MA, USA

Laura L. Daniel, BS Department of Biomedical Sciences, East Tennessee State University, Johnson City, TN, USA

Lisandra E. de Castro Brás, PhD San Antonio Cardiovascular Proteomics Center and Mississippi Center for Heart Research, Department of Physiology and Biophysics, University of Mississippi, Jackson, MS, USA

Guido R.Y. De Meyer, PharmD, PhD Department of Physiopharmacology, University of Antwerp, Antwerp, Belgium

Naranjan S. Dhalla, PhD, MD (Hon), DSc (Hon) Department of Physiology, Faculty of Medicine, Institute of Cardiovascular Sciences, University of Manitoba, Winnipeg, MB, Canada

John R. Dimitry, MD, MPH, FRCPC Division of Cardiology, Department of Medicine, University of Alberta and Mazankowski Alberta Heart Institute, Edmonton, AB, Canada

Justin A. Ezekowitz, MBBCh, MSc Division of Cardiology, Department of Medicine, University of Alberta, Edmonton, AB, Canada

Nikolaos G. Frangogiannis, MD Department of Medicine (Cardiology), Albert Einstein College of Medicine, Bronx, NY, USA

Hanna K. Gaggin, MD, MPH Department of Medicine, Cardiology Division, Massachusetts General Hospital, Boston, MA, USA

Atsushi Hoshino, MD Department of Cardiovascular Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Andrzej M. Janczewski, MD, PhD Department of Internal Medicine, PCK Marine Hospital, Gdynia, Poland

James L. Januzzi Jr., MD Cardiology Division, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA

Anwar Jelani, MBBS, SBIM, FACC Department of Medicine, Section of Cardiology, King Abdulaziz Hospital, Al-Hasa, Saudi Arabia

Yu-Fang Jin, PhD San Antonio Cardiovascular Proteomics Center, Department of Electrical and Computer Engineering, University of Texas at San Antonio, San Antonio, TX, USA

William L. Joyner, PhD Department of Biomedical Sciences, East Tennessee State University, Johnson City, TN, USA

Bodh I. Jugdutt, MD, MSc, DM, FRCPC 2C2 W.C. Mackenzie Health Sciences Centre, Division of Cardiology, Department of Medicine, Mazankowski Alberta Heart Institute, University of Alberta and Hospitals, Edmonton, AB, Canada

C. Tissa Kappagoda, MBBS, PhD Department of Internal Medicine, University of California, Davis, Sacramento, CA, USA

Pedram Kazemian, MD, MSc Department of Cardiac Electrophysiology, Brigham and Women's Hospital/Harvard, Newton, MA, USA

Edward G. Lakatta, MD National Institute on Aging/NIH, Baltimore, MD, USA

Merry L. Lindsey, PhD San Antonio Cardiovascular Proteomics Center and Mississippi Center for Heart Research, Department of Physiology and Biophysics, University of Mississippi, Jackson, MS, USA

Department of Physiology and Biophysics, University of Mississippi Medical Center, MS, USA

Wim Martinet, PhD Department of Physiopharmacology, University of Antwerp, Antwerp, Belgium

Satoaki Matoba, MD, PhD Department of Cardiovascular Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Hiroaki Matsubara, MD, PhD Department of Cardiovascular Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Mathew S. Maurer, MD Department of Medicine, Columbia University Medical Center, New York, NY, USA

Michael Sean McMurtry, MD, PhD Division of Cardiology, Department of Medicine, University of Alberta, Edmonton, AB, Canada

Nirankar S. Neki, MD, FRCP, FACP (USA), FAMS Department of Internal Medicine, Government Medical College and Guru Nanak Dev. Hospital, Amritsar, Punjab, India

Nguyen T. Nguyen, MS San Antonio Cardiovascular Proteomics Center, Department of Electrical and Computer Engineering, University of Texas at San Antonio, San Antonio, TX, USA

William J. Nienaber, MD Cheyenne Cardiology Associates, Cheyenne, WY, USA

D. Ian Paterson, MD, FRCPC Department of Cardiology/Medicine, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, AB, Canada

Edith Pituskin, PhD(c) Department of Oncology, University of Alberta, Cross Cancer Institute, Edmonton, AB, Canada

Fuzhong Qin, MD, PhD Cardiovascular Medicine Section, Boston University Medical Center, Boston, MA, USA

Paolo Raggi, MD Division of Cardiology, Mazankowski Alberta Heart Institute, Edmonton, AB, Canada

Michael W. Rich, MD Washington University School of Medicine, St. Louis, MO, USA

Dorien M. Schrijvers, PhD Department of Physiopharmacology, University of Antwerp, Antwerp, Belgium

Nakul Chander Sharma, MD, FRCP Division of Cardiology, Department of Medicine, Mazankowski Heart Institute, Edmonton, AB, Canada

Henry Han-Jen Shih, MD School of Medicine, Tufts University, Boston, MA, USA

Arti V. Shinde, PhD Department of Medicine (Cardiology), Albert Einstein College of Medicine, Bronx, NY, USA

Ken Shinmura, MD, PhD, FAHA Division of Geriatric Medicine, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Mahipal Singh, PhD Department of Biomedical Sciences, East Tennessee State University, Johnson City, TN, USA

Krishna Singh, PhD Department of Biomedical Sciences, East Tennessee State University, Johnson City, TN, USA

Harold A. Spurgeon, PhD Laboratory of Cardiovascular Science, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA

Satoshi Suzuki, MD, PhD Department of Advanced Cardiac Therapeutics, Fukushima Medical University, Fukushima, Japan

Yasuchika Takeishi, MD, PhD Department of Cardiology and Hematology, Fukushima Medical University, Fukushima, Japan

Paramjit S. Tappia, PhD Office of Clinical Research, Asper Clinical Research Institute, St. Boniface Hospital Research, Winnipeg, MB, Canada

Carsten Tschöpe, MD Department of Cardiology and Angiology, Charité - Universitätsmedizin Berlin, Berlin, Germany

Pim van der Harst, MD, PhD Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

Dirk J. van Veldhuisen, MD, PhD Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

Dirk Westermann, MD Department of General and Interventional Cardiology, University Heart Center Hamburg Eppendorf, Hamburg, Germany

Joseph Szeman Wong, MBBS, MRCP, FHKCP, FRCPC Division of Cardiology, Department of Medicine, University of Alberta Hospital, Edmonton, AB, Canada

Andriy Yabluchanskiy, MD, PhD San Antonio Cardiovascular Proteomics Center and Mississippi Center for Heart Research, Department of Physiology and Biophysics, University of Mississippi, Jackson, MS, USA

1 Changing Demographics of the Aging Population with Heart Failure and Implications for Therapy

Bodh I. Jugdutt

Introduction

Cardiovascular (CV) aging is an intrinsic part of the natural biological aging process and is inevitable with the passage of time. Heart failure (HF) is prevalent in the aging population worldwide and its prevalence increases with age [1]. It has become a significant healthcare burden in developed countries and is becoming one in developing countries, especially in elderly people (age ≥65 years) [2–5]. Importantly, HF is a progressive disorder [6–9]. Its prevalence increases steeply with age, from <1 % in the 20- to 39-year age group to >20 % in individuals aged ≥80 years [4, 5]. It is commonly the end stage in the CV disease (CVD) continuum and the final common pathway of several CV diseases, particularly coronary heart disease (CHD) and hypertension (Fig. 1.1).

With regard to pathophysiology and therapeutics, it is useful to view HF as a progressive chronic disorder that is superimposed on an ongoing biological aging process in an aging-HF continuum leading to ultimate disability and death (Fig. 1.1). The aging process results in a host of physiological and biological changes in the CV system and other systems (Table 1.1) [10], and several of these age-related changes contribute to progression of the HF syndrome. In that construct, CVD risk factors and comorbidities such as type 2 diabetes, obesity, hyperlipidemia, and oxidative stress (Table 1.2) contribute to the march towards HF, end-stage heart disease, and death (Fig. 1.1). With regard to prevention, time, and timing, therefore, matter and preventive measures should ideally begin early in the aging-HF continuum [11].

Towards a Modern Definition of the Elderly Population

The current chronological definition of elderly is arbitrary and there is no accurate biomarker of biological aging. In most developed countries, the chronological age of 65 years that coincides with the retirement age has become the accepted cutoff for defining the elderly, and it is also regarded as the onset of old age [12]. This definition originated in the postindustrial revolution England of the nineteenth century. The British Friendly Societies Act of 1875 defined old age as any age after 50 years, and the age of 60 or 65 years was used for eligibility in pension plans [13]. Subsequently in 1889, Otto von Bismarck introduced the old age and disability insurance bill in Germany to provide pension annuity for workers who reached the age of 65 years at a time when life expectancy of the average Prussian was 45 years [14]. In the absence of a better definition, the age of eligibility

B.I. Jugdutt, MD, MSc, DM, FRCPC (✉)
2C2 W.C. Mackenzie Health Sciences Centre, Division of Cardiology, Department of Medicine, Mazankowski Alberta Heart Institute, University of Alberta and Hospitals, 727, Todd Landing NW, Edmonton, AB, Canada T6G 2B7
e-mail: bjugdutt@ualberta.ca

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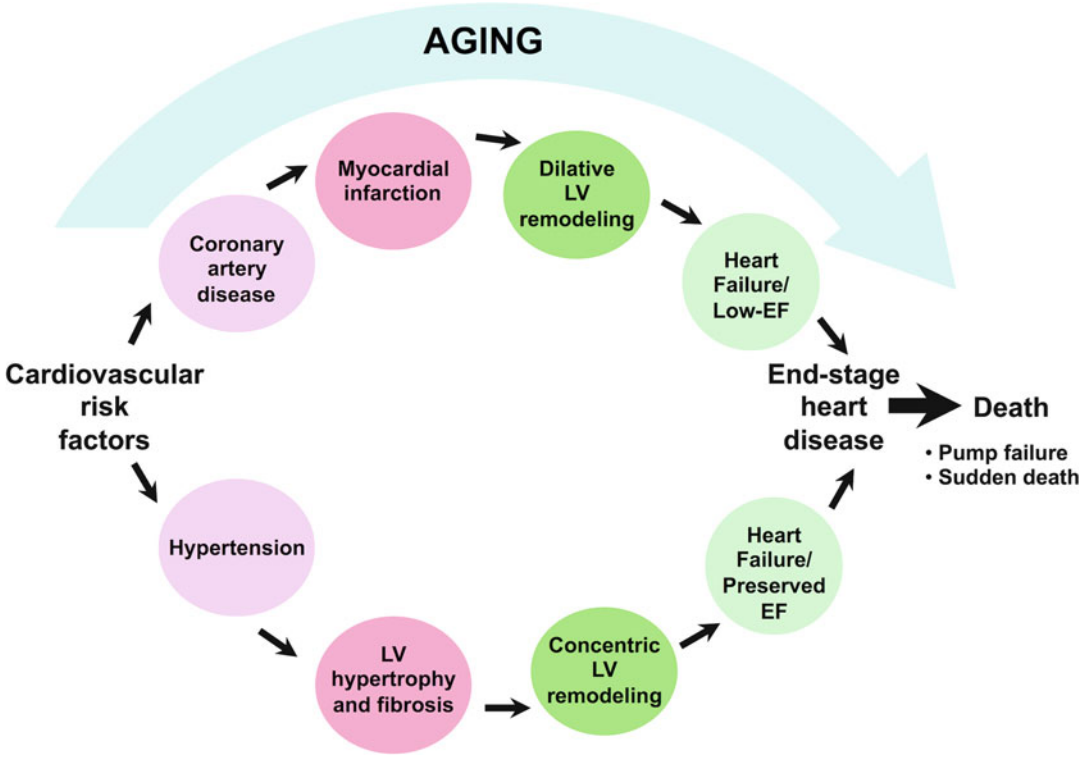

Fig. 1.1 The heart failure, aging, and cardiovascular disease continuums. Heart failure can be viewed as a progressive disorder in a disease continuum superimposed on the aging process and leading to disability and ultimate death. Progressive changes during aging and the cardiovascular disease continuum contribute to augment the heart failure burden in the elderly. *EF* ejection fraction; *LV* left ventricular (reprinted from Jugdutt BI. Aging and Heart Failure: changing demographics and implications for therapy in the elderly. Heart Failure Rev 2010; 15:401–405. With permission from Springer Science + Business Media)

for retirement pensions became the accepted definition simply by default [12].

Clearly, this arbitrary definition of elderly as age ≥65 years was based on purely socioeconomic and political considerations. Recognizing that aging is a progressive biological process, old age was subsequently considered to begin when active contribution to society is no longer possible [15]. In developing countries, social role has been the predominant means of defining old age [16]. Recent socioeconomic studies have suggested that a multidimensional definition that combines chronological, functional, and social factors might be preferable [12]. However, such a definition does not take into account the changes in population health and healthcare delivery, CV health in particular, which have a major impact on function and quality of life in the aging population.

In developed and industrialized countries, the advances in therapy for CVD—including CHD, acute coronary syndromes (ACS), myocardial infarction (MI), hypertension, and HF—are expected to expand the future elderly population, and a significant proportion can be expected to contribute more and more meaningfully to society beyond the arbitrary cutoff age of 65 years. Given the trend towards prolonged longevity and inevitable growth of the elderly population, efforts should be directed towards promoting a healthy elderly population in developed and industrialized countries. The time has come for the more than a century-old arbitrary socioeconomic cutoff age of 65 years used for defining the elderly to be revised upwards to ≥85 years so as to match the modern trends, progress in therapy, longer survival with improved quality of life, and social expectations [1].

Table 1.1 Cardiovascular risk factors, aging, and heart failure

Risk factors
Age[a]
Genetic factors
Diet
Smoking
Sedentary lifestyle
Stress[a]
Dyslipidemia
Diabetes type 2[a]
Obesity[a]
Metabolic syndrome
Hypertension[a]
Exposure to toxins

Modified from Jugdutt BI. Aging and Heart Failure: changing demographics and implications for therapy in the elderly. Heart Failure Rev 2010; 15:401–405. With permission from Springer Science + Business Media
[a]Especially important in heart failure progression during aging

Table 1.2 Aging-related physiological and biological changes pertinent for heart failure

Processes
Cardiovascular aging
• ↑ Fibrosis, extracellular matrix, and fibrillar collagen
• ↑ Advanced glycation end-products (AGEs)
• ↑ Oxidative stress, ↑ oxygen free radicals, ↑ oxidative damage
• ↑ Levels of angiotensins and endothelins
• ↓ Myocyte number, ↑ myocyte size
• Altered vascular matrix, ↑ elastin fragmentation, calcification, collagen
Physiological changes
• Ventricular/arterial stiffening, LV diastolic dysfunction
• ↑ LV concentric remodeling, ↑ LV mass/volume ratio
Biological changes
• ↓ Leukocyte and tissue telomere lengths
• Altered cellular and subcellular functions
• Dysregulation of repair mechanisms, altered response to injury
• Mitochondrial dysfunction, altered mitochondrial population
• Altered contractile pathways, cardiac/arterial responses to stress
• Altered neurohumoral, immune, stress response pathways
• Altered metabolism and metabolic reserve

↑, increased; ↓, decreased; *LV* left ventricular

Categories of Heart Failure

The currently available HF management guidelines consider HF to be the result of structural and functional cardiac disorders that impair ventricular filling and ejection [6–9] and classify it into two broad categories to guide management: (1) diastolic heart failure (DHF), HF with preserved ejection fraction (HF/PEF), HF with preserved systolic function (HF/PSF), or HF with normal EF (HF/NEF) and (2) systolic heart failure (SHF) or HF with low EF (HF/low EF).

It is important to remember that these guidelines were based on data from randomized clinical trials (RCTs) of CV drug therapies in mostly non-elderly people, and mostly men. While the data from RCTs have obvious limitations with respect to the elderly, the consensus from the panel of experts took a pragmatic rather than nihilistic approach because both older adults (non-elderly) and the albeit fewer elderly HF patients who were included in the trials showed benefit.

Changing Demographics and Epidemiology

The elderly population (i.e., age ≥65 years) has been increasing steadily over the last 30 years [4, 10, 17]. In the USA the statistical updates of the American Heart Association (AHA) and American College of Cardiology (ACC) task force on heart disease and stroke, longitudinal population data from the Framingham Heart Study (FHS), data from the National Health and Nutrition Examination Survey (NHANES), and the National Heart, Lung, and Blood Institute (NHLBI) have provided a rich resource on demographic and epidemiological trends in a major developed and industrialized country. The European Society of Cardiology (ESC) has provided resourceful data for developed and developing countries in Europe.

In the USA, it was estimated that there will be 72.1 million elderly people by the year 2030, nearly double the 40.4 million in 2010 [4]. A 1996 projection was for nearly 20 % aged ≥65 years

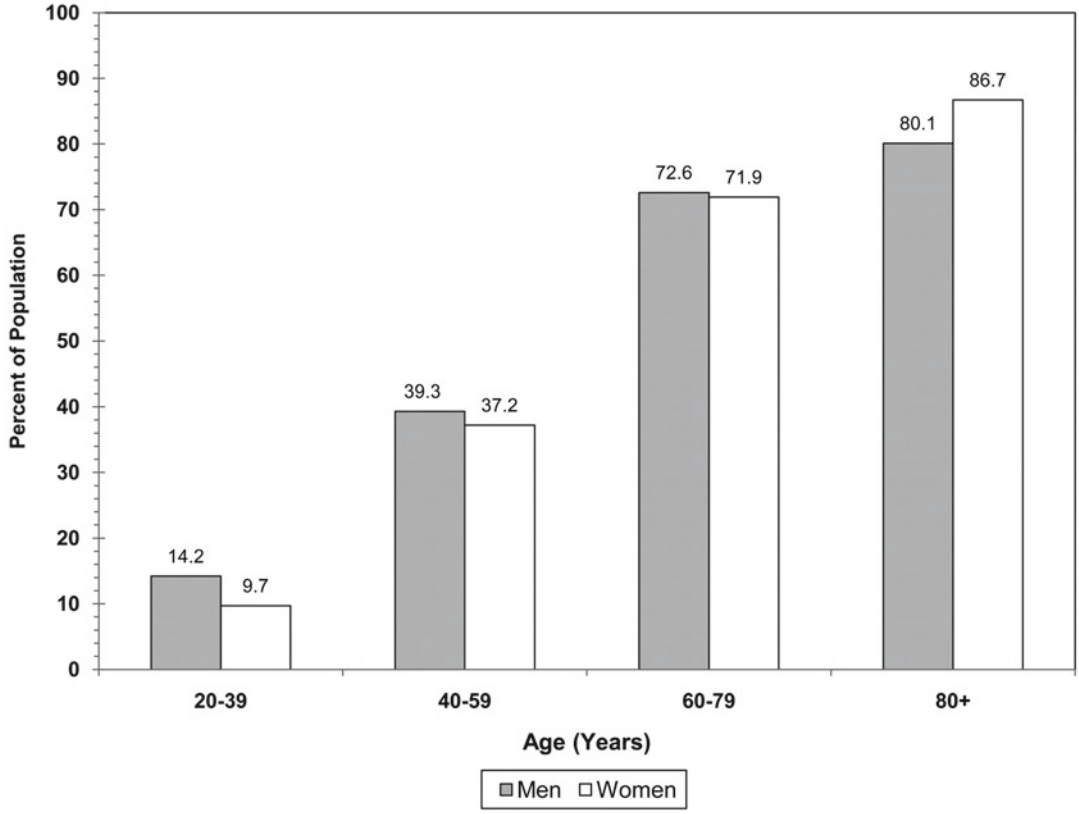

Fig. 1.2 Chart 3-1. Prevalence of cardiovascular disease in adults ≥20 years of age by age and sex (National Health and Nutrition Examination Survey: 2005–2008). *Source*: National Center for Health Statistics and National Heart, Lung and Blood Institute. These data include coronary heart disease, heart failure, stroke, and hypertension (reprinted from Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB et al. Heart disease and stroke statistics-2012 update: a report from the American Heart Association. Circulation 2012; 125:e2–e220. With permission from Wolter Kluwers Health)

by 2030 and nearly 18 % aged ≥85 years by 2040 [18]. Interestingly, a 2008 World Health Organization (WHO) figures on life expectancy were 78 years for the USA, 80 years for the UK, 81 years for Canada, and 83 years for Japan.

In the USA, it was forecast in 2011 that 40.5 % of the population will have some form of CVD, including CHD, hypertension, and HF [17]. In chart 3-1 of the 2012 heart disease and stroke statistics update [5], the prevalence of CVD increases steadily in men and women subsets aged 20–39, 40–59, 60–79, and 80+ years (Fig. 1.2). In chart 3-2 of the same update [5], the incidence of CVD increases steeply in men and women subsets aged 45–54, 55–64, 65–74, 75–84, and 85–94 years (Fig. 1.3). In chart 3-6 of the same update [5], deaths from CVD rise exponentially from age <45 years to age ≥85 years (Fig. 1.4). Over 80 % of all the CVD-related deaths are found in the elderly [4, 18]. Importantly, the CVD deaths exceed those from cancer in the >75–84 year range and more so in the ≥85 year range [5]. From the FHS data between 1980 and 2003, the average annual rates for a first CV event rose from 3/1,000 men at age 35–44 years to 74/1,000 men at age 85–94 years [5, 19]. Comparable CVD death rates occur 10 years later in women and the gap narrows as age advances [5, 19].

Concurrently with the increase in the elderly population, the prevalence of HF in the elderly has increased and with it, the associated high mortality,

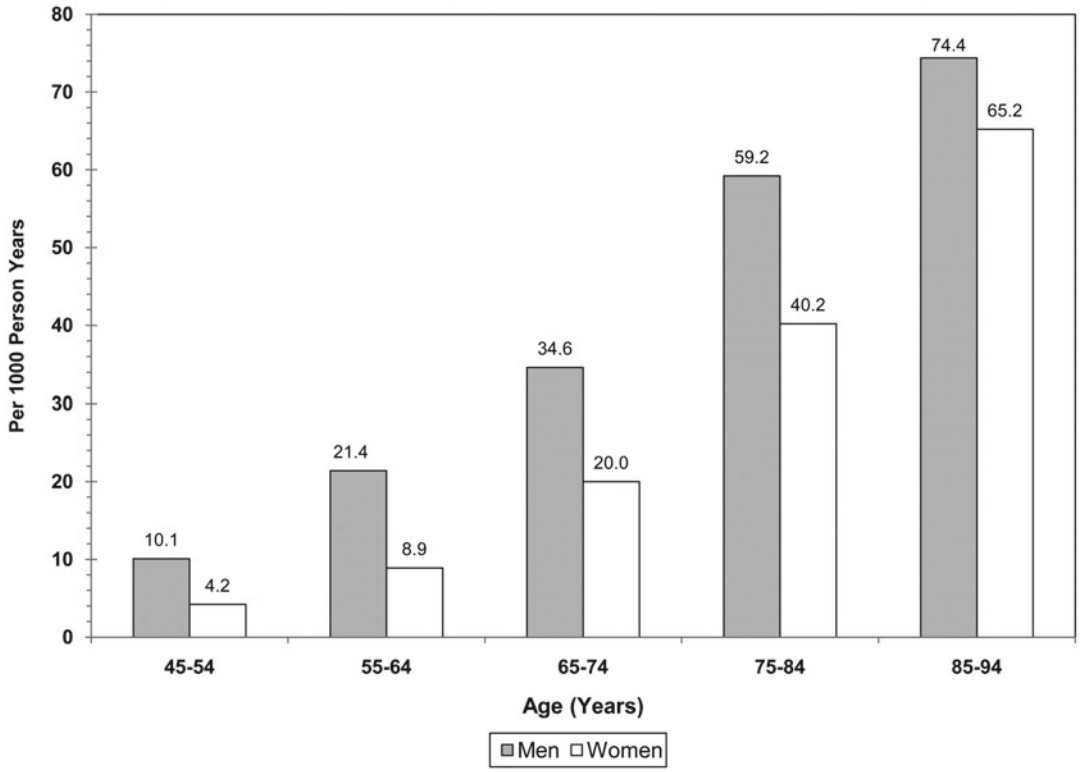

Fig. 1.3 Chart 3-2. Incidence of cardiovascular disease (Coronary heart disease, heart failure, stroke, or intermittent claudication. Does not include hypertension alone) by age and sex (Framingham Heart Study, 1980–2003). *Source*: National Heart, Lung and Blood Institute (reprinted from Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB et al. Heart disease and stroke statistics-2012 update: a report from the American Heart Association. Circulation 2012; 125:e2–e220. With permission from Wolter Kluwers Health)

prolonged morbidity, frequent hospitalizations, and utilization of costly resources [4–8, 17]. In fact, HF is the commonest reason for hospitalization [20]. Despite advances in HF therapy, outcome in elderly patients remains poor. An early US community study published in 1991 showed that the mean age for HF was 76 years, and the 5-year mortality was 67 % [21]. In an early Scottish study between 1986 and 1996, the 1-year fatality rates among patients hospitalized with HF rose from 14 % in those aged <55 years to 58 % in those aged >84 years [22]. The estimated cost associated with HF in the USA was ~39.2 billion dollars for 2010 [4].

In summary, the demographic and epidemiological data on CVD since the 1980s in the USA provide evidence for the HF epidemic in the growing elderly population extending to beyond the age of 95 years. Importantly, the data provide a valuable reference base for future research efforts to improve and optimize the therapy of HF in the aging population.

Why the Heart Failure Epidemic in the Elderly?

Three main factors may explain the alarming statistics and high prevalence of HF in the elderly in developed countries: (1) aging-related biological factors, (2) prolonged exposure to cardiovascular risk factors during aging, and (3) comorbid conditions associated with aging [10, 23]. Several studies showed that HF begins to increase after the age of 45 years [24]. The two most common causes of HF—MI and hypertension—are also

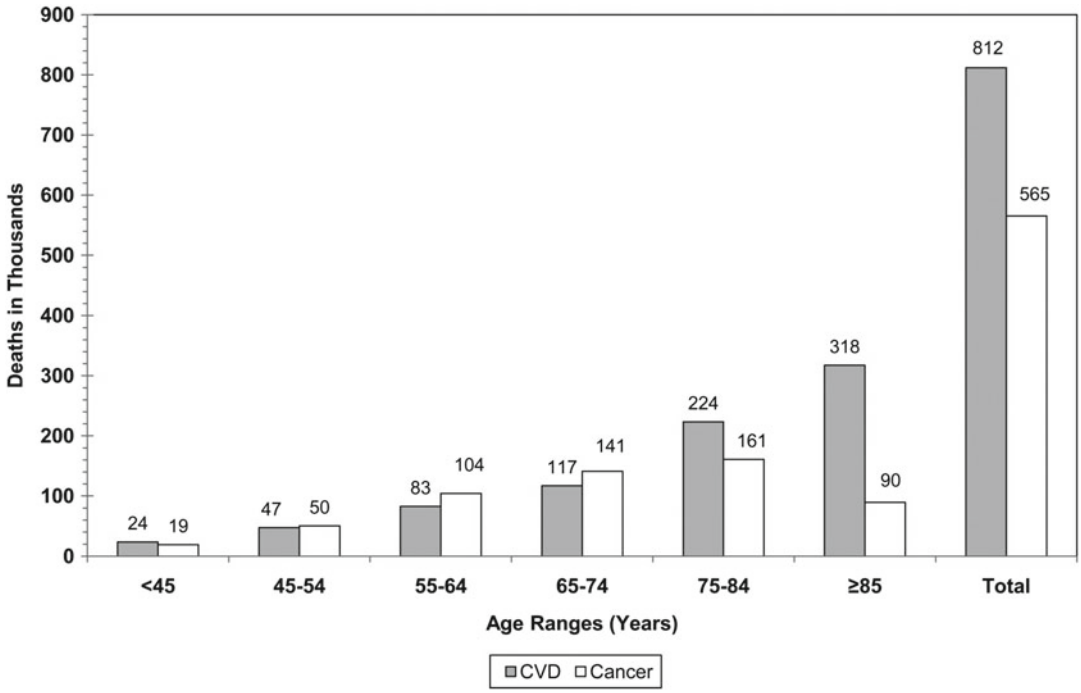

Fig. 1.4 Chart 3-6. Cardiovascular disease (CVD) deaths versus cancer deaths by age (United States: 2008). *Source*: National Center for Health Statistics. CVD includes International Classification of Diseases, 10th Revision codes 100–199, Q20–Q28: and cancer, C00–C97 (reprinted from Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB et al. Heart disease and stroke statistics-2012 update: a report from the American Heart Association. Circulation 2012; 125:e2–e220. With permission from Wolter Kluwers Health)

more common in the elderly and the risk of HF increases with antecedent MI and hypertension [4]. The average age for a first MI is 64.5 years in men and 70.3 years in women [5] and post-MI HF increases with age. Several studies have shown that HF is predominant in older adults (non-elderly) and elderly patients, with higher prevalence among the elderly. In the USA, the reported incidence of HF is 20 % at age 80 years and increases with the severity of hypertension [4]. Among elderly HF patients, 80 % men and 70 % women are estimated to die within 8 years [4].

HF/Low EF Versus HF/PEF

Patients with MI, especially ST-segment elevation MI (STEMI), usually develop dilative left ventricular (LV) remodeling leading to HF/low EF [10] (Fig. 1.1). Several clinical trials have shown that both LV remodeling and dysfunction post-STEMI are more severe in the elderly than non-elderly (i.e., age <65 years) patients [10, 23]. In contrast, patients with hypertension usually develop concentric LV remodeling and fibrosis [4, 8–10] leading to HF with preserved LV ejection fraction (HF/PEF) (Fig. 1.1).

In population studies of HF/low-EF patients between 1980 and 2000, most were elderly, with many aged >80 years [24, 25]. Readmission rates ranged between 27 and 47 % within 3–6 months after discharge [26] and have not improved [27]. Importantly, HF/PEF accounts for ~50 % of all HF patients and its prevalence is higher in the elderly [28–30]. In an early study, nearly 53 % elderly patients had HF/PEF [31]. Other studies suggested HF/PEF is more prevalent in the elderly [18], with figures between 50 and 70 %. Based on 2006 FactBook from the NHLBI, approximately 74.5 million Americans have hypertension, 17.6 million have CHD, and 5.8 million have chronic HF, and the large majority

are elderly. Since most elderly patients have hypertension [32], it is not surprising that HF/PEF is more common in the elderly. In a study of HF/PEF patients reported in 2009, all were aged >80 years, with a mean age of 87 years [33].

In recent studies of HF/PEF, the LV ejection fraction (LVEF) cutoff for HF/PEF has been revised upwards from 45 % to 50 % [9]. Most early studies of HF/low EF used an LVEF cutoff of ≤35 %. An LVEF between 35 and 50 % therefore represents a grey zone for RCTs.

Recent studies suggest that the mode of death may also differ between the two categories of HF. Data from clinical trials suggest that ~90 % of HF patients die from CV causes, with 50 % from progressive HF and pump failure (non-sudden death) and the rest from sudden death related to arrhythmia and ischemic events [34]. The Seattle Heart Failure Model (SHFM) score was shown to predict relative risk of sudden death (low score) versus pump-failure death (high score) in ambulatory NYHA class II to IV HF patients [35]. Interactions among the major underlying mechanisms of death in HF patients—including adverse LV remodeling, ischemia, pump failure, and arrhythmia—may occur [34]. Autopsy data suggest that ischemia is the single most important cause of death in HF patients [34].

STEMI is not only more prevalent in the elderly but survivors develop HF/low EF [4]. Clinical studies show that elderly STEMI patients represent a high-risk group with higher morbidity and mortality [4–12, 23]. Despite improved post-STEMI therapies with coronary reperfusion by percutaneous coronary intervention (PCI) and pharmacological drugs such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor blockers (ARBs), beta-blockers, and statins, an excess of CV deaths still occur in the elderly [10, 23]. Survival has not improved significantly in elderly compared to non-elderly STEMI patients [4, 23]. Elderly survivors continue to do poorly, with more adverse LV remodeling and HF compared to non-elderly survivors [10, 23]. While improved post-STEMI therapy may produce an early mortality gain, this may be at the cost of prolonged morbidity.

The management of elderly patients with ACS and STEMI as recommended in the ACC/AHA guidelines [23, 36] may reduce mortality, but survivors may remain at risk and contribute further to the already increasing HF burden [10]. This suggests that current therapy for ACS and STEMI for the elderly may not be optimal.

A major factor may be aging-related changes in biochemical, cellular, and subcellular levels and defective healing of the wound after STEMI [10]. If this is confirmed by ongoing translational research studies, it will provide an excellent opportunity for improving HF therapy through novel pathways, therapeutic targets, and strategies.

In order to realize this goal, more funding for HF research in CV aging both at the basic level using aging experimental animal models and at the clinical level with enrolment of subsets of elderly patients will be needed from granting bodies and the pharmaceutical industry.

Heart Failure Therapies and Implications for the Elderly

The current ACC/AHA [6, 7] and ESC [8, 9] guidelines for HF management recommend a comprehensive therapeutic approach that addresses the four stages in the progression of structural and functional changes associated with HF in non-elderly as well as elderly patients: (1) stage A with risk of HF but no structural changes or symptoms, (2) stage B with structural changes but no signs or symptoms, (3) stage C with structural changes and prior or current symptoms, and (4) stage D with severe refractory HF requiring specialized interventions.

Despite the aforementioned preponderance of CVD in older people, data on therapy exclusively for elderly patients with HF/low EF or HF/PEF from RCTs is lacking. The elderly were undeniably underrepresented in RCTs of HF/low-EF therapies. Some recent studies included subsets of elderly people but they were mostly men. There is a paucity of RCTs in older adult (non-elderly) and elderly women.

The main reasons for exclusion of elderly patients include concern over aging-related issues

Table 1.3 Aging-related issues with pharmacological therapies in heart failure patients

Defect	Effect
CV aging-related changes	
• ↓ Baroreceptor sensitivity	↑ Orthostatic hypotension with vasodilators (nitrates, α-adrenergic blockers)
• ↑ LV stiffness, ↓ CV compliance, ↑ peripheral vascular resistance	↓ Cardiac output with β-blockers
• ↓ CV responsiveness to β-agonists and β-blockers	↓ Sensitivity to β-agonists and β-blockers
• ↓ Cardiac reserve	Exacerbation of heart failure with CCBs
• Sinus and AV node dysfunction	↑ Risk of heart block with β-blockers and CCBs
Other aging-related changes	
• ↓ Body mass and water, ↑ body fat, ↓ albumin/ glycoproteins, perfusion	Altered pharmacokinetics/dynamics (β-blockers, α-agonists, ACE inhibitors, digoxin, disopyramide, lidocaine, warfarin, propranolol)
• ↓ Hepatic mass, blood flow, metabolic reserve	↑ Drug metabolites (propranolol, labetalol, nitrates, lidocaine, diltiazem, warfarin)
	↑ Sensitivity to anticoagulants, ↑ bleeding risk
• ↓ Renal function (glomerular, tubular), ↓ blood flow	↓ Renal clearance (ACE inhibitors; digoxin; β-blockers atenolol, sotalol, nadolol; other antiarrhythmic drugs)
• ↓ GI function, motility, absorption, ↓ blood flow	↓ Drug absorption
• ↓ Cognition	Poor compliance and adherence to therapy
• ↓ Thirst mechanism	Prone to dehydration
Comorbidities and polypharmacy	
• Hypertension, diabetes mellitus, arthritis, chronic pulmonary disease, neurological disease, renal disease, osteoporosis, atrial fibrillation	↑ Drug–drug interactions
	↑ Drug–disease interactions
	Bradycardia and hypotension (CCBs), depression (β-blockers), hypo/hyperglycemia (diabetic drugs), ↑ blood pressure, and exacerbation of HF (NSAIDs) hyperkalemia (RAAS inhibitors), arrhythmias (digoxin), myopathy and rhabdomyolysis (statins), bone marrow suppression (allopurinol), bleeding (anticoagulants)

↑, increased, enhanced; ↓, decreased; *CCBs* calcium channel blockers, *CV* cardiovascular, *HF* heart failure, *NSAID* nonsteroidal anti-inflammatory agent, *LV* left ventricular

that confound interpretation of data. These include changes in CV responses to drugs due to aging, increased risk of hypotension, presence of comorbidities often multiple, polypharmacy, adverse drug reactions (ADRs), drug–drug and drug–disease interactions, poor adherence, and poor compliance (Table 1.3).

Therapy in Elderly with HF/Low EF

Despite the concerns and limitations of RCTs, the guidelines provide recommendations for the use of pharmacological as well as non-pharmacological therapies in both non-elderly and elderly HF/low-EF patients. No major distinction in therapy is made in treating the elderly except for the need for caution with respect to some aging-related issues (Table 1.3) and certain caveats for the elderly [6–8], such as avoidance of hypotension with the use of vasodilators (Table 1.4).

As mentioned, the rationale for treatment recommendations is because RCTs of medical therapies primarily for non-elderly patients with HF/low EF over the last three decades have shown definite mortality and morbidity benefits with RAAS inhibitors (such as ACE inhibitors, ARBs, and aldosterone antagonists) and beta-blockers in elderly patient subgroups with HF/low EF as well [6–8]. The guidelines also support the use of hydralazine, nitrates, digoxin, and diuretics for HF/low EF.

Table 1.4 Caveats with pharmacological therapies for heart failure in the elderly

Caveat	Approach/rationale
• Use the simplest dose regimen	↓ Number of drugs, ↓ cost, ↑ compliance/adherence
• Start with low dose, escalate slowly	↓ ADRs from drug–disease interactions: nitrates, ACE inhibitors, ARBs, MRAs
• Do regular medication reviews	↓ ADRs from drug–drug interactions: over-the-counter (OTC) drugs, herbal medications
• Monitor liver and kidney function	↓ ADRs from drug–disease interactions
• Monitor fluid/electrolyte balance	↑ Vigilance for ADRs
	Beware of: ↓ Na+, K+, Mg++ with loop diuretics; overdiuresis due to ↓ thirst; bradycardia with CCBs, β-blockers; hyperkalemia with RAAS inhibitors; RAAS inhibitors in stage IV/V CKD; ↑ drug toxicity with ↓ K+, Mg++, and ↑ Ca++
• Monitor for ADRs at all times	Suspect autonomic dysfunction with falls/syncope
	Beware of: postural hypotension with vasodilators; exacerbation of cognitive dysfunction, loss of memory, disorientation, irritability (digoxin); preload dependent and volume sensitive HF/PEF patients; NSAID-induced exacerbation of HF due to Na+/water retention, causing resistance to ACE inhibitors, ARBs, diuretics, and β-blockers
• Monitor for low energy and fatigue	Suspect hypoK+/Mg++, anemia, other causes (cancer)

↑, increased; ↓, decreased; *ADR* adverse drug reaction, *CCBs* calcium channel blockers, *CKD* chronic kidney disease, *HF* heart failure, *MRA* mineralocorticoid receptor antagonist, *NSAID* nonsteroidal anti-inflammatory agent, *RAAS* renin-angiotensin-aldosterone system

Therapy in Elderly with HF/PEF

Specific medical therapy for HF/PEF has been totally lacking until recently and several studies are in progress. The mainstay of treatment in the hypertension guidelines is primarily pharmacological [32]. Current recommendations for the treatment of HF/PEF include control of hypertension, control of ventricular rate in patients with atrial fibrillation, control of pulmonary congestion and peripheral edema with diuretics, treatment of coronary artery disease and demonstrable myocardial ischemia with coronary revascularization, restoration and maintenance of sinus rhythm in patients with atrial fibrillation, and use of digoxin in selected patients [6–8].

Since fibrosis is a major cause of diastolic dysfunction in the elderly and RAAS inhibitors are antifibrotic, elderly patients may benefit from them [10]. Several experimental studies had suggested that dual inhibition of ACE and neutral endopeptidase (NEP) pathways in an engineered single molecule such as omapatrilat (OMA) may provide added benefits in that regard for SHF after MI and DHF in hypertensive patients. However, despite demonstrated superior antihypertensive efficacy of OMA over an ACE inhibitor [37] and equal anti-remodeling efficacy in HF patients [38], the Federal Drug Administration (FDA) bureau did not approve OMA for patients with hypertension because of concern with angioedema.

Recently, however, the concept of dual-action molecules has been revived with the novel drug LCZ696, which combines neprilysin (NEP) and the ARB valsartan. The results of the recent study released at the 2012 ESC Congress suggested that LCZ696 may be beneficial in HFPEF patients [39]. It is also currently being evaluated in HF/low-EF patients [39, 40].

Non-pharmacological Therapies

Several non-pharmacological therapies are recommended for systolic and diastolic HF therapy (Table 1.5). Although data specifically on the elderly is lacking, this group can benefit significantly from implantable cardioverter-defibrillator (ICD) devices, cardiac resynchronization therapy (CRT), and other specialized therapies [8]. From the ACC/AHA/ESC guidelines, the consensus appears to be that ICDs are indicated in patients with LVEF <35 % 40 days after MI and in those with a low EF and NYHA II to III symptoms and expected to survive >1 year [9]. ICDs have been used in patients aged >80 years so that older age

Table 1.5 Aging and non-pharmacological therapies for heart failure

Therapies
Implantable cardioverter-defibrillator (ICD)[a]
Cardiac resynchronization therapy (CRT)[a]
Myocardial revascularization: CABG[a]
Heart transplantation
Total artificial heart (TAH)
Mitral valve repair or replacement
Left ventricular reconstruction
Ventricular assist devices (VADs)
LVAD: first- and new-generation devices
RVAD: first generation
Passive cardiac restraint devices
Cardiac regeneration approaches
Myocardial tissue engineering

Modified from Jugdutt BI. Aging and Heart Failure: changing demographics and implications for therapy in the elderly. Heart Failure Rev 2010; 15:401–405. With permission from Springer Science + Business Media
CABG coronary artery bypass surgery, *LVAD* left ventricular assist device, *RVAD* right ventricular assist device
[a]Widely used

is not an absolute contraindication. Some studies have shown that CRT therapy as well as CRT plus ICDs may be beneficial. Mechanical support devices may also be used in elderly patients as a bridge to decision, bridge to recovery, bridge to destination, or bridge to possible transplantation. Advanced age should not be considered an absolute contraindication for ventricular assist devices (VADs). Barring certain caveats, the eligible elderly HF patient should not be denied these treatments. However, more research data on aging subsets is needed.

Outcomes with Contemporary HF Therapy in the Elderly

Over the last 30 years, an undeniable fact is that improvement in therapies for CVD, especially for STEMI and hypertension [4–6], has increased the number of non-elderly patients who have survived into old age, thereby expanding the elderly population with HF [4–11]. Several studies have suggested that outcome is poor in the elderly [41, 42]. The main reason is that recommended evidence-based HF therapy is not optimally applied in the elderly and very elderly [43]. In addition, trial data on therapy of HF/PEF using those therapies or novel pharmacological drugs have not shown mortality benefit in non-elderly or elderly patients [6–9]. This is of particular concern since HF/PEF accounts for nearly half of all HF patients and its prevalence is even higher in the elderly [29, 30]. Also, current medical therapies were found to be suboptimal for very elderly patients with HF/PEF, with 69 % of patients aged >80 years dying over 5 years [33].

Problems and Caveats with Contemporary Medical Therapy of HF in the Elderly

As underlined in the foregoing discussion, contemporary medical treatment of the elderly with HF is suboptimal. The commonly quoted reasons include underdiagnosis, undertreatment, underuse, and underdosage of recommended pharmacotherapies in patients with HF/low EF [43]. Comorbidities are common, aggravate HF, complicate therapy, and increase the total HF burden. Other problems can complicate management and need special attention. Polypharmacy can lead to drug interactions (Table 1.3), raising issues of efficacy and safety. Frailty and cognitive impairment lead to reduced compliance (Table 1.4). Response to diuretics, ACE inhibitors, beta-blockers, and/or positive inotropes may be blunted. The elderly show increased susceptibility to renal dysfunction, impairment of sodium and water excretion, and postural hypotension and aggravation of hypotension with the treatments (e.g., ACE inhibitors, beta-blockers, nitrates, hydralazine). Hypotension may be complicated by impaired balance and proprioception, sick sinus syndrome, and bradyarrhythmias that may be further aggravated by drugs that reduce heart rate such as beta-blockers and digoxin. However, beta-blockers should not be withheld unless contraindicated since they reduce mortality.

Because of physiological and pathophysiologic changes associated with aging, several

precautions are necessary with HF pharmacotherapy in the elderly. Therapy must be individualized and consider aging-specific changes in physiology, drug metabolism, drug pharmacokinetics and tolerance, comorbidities, polypharmacy, and drug–drug interactions [6–9]. However, these considerations should not deter therapy.

Aging Subsets and HF Therapy in the Elderly

The elderly population is heterogeneous and so is the elderly HF population. The aging process is progressive and rates of aging differ among individuals [10, 11]. The conventional socioeconomic and politically driven threshold age of 65 years has little meaning in the context of an aging continuum [11]. The notion among many geriatricians that CV aging is not apparent until age 75 years is flawed. Different aging subsets in the aging-HF continuum [11] would be expected to have different therapeutic implications and different sets of problems.

In order to optimize HF therapy in the elderly, future RCTs need to consider aging subsets as well as aging-specific CV changes and issues. Several studies have used three or more elderly subsets that may be more appropriate in efforts to optimize therapy [10, 11, 44, 45]. In a population study that spanned two decades (1975–1995), the risk of MI increased progressively across three elderly subgroups: the younger elderly aged 65–74 years, the older elderly aged 75–84 years, and the very elderly aged >85 years [44]. In the INTERHEART study that ranked potentially modifiable CVD risk factors for MI in five age groups ranging from younger adults to the older elderly (<45, 46–55, 56–65, 66–70, and >70 years), a similar trend was found [45].

In summary, pharmacotherapy for HF in the elderly is challenging and needs to be individualized. Future RCTs need to systematically stratify elderly HF patients into incremental aging subsets with increasing chronological age so as to guide therapy for maximizing benefits in specific age subsets. To individualize therapy, RCTs must provide solid data for guidance, instead of putting the onus entirely on the physician's shoulders. This is especially pertinent as the elderly HF patient is more likely to be seen and managed by a non-cardiologist in general practice. Even cardiologists may not be familiar with specific problems of the elderly. More multidisciplinary HF clinics specializing in the needs of the elderly HF patient are necessary.

Expanding Knowledge of the Biology of Cardiovascular Aging

Autopsy data documented specific findings in aging hearts in the 1950s [46]. Gerontology research began to seriously focus on aging-related CV changes in the early 1980s [46–50]. The need for more clinical research on aging was underscored in the late 1970s [51]. The need for inclusion of elderly patients in clinical trials was emphasized in the 1990s [52].

A common clinical finding is that individuals differ in age of onset and rate of progression of CV diseases, including hypertension, CHD, and HF. This interindividual variability has been explained by a genetic predisposition or protection to CV disease and genetically determined variability in biological aging. Evidence since the 1990s suggest that telomeres serve as a mitotic clock [53], and mean telomere length may serve as an inherited marker of individual biological aging at the cellular level [54]. Telomere shortening has been linked to cellular aging and CV disease and HF [55]. In contrast, preserved telomere length appears to reflect healthy aging [56].

From the foregoing discussions, prevention of HF in the elderly should be a health-care priority. More translational research into CV aging and more RCTs in elderly HF patients are needed to fully understand the effects of biological aging in the growing elderly HF population before preventive measures can be formulated and implemented to reduce the burden of HF in elderly men and women. It is important to recognize that CV aging is a continuous lifelong process and becomes risky because concomitant lifelong exposure to adverse CV risk factors fuels the march to HF (Fig. 1.1).

Conclusions

The changing demographics of the HF and elderly population have major implications for HF therapy in the elderly. HF is a growing problem worldwide. This growth is associated with increased morbidity, morbidity, hospitalization, and costs due to HF. There is therefore an urgent need for increased awareness, more research not just into the biology of aging at the basic level but also at the clinical level, with more RCTs in elderly patients with HF/low EF as well as HF/PEF. Only more research will lead to novel strategies and discovery of new therapeutic targets for managing the two main classes of HF in the elderly.

Expanding knowledge of the biology and molecular mechanisms of cardiovascular aging should be used to provide the foundation for more serious efforts to delay or arrest its progression and the march to HF in future. This will result in a reduction in healthcare costs and promote a healthy elderly population. To fully promote the concept of healthy aging, it is necessary to match prolonged longevity with healthy aging of the CV system and other systems in both elderly and non-elderly populations.

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Biology of Aging and Implications for Heart Failure Therapy and Prevention

2

Bodh I. Jugdutt

Introduction

The elderly population (age ≥65 years) with heart failure (HF) has been increasing significantly in developed countries since the early 1970s and is currently increasing in most developing countries. The projections from population studies in the United States (USA), Europe, and other developed countries suggest that the worldwide trend in the growing burden of HF will very likely continue and tax healthcare systems worldwide [1, 2]. In the USA, the number of elderly people is expected to double by 2030 [1], and the very old aged ≥85 years will likely triple by 2050 [2]. While improvements in public health, nutrition, medical therapies, and healthcare delivery systems have undoubtedly contributed to growth of the elderly population, there has been a concurrent even steeper growth of the elderly with HF in the USA and Europe [3–5]. Data from the National Health and Nutrition Examination Survey (NHANES) in the 2010 Heart Disease and Stroke Update of the American Heart Association (AHA) have clearly shown that the increase in HF prevalence is age dependent and the prevalence highest in elderly men and women [4]. Similar trends as in the USA [5] were found in Canada [6, 7]. Unless appropriate preventive strategies and measures are implemented urgently, the prevalence, related complications, and total burden of HF in elderly men and women will very likely expand and tax the future healthcare systems even more.

Many authors since the 1990s have commented on the increasing economic burden due to mortality, morbidity, hospitalization, and emergency department visits in the growing adult and elderly populations with HF [5–14]. Prevention of HF in the present and future elderly populations should therefore be a healthcare priority. However, when, where, and how to begin needs to be clearly defined [15]. Because aging is a progressive biological process, objective management and prevention of HF should consider the pathobiology of aging and the pathophysiological changes associated with cardiovascular (CV) aging in the context of the aging-HF continuum [11, 15] and the possible need for different treatment strategies for different age groups [9, 15]. Furthermore, preventive measures should logically begin early, in younger age groups, from the pediatric age through early and late adulthood for maximal effectiveness in combating the rising burden of HF [15]. This chapter addresses these points and suggests some potential preventive strategies for achieving optimal impact.

B.I. Jugdutt, MD, MSc, DM, FRCPC (✉)
2C2 W.C. Mackenzie Health Sciences Centre,
Division of Cardiology, Department of Medicine,
Mazankowski Alberta Heart Institute,
University of Alberta and Hospitals, 727, Todd Landing NW, Edmonton, AB, Canada T6G 2B7
e-mail: bjugdutt@ualberta.ca

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Aging, the Elderly, and Cardiovascular Disease

There are several definitions of aging in humans, including chronological, biological, physiological, and clinical (Table 2.1). Despite advances in the biology of aging, the chronological age of 65 years is still the accepted age cutoff for the elderly in most developed countries, although it has been shown to have considerable relevance in population studies and clinical trials [9]. Population and epidemiological studies have established that the population of elderly people aged ≥65 years is not only increasing worldwide but the elderly group has the greatest burden of HF and the highest morbidity and mortality from CV disease (CVD) and other comorbidities [4, 16–18]. These studies also show that increasing chronological age is associated with increased CVD risk, including that for hypertension, coronary heart disease (CHD), stroke, and HF [4]. Importantly, this aging-related growth in healthcare burden has resulted in concurrent increase in healthcare costs [4], thereby providing strong justification for more research to address how aging might lead to CVD and HF.

Biology of Aging and Risk of Cardiovascular Disease

Cumulative evidence indicates that aging is an inevitable, natural biological process that progresses with the passage of time. The aging process may therefore result in important biological differences between young, adult, and old patients that may differentially impact pathophysiology and optimal management of HF [19–21]. For example, aging is associated with biological and CV changes that impact disease expression and response to therapy [19–21]. As mentioned above, aging also results in increased CVD risk, including hypertension and CHD [4] which lead to HF [10, 19–21]. Recent studies suggest that aging is associated with defective responses to myocardial injury and impaired wound healing, leading to adverse LV remodeling and HF [10, 19–21].

Table 2.1 Definitions of aging

Type	Basis
Chronological	Socioeconomic and political
Biological	Telomere length, telomere activity
Physiological	Aging phenotype
Clinical	Biomarker

Table 2.2 Aging phenotype and heart failure

Increased LV concentric remodeling
Increased LV mass to volume ratio
Increased extracellular matrix, fibrillar collagen content, fibrosis
Impaired LV diastolic function and relaxation
Heart failure-preserved ejection fraction

LV left ventricular

At the cellular level, aging is genetically driven and characterized by progressive decline in the capacity of cells to divide and carry out their specific functions [19]. Several markers correlate with the aging phenotype (Table 2.2). As discussed below, telomeres, which are DNA sequences at the end of chromosomes, shorten with every cell division and therefore with aging. On the other hand, telomerase, the cellular enzyme that adds telomeric repeat sequences to chromosomal ends, preserves telomere length. Telomerase may also decrease with aging under certain conditions. Low telomerase activity and short telomere lengths may be early markers of CV risk. In the West of Scotland Coronary Prevention Study (WOSCOPS), where patients aged 45–65 years were randomized to placebo or pravastatin, shorter leukocyte telomere length predicted CHD in middle-aged men. Importantly, for every 10 years increase in age, telomere length decreased by 9 % [22]. In a recent nested case-control study, shorter telomere length was related to risk of myocardial infarction [23].

Pathophysiologic Correlations and Remodeling During Aging

At the clinico-pathophysiological level, several biological changes that occur with aging contribute to adverse cardiac remodeling and the relentless march to HF [19, 20]. We previously

Table 2.3 Heart failure and changes in cardiovascular physiology and pathophysiology with aging

• Vascular remodeling
– ↑ Ventricular-arterial stiffening and altered coupling
– ↑ Systolic blood pressure and pulse pressure
• Ventricular remodeling and ↑ mass/volume ratio
– ↑ Extracellular matrix (fibrillar collagen) and ↑ fibrosis
– ↑ Advanced glycation end products (AGES)
– ↑ Collagen cross-linking
– Diastolic dysfunction and impaired relaxation
– ↓ Cardiac reserve
• Atrial remodeling and atrial fibrillation
– Cellular and subcellular remodeling
– Altered responses to stress
– Altered responses to injury and impaired healing
• CV remodeling due to lifelong exposure to CV risk factors
– ↑ Interaction with CV risk factors
– ↑ Risk of coronary heart disease and sequelae
– ↑ Risk of peripheral artery disease and sequelae
– ↑ Risk of cerebrovascular disease and sequelae
– ↑ Risk of comorbidities and sequelae
– ↑ Cardiorenal interactions and sequelae
– ↑ CV events

↑, increase; ↓, decrease; *CV* cardiovascular

Table 2.4 Heart failure and changes in cardiovascular biology and pathobiology with aging

• ↓ Leukocyte and tissue telomere length
• Altered gene regulation
• Altered cellular and subcellular functions
• Altered mitochondrial population and function
• ↓ Myocyte number, ↑ myocyte size
• Altered contractile pathways, ↓ myocardial contractility
• Isomyosin shift
• ↓ Excitation–contraction coupling
• ↑ Fibrosis-related genes, ↑ fibrosis and collagen matrix
• ↑ Myocardial stiffness, ↑ vascular remodeling and stiffness
• ↑ End-systolic stiffness (chamber elastance)
• ↓ Diastolic compliance
• Altered immune responses, altered repair responses
• Altered responses to injury, impaired healing
• Remodeling of beta-adrenergic system
• Altered neurohumoral pathways
• ↑ Angiotensins and endothelins, ↑ angiotensin II
• Altered stress response pathways
• ↑ Oxygen-free radicals, ↑ oxidative stress and damage
• Altered cardiac and arterial responses to stress
• Altered metabolism and metabolic reserve

↑, increase; ↓, decrease

hypothesized that aging is associated with global remodeling that involves changes in CV structure as well as cellular, subcellular, biochemical, molecular, physiological, and pathophysiological pathways and responses [19–21]. As a corollary, the collective aging-related biological and CV changes may impact both disease expression and response to therapy and have important therapeutic implications for HF management. Importantly, several biological changes contribute to adverse cardiac remodeling and the march to HF during aging [15, 19]. Since the aging process is progressive, it follows that HF management must consider the aging-dependent pathophysiological changes (Tables 2.3 and 2.4) and possibly the need for different treatments for different age groups in order to maximize benefits. Therapy of CVD that is optimal for the young patient may therefore not be optimal for the old patient. This also applies to HF.

Expanding knowledge of the biology of aging [8–11] and aging-related changes in CV structure and function [24–27] suggest that the aging heart may itself be a substrate for CVD including HF. In the last three decades, a constellation of typical aging-related physiological and pathophysiological changes typical in the CV system (Table 2.3) and pathobiological changes (Table 2.4) as well as an aging phenotype (Table 2.2) have been recognized [8, 10]. Several lines of evidence strongly suggest that aging is a continuous biological process during which progressive changes in CV structure, physiology, and biochemistry occur and negatively impact cardiac function and contribute to HF [8, 10]. Taken together, these characteristic changes can provide the rational basis for identifying targets for specific interventions during the aging process with the goal of preventing the march to HF.

Telomeres, Telomere Length and Telomerase Activity, and Implications for Prevention

Evidence since the 1990s suggest that telomeres serve as a mitotic clock [28] and mean telomere length may serve as a marker of biological aging at the cellular level [29] that is heritable [30]. Telomeres are DNA-protein complexes at the ends of chromosomes that maintain chromosome stability and control cell cycles [31]. In humans, telomeres consist of repeats of DNA sequences of six nucleic acid–base pairs, with TTAGGG on one strand and AATCCC on the other strand. Telomere length is genetically determined [30], and every individual appears to have a characteristic length in different organs [32]. During aging, telomeres get progressively shorter with every cell division [33], decreased telomere length to a critical value triggers cellular senescence [31], and shorter telomeres mark increased biological age [29]. Increased oxidative stress is an important mechanism for increased telomere loss per cell division and cellular aging [34] and aging-related CV diseases such as hypertension [35] and homocysteine-induced endothelial senescence [34]. In the latter study, increased levels of pro-atherogenic intracellular adhesion molecule-1 (ICAM-1) and plasminogen activator inhibitor-1 (PAI-1) correlated with the degree of endothelial senescence [34]. A second mechanism for telomere attrition involves inflammation. For example, stem cell cultures enriched with cytokines such as interleukin-6 (IL-6) and stem cell factor (SCF) show increased telomere attrition [29]. In a population of men and women aged 35–55 years and free of overt CV disease, increased levels of inflammation and oxidative stress markers such as IL-6 and hs-CRP (as well as fibrinogen in men and oxidized LDL and uric acid in both genders) were associated with shorter telomere lengths [36].

Aging-Related Telomere Shortening in Cardiovascular Disease from Population Studies

Several population studies [22, 23, 35–48] have documented the association of telomere shortening in circulating leukocytes with aging-related CVDs (Table 2.5). At least eight pertinent points from these studies deserve emphasis:

Table 2.5 Population studies of telomere shortening and aging-related cardiovascular diseases

Diseases [reference]	Age (years)
Coronary artery disease [22]	45–64
Increased risk of myocardial infarction [23]	40–84
Hypertension, insulin resistance, and oxidative stress [35]	40–89
Inflammation and oxidative stress [36]	35–55
Atherosclerosis [37]	42–72
Increased mortality (heart disease, infectious disease) [38]	60–97
Premature myocardial infarction [39]	<50, mean 42.3 ± 5.7
Myocardial infarction in men and stroke [40]	>65, mean 74.2 ± 5.2
Carotid artery atherosclerosis in hypertensive patients [41]	63.6 ± 1.0
Chronic heart failure [42]	66 ± 8.7
Left ventricular dysfunction in the oldest old [43]	84.9–85.7
Type 1 and type 2 diabetes in men [44]	17–48, 24–75
Type 2 diabetes and/or insulin resistance in men [45][a]	~40–70
Increased pulse pressure and pulse wave velocity in men [46]	56 ± 11
Obesity and cigarette smoking in female twins [47]	18–75
Smoking, obesity, and lack of exercise in low-economic status in female twins [48]	~32–68

[a]All telomere length in leukocytes except for monocytes here in [45]

1. Telomere shortening precedes clinical disease, and the extent of telomere shortening may explain interindividual biological variability in response to CV risk factors (49 for review).
2. Differences in telomere length in individuals with or without CAD are not explained by differences in CV risk factors [49].
3. Individuals prone to CHD are biologically older, with telomere lengths equivalent to those in normal subjects who are 8–12 years older [22, 37, 39].
4. Telomere lengths are longer in women than men [46] suggesting that for a given chronological age, biological age is more advanced in men and may be linked to the effect of estrogens on telomerase activity [50].
5. Increased oxidative stress and inflammation may play a major role in telomere shortening and progression of CVD [35, 36, 44, 45].
6. In HF patients, shorter telomere lengths correlate with greater severity of atherosclerotic heart disease [42].
7. Marked telomere shortening may play a role in the pathogenesis of type 1 diabetes via increased pancreatic inflammation [44].
8. A study of chronic stress arousal in healthy women suggested that low leukocyte telomerase activity may be an earlier marker of CV risk than telomere shortening [51].

Telomere Shortening and Cellular Senescence in Human Pathological Studies

Several human pathological studies of aging have documented shortened telomeres, including in different tissues of the same individual [32]; coronary endothelial cells of arteries from autopsied hearts with CHD [52]; atherosclerotic cells in intima and media of autopsied abdominal aortas, especially at distal sites [53]; vascular smooth muscle cells in atherosclerotic plaques, cell cycle inhibitor $p16^{INK4a}$ positive and c-Kit-positive cells, and myocytes [54]; and dilated cardiomyopathy [55]. While telomere shortening associated with CHD and other CVDs during aging can be explained by increased cell turnover and replicative stress that occur in these diseases, emerging evidence suggests that it may play a role in their pathogenesis. Thus, early atherosclerotic plaques show early evidence of endothelial [56] and smooth muscle [54] cell senescence and increased expression of intracellular adhesion molecule-1 (ICAM-1) and decreased endothelial nitric oxide synthase (eNOS) that are implicated in atherogenesis [57]. These findings support the telomere hypothesis (49 for review) that short telomeres contribute to coronary and CVD risk through cellular senescence.

Telomere Shortening and Heart Failure

Telomere shortening may also contribute to HF. In human end-stage HF, cardiomyocyte apoptosis is associated with downregulation of specific telomere repeat-binding factor TRF-2, activation of checkpoint kinase Chk2 that is linked to DNA damage and apoptosis, and telomere shortening [58]. Experimentally in cultured rat cardiomyocytes, suppression of TRF-2 triggers telomere shortening, Chk2 activation, and apoptosis, whereas exogenous TRF-2 confers protection from oxidative stress [58]. Mechanical stress induced by aortic constriction in mice results in telomere shortening, downregulation of TRF-2, and Chk2 activation as in human HF [58]. Forced transgenic expression of telomerase prevented telomere shortening, downregulation of TRF-2, activation of Chk2, and apoptosis [58]. Together, these findings implicate telomere dysfunction via stress-induced downregulation of TRF-2 in HF [58]. Furthermore, telomerase knockout mice develop short telomeres and HF [59], suggesting that telomere shortening with aging contributes to HF and may be targeted for therapy.

Stress Protein and Aging-Related Cardiovascular Disease

Studies of aging animals are unique in that they are protected from the usual environmental risk factors. In a recent study, LV proteomic analysis in aging mice revealed that several stress proteins associated with aging and CV disease, such as mortalin, peroxiredoxin-3, epoxide hydrolase, and superoxide

dismutases SOD-1 (Cu/ZnSOD) and SOD-2 (MnSOD), can differentiate between young, middle-aged, and old mice [60] and may therefore serve as potential markers of cardiac aging. However, telomere lengths were not measured in that study.

Preserved Telomere Length and Healthy Aging

While telomere shortening has been linked to cellular aging and CV disease, preserved telomere length appears to reflect healthy aging. Three recent population studies that addressed healthy aging and longevity deserve mention. First, in elderly individuals aged 70–79 years, shorter telomere length correlated with poorer health status and survival and shorter life spans, suggesting that telomere length may be a biomarker of survival and healthy aging [61]. Second, gene expression profiles in individuals aged 57–97 years demonstrated that cell division cycle 42 (CDC42) and coronin (CORO1A) are strongly associated with biological age and survival, and gene expressions that increase with age were associated with increased mortality, whereas those that decrease with age were generally associated with reduced mortality [62], thereby supporting a genetic contribution to longevity. Third, in individuals aged 20–59, ≥90, and ≥98 years, three genes (HRAS1, LASS1, and APOE) that reduce age-related lipotoxicity were associated with increased survival, and LASS1 appeared to contribute to healthy aging and greater survival in the tenth decade of life [63]. Unfortunately, neither of the latter gene studies measured telomere lengths [62, 63].

The Aging Continuum, Cardiovascular Risk Exposure, and the March to Heart Failure

Population studies have established the role of environmental, lifestyle, and genetic factors in the development of hypertension (CAD and HF) [1–4]. During the aging continuum, lifelong exposure to the adverse influence of CV risk factors can lead to pathophysiologic alterations that converge and contribute in the march to HF (Fig. 2.1). Major risk factors include age, genetic factors, diet,

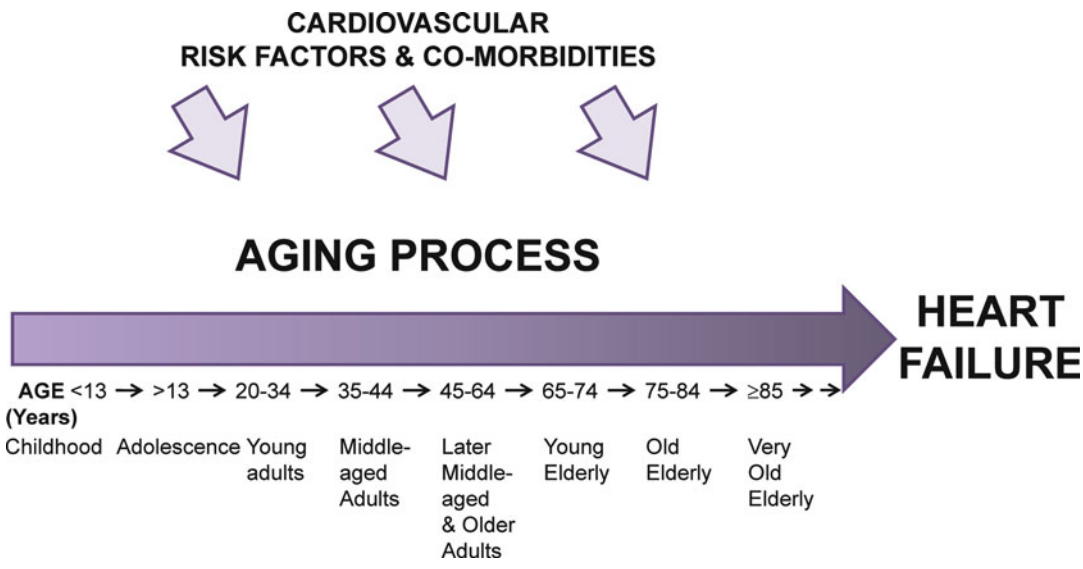

Fig. 2.1 Prevention and the march to heart failure during aging. Lifelong exposure to cardiovascular risk factors during the aging process, as well as comorbidities in later stages, fuels the relentless march to heart failure. It is proposed that, for maximal benefit and to promote healthy aging, preventive measures need to be applied throughout the aging process and begin early. Additionally, therapy should target different age subsets during the aging-heart failure continuum (reprinted from Jugdutt BI. Prevention of heart failure in the elderly: when, where and how to begin. Heart Fail Rev 2012; 17:531–544. With permission Springer Science + Business Media)

smoking, sedentary lifestyle, stress, dyslipidemia, and exposure to toxins. In this construct, fundamental physiological, biological, and structural changes associated with CV aging itself lead to increased fibrosis, increased ventricular-arterial stiffening, ventricular diastolic dysfunction, and HF with preserved ejection fraction [8–11, 19–21]. In addition, interactions among CV risk factors and the aging heart substrate compounded by the effect of comorbidities can be expected to act in concert and further fuel the march to HF. Major comorbidities include hypertension, CAD, type 2 diabetes, metabolic syndrome, and obesity. In fact, population studies have shown that the interactions between CV risk factors and the aging CV system lead to vascular disease progression. Such is the case with hypertension. Several CV risk factors lead to hypertension, which in turn interacts with other risk factors and comorbidities resulting in complications and end-organ pathologies, including stroke, myocardial infarction, HF, and renal failure [4]. Not surprisingly, the risk of HF increases steeply in the presence of antecedent hypertension and myocardial infarction [4].

The Aging Continuum, Cardiovascular Risk, and Implications for Prevention

Pertinent in the context of prevention, prolonged exposure to CV risk factors during aging has a cumulative effect on CVD progression, and the risk of end-organ damage and HF increases with age [64, 65]. This is true among non-elderly and elderly groups and is borne out in many studies. For example, in a population study spanning two decades (1975–1995), Goldberg et al. showed that the risk of myocardial infarction increases progressively across three elderly subgroups: the younger elderly aged 65–74 years, the older elderly aged 75–84 years, and the very elderly aged >85 years [66]. The more recent INTERHEART study that ranked potentially modifiable CV risk factors for myocardial infarction in five age groups ranging from younger adults to the older elderly (<45, 46–55, 56–65, 66–70, and >70 years) showed a similar trend [67].

A leading pioneer of preventive cardiology, the late Dr. William B. Kannel, who led the Framingham Heart Study (FHS) from 1966 to 1979 [68], was among those who are credited with coining the term "coronary risk factors" [69]. Kannel played a major role in identifying correctable predisposing CV risk factors [70]. In a longitudinal study of 186 men and women aged between 30 and 59 years, Kannel and associates confirmed the association of three risk factors (hypertension, hypercholesterolemia, and electrocardiographic evidence of left ventricular hypertrophy) with increased risk of CHD over a 6-year period [69].

At least five other population studies expanded the list of risk factors and documented the lifetime risk of coronary heart disease [71–73], including in the oldest old [74]. In one FHS cohort of 7,733 men and women, the lifetime risk of CHD (defined by angina pectoris, coronary insufficiency, myocardial infarction, or coronary death) increased from 1:2 for men and 1:3 for women at age 40 years to 1:3 for men and 1:4 women at age 70 years [71]. In another FHS cohort of 3,564 men and 4,362 women without atherosclerotic CV disease (defined by angina, coronary insufficiency, myocardial infarction, stroke, claudication) and absence of risk factors (based on normal body mass index and absence of smoking, hypertension, hypercholesterolemia, and diabetes) at age 50 years was associated with low lifetime risk for CV disease to age 95 years and longer survival [73]. In a third FHS cohort of 3,757 men and 4,472 women aged 35–84 years and without HF followed for 25 years (1971–1996), the overall lifetime risk of HF was 1:5 in both men and women and 1:9 for men and 1:6 in women without antecedent myocardial infarction [64]. In a fourth FHS cohort of 2,302 men and women with mean age 44 years, the presence of parental CV disease predicted the risk of future events in the middle-aged adults over 8 years [72]. In a fifth FHS cohort of 2,531 men and women aged 40–50 years and followed to the age of 85 years, lower levels of key CV risk factors (electrocardiographic evidence of left ventricular hypertrophy, body mass index, blood lipids, smoking, glucose intolerance, physical activity,

and alcohol intake) at middle age predicted survival and major morbidity-free survival to age 85–100 years [74]. Collectively, these five studies support education, screening, early recognition, and treatment of CV risk factors [71–73], with attention to family history [72] and aggressive measures to control hypertension and prevent myocardial infarction [64] and delay or prevent aging-related morbidity and mortality [74] in both young adults and the elderly.

Clustering of Cardiovascular Risk and Implication for Prevention

Kannel also underscored the clustering of major risk factors on the basis of long-term epidemiological data over six decades in the FHS [70], implying metabolic linkage as pertinent for the metabolic syndrome. Major risk factors for CAD in the Framingham Risk Score (FRS) included age, hypertension, cigarette smoking, diabetes mellitus, and hyperlipidemia [69, 75, 76]. This multivariable CV risk algorithm was later expanded to include sex, levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), and treatment of hypertension to estimate the risk of myocardial infarction or death as a result of CHD [77–80]. The Reynolds Risk Score (RRS) which added parental family history of premature coronary heart disease and high-sensitivity C-reactive protein (hs-CRP) to the traditional risk factors provided additional predictive information for subclinical atherosclerosis compared to the FRS in women [81, 82] and men [83]. The risk algorithms were further expanded with increasing knowledge of the biology of CV risk and atherosclerosis, atherothrombosis, inflammation, endothelial dysfunction, plaque rupture, metabolic syndrome, and aging. Several epidemiological studies confirmed the risk factors for CAD and further expanded the list to include age (a major determinant), male sex, cigarette smoking, diabetes, cholesterol (TC, LDL-C, ApoA-1, or ApoB), HDL-C, blood pressure, family history of premature coronary disease (age <60), and added inflammatory biomarkers such as hs-CRP, hyperglycemia, glycated hemoglobin-A_1C (HbA_1C), creatinine, homocysteine, overweight, obesity, poor nutrition, calorie excess, physical inactivity, and psychological stress. Emerging factors proposed for improving risk prediction include the metabolic syndrome [84], chronic kidney disease [85], and chronic inflammatory diseases (such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis) and chronic HIV that need further evaluation [86]. Other studies have underscored the importance of family history in coronary artery calcification [87], a high body mass index (BMI) [88], and statin therapy for reducing cholesterol [89] and inflammatory markers [90, 91].

In the last paper before his death in 2011 at age 87 [79], Kannel emphasized the importance of multivariable risk factor influences on CVD, including CAD, stroke, peripheral artery disease, and HF. Kannel therefore favored use of multivariable risk factor assessment in primary care and noted that 40–50 % of people having CV events are not considered high risk by most current risk profiles [70]. Interestingly in INTERHEART, nine factors accounted for most of the risk of myocardial infarction; the factors were smoking, fruit and vegetable intake, exercise, alcohol intake, hypertension, diabetes, abdominal obesity, psychosocial, and blood lipid levels as ApoB/ApoA-1 ratio [67].

The collective evidence indicates that several CV risk scoring systems, such as the FRS and RRS systems, provide best estimates of the probability of individuals to develop CVD with aging over the subsequent 5 or 10 years and those most likely to benefit from prevention. For example, the FRS can be used to categorize individuals as low risk (≤10 %), intermediate risk (10–20 %), and high risk (≥20 %) for CAD at 10 years. Importantly, in every algorithm, age is the strongest predictor of CV risk, and nearly all elderly individuals aged ≥70 years and nearly none of adults aged <40 years are at high risk. It follows that adults aged >40 years are mostly likely to benefit from preventive measures (such as smoking cessation, healthy diet, and regular exercise) and the elderly mostly likely to benefit from preventive medical therapy (such as antihypertensive

agents, cholesterol-lowering agents, and low-dose aspirin). A recent study reported a decrease in coronary heart disease mortality rates between 1994 and 2005 that was associated primarily with trend in risk factors (decreased blood pressure and cholesterol, increased diabetes and BMI) and improved medical treatments for hypertension and hyperlipidemia [92].

Biomarkers and Cardiovascular Risk and Implication for Prevention

Kannel also suggested that risk assessment may be improved by use of biomarkers, genetic markers, and vascular imaging and biomarkers may be useful for assessing the benefits of therapy and stratifying those with intermediate CV risk [70]. Indeed recent studies suggest that biomarkers [91, 93–100] and vascular imaging [87, 101–103] can stratify subgroups at risk of CVD [87, 101–103] and HF [95–99] and guide HF management [97]. Importantly, evidence suggests that several biomarkers [91, 93–100] including hs-CRP [91], N-terminal pro-B-type natriuretic peptide (NT-proBNP) [95–97], cardiac troponin I (cnI) [98], and cardiac troponin T (cnT) [95, 99] can be used to predict HF [95–99], adverse remodeling [97], and CV death in older adults and the elderly [95, 98, 99]. In one study of young elderly patients with chronic systolic HF (mean ages 66 and 67 years), high serum levels of cortisol and aldosterone were shown to be independent predictors of increased mortality risk [104].

Although a strategy to suppress NT-proBNP levels in older adult patients (mean age 63 years) with chronic systolic HF has been shown to reduce adverse events compared to the standard approach [97], BNP levels may not distinguish patients with systolic and diastolic HF. Thus, a recent study showed that elderly patients (mean age 70 years) with diastolic HF had similar although less severe pathophysiological characteristics than those with systolic HF, including BNP levels [105]. However, among predominantly elderly patients (mean age 70 years, range 18–105) presenting to the emergency department with congestive HF, BNP levels were lower in those with non-systolic HF than those with systolic HF but provided only modest discrimination of the subgroups compared to traditional parameters and felt to be best for distinguishing patients with or without congestive HF [106]. In another report of older adults presenting to the emergency department with congestive HF (mean age 64 years) in REDHOT, BNP levels predicted 90-day outcomes and aided stratification and triage [107]. Taken together, judicious application of biomarkers can be used to guide efforts to reduce CV risk on an individual basis during aging, and biomarkers such as NT-proBNP can guide measures to reduce hospitalization in elderly patients with HF.

Comorbidities in Aging-Related Heart Failure: Hypertension and Myocardial Infarction

As reviewed before [10], hypertension and myocardial infarction are prevalent in the elderly and the two major contributors to HF in that population segment. Importantly, hypertension results in predominantly diastolic HF, or HF with preserved systolic function or preserved ejection fraction (HF-PEF), whereas myocardial infarction results in predominantly HF with systolic dysfunction or low ejection fraction (HF-low EF) [10]. Whereas most myocardial infarctions are due to coronary artery disease, hypertension involves renal, vascular, neural, and humoral mechanisms as well as genetic and various behavioral factors. An early study on patients in the SOLVD registry underscored the importance of decreased ejection fraction as a major factor in neurohormonal activation in patients with HF [108]. Hypertension is also a major risk factor for coronary heart disease, left ventricular hypertrophy, and HF. Since both aging and hypertension are associated with left ventricular hypertrophy, fibrosis, and diastolic dysfunction (Table 2.2), the elderly with hypertension is at enhanced risk for HF-PEF. Similarly, the elderly patient with myocardial infarction and cardiac changes associated with aging (Tables 2.3 and 2.4) is at enhanced risk for severe

HF-low EF. Hypertensive patients with myocardial infarction develop mixed left ventricular hypertrophy and HF-low EF. While management guidelines for elderly hypertension [109] and elderly acute non-ST-elevation and ST-elevation myocardial infarction [16, 17] have been developed and the guidelines for HF management in adults mention the elderly [110], specific detailed management guidelines for that growing elderly population with HF are lacking.

Comorbidities in Aging-Related Heart Failure: Type 2 Diabetes, Metabolic Syndrome, and Obesity

Besides hypertension and myocardial infarction, several other comorbidities prevalent in older adults and the elderly such as type 2 diabetes, metabolic syndrome, and obesity amplify CV risk. Numerous studies have shown that these comorbidities accelerate the progression toward vascular complications and end-organ pathologies, including stroke, myocardial infarction, HF, renal failure, peripheral arterial disease, disability, and death [84, 86, 111]. In the USA, the prevalence of obesity (defined as BMI > 30 kg/m^2 in adults) nearly doubled (from 15 % to 33 %) over the last 24 years, and nearly 67 % are either overweight or obese [112]. Also in the USA, the lifetime risk of diabetes increased between age 35 and 70 years and plateaued thereafter [113]. The overall risk of diabetes ranges from 35 % to 45 % in men and 30 % to 55 % in women. Elderly patients with diabetes and hypertension were shown to have higher mortality [114, 115]. Diabetes also increases the risk of HF in the elderly [116]. The ONTARGET/TRANSCEND study of high-risk elderly patients showed that the fasting blood glucose was an independent predictor of HF hospitalization [117] and supported lowering of blood glucose to reduce HF risk [118]. The ONTARGET/TRANSCEND study also showed the clinical effectiveness of therapy with the angiotensin II receptor blocker telmisartan for controlling hypertension and vascular risk in the elderly [65].

Several studies have established that the increased CV risk with type 2 diabetes is due to high blood glucose levels. High glucose levels have been implicated in microvascular damage, and several pathways of vascular glucotoxicity have been identified [119, 120]. The longitudinal STENO-2 study of CV risk reduction in high-risk older adult and young elderly patients (aged 50–66 years) with diabetes using a multifactorial intervention involving tight glucose regulation and renin angiotensin blockers, aspirin, lipid-lowering agents, and behavior modification over 7.8 years showed sustained decrease in vascular complications and deaths from CV and any cause during follow-up over 5.5 years [121]. It is pertinent to note that in STENO-2, the mortality curves for intensive versus conventional therapy took 8 years to diverge [121], suggesting that diabetes is a long-acting risk factor that affects multiple systems and needs to be targeted early with long-term glycemic control. High blood glucose and HbA_1C are important biomarkers of CV risk in diabetes. Although hyperglycemia is common after myocardial infarction and is a predictor of adverse outcomes, firm guidelines await completion of randomized clinical trials [122]. Data in the elderly and very old with HF and diabetes is lacking.

Comorbidities in Aging-Related Heart Failure: Atrial Fibrillation

Another important comorbidity in the elderly is atrial fibrillation; it is not only common in the elderly [123, 124] but also worsens HF [125] and results in additional complications such as embolism and stroke [126]. The median age of patients with atrial fibrillation is about 75 years, and nearly 70 % are aged between 65 and 85 years [126]. Atrial fibrillation is more prevalent in men and doubled in men compared to women between the 1970s and 1990s [127]. It is also more prevalent in Caucasian than Afro-Americans with HF [128] and is approaching epidemic proportions [129]. Pertinent for primary prevention, the main conditions associated with atrial fibrillation include hypertension, ischemic heart disease, HF,

valvular heart disease, and diabetes [130]. Importantly, the risk of new atrial fibrillation in elderly patients aged ≥65 years is nearly 2 % per year [131]. Furthermore, regardless of treatment, survival is worse in elderly patients aged ≥65 years with atrial fibrillation and a history of concomitant coronary artery disease or abnormal LV ejection fraction [132].

Chronological Definition of Elderly, Biological Aging, and Implications for Prevention

In the context of the aging continuum hypothesis, definition of elderly by an arbitrary age is not logical. The original definition of the elderly by the chronologic age of 65 years was only adopted by default and based on socioeconomic and political factors prevalent in the late 1800s rather than on the biology of aging [9]. Nevertheless, even this arbitrary chronological cutoff was subsequently found to have clinical relevance as early trials showed that not only the prevalence of hypertension increases progressively with aging but also the vascular complications associated with the disease increased sharply after the age of 65 years, including stroke, myocardial infarction, HF, and renal failure [4]. However, despite exposure to similar CV risk factors and risk profiles, a common finding in clinical practice is that individuals differ in susceptibility, age of onset, and rate of progression of CVDs, including hypertension, CAD, and HF. Clinical scenarios of young adults developing severe CAD or very elderly individuals having normal or low CV risk scores are fairly frequent. Such interindividual variability can be explained by a genetic predisposition or protection to CVD and genetically determined variability in biological aging.

Prevention Considering Biological Aging and the Aging Continuum

Further to the foregoing discussions, prevention of HF in the elderly should be a healthcare priority. Appropriate preventive measures need to be urgently formulated and implemented to reduce the burden of the rising HF prevalence and related complications in elderly men and women of tomorrow. In formulating strategies, it is important to recognize that CV aging is a continuous lifelong process and is risky because concomitant lifelong exposure to adverse CV risk factors throughout the process fuels the march to HF (Fig. 2.1). Efforts need to be focused on promoting healthy aging and preventing development of CVDs that contribute to HF.

When and Where to Begin?

Three critical areas need consideration in planning preventive strategies to reduce the growing burden of HF in the elderly: (1) biological factors in aging-related HF, (2) pathophysiological causes of aging-related HF, and (3) major CV risk factors and comorbidities that impact aging-related HF. From the collective evidence about the pathobiology and pathophysiology of CV aging and aging-related HF (Tables 2.3 and 2.4) and the data from population studies, it is clear that to achieve fullest impact in reducing the burden of HF in the growing aging population, preventive strategies need to address the entire aging-HF continuum and the cumulative impact of lifelong exposure to CV risk factors. Ideally, preventive measures should be applied during the entire lifetime and before individuals reach the chronological elderly age. The prevention measures need to target major CV risk factors as well as major comorbidities early during the aging continuum. In addition, it is important to recognize that the rate of biological aging can differ markedly among individuals and impact disease onset and progression irrespective of gender or ethnicity.

How to Begin?

There are three logical steps. The first step is to acknowledge the increasing trend in the elderly population with HF and the potential implication for healthcare systems. The second step is to have

a clear understanding of the major contributors to the problem. The third step is to plan strategies for addressing the problem in its entirety. In its broadest sense, implementation of conventional primary and secondary prevention measures should begin in early childhood and span adolescence and young and older adulthood in order to maximally reduce the negative effect of adverse CV risk factors, interrupt the march to HF, and reduce HF in the elderly groups (Fig. 2.1).

Benefits of Prevention and Healthy Aging

The potential benefits of healthy aging for the healthcare system are obvious. The benefits of decreased HF hospitalizations for adult and elderly patients in terms of healthcare cost savings alone would be staggering. Aggressive implementation of the published guidelines for optimal management [5, 77, 109, 110, 121, 125, 133] and prevention [79, 133–137] of CVD is needed to reduce HF hospitalizations [138]. The AHA statements have emphasized implementation of guideline-driven interventions at early stages of HF [5, 137]. Recent management guidelines have also addressed the two major contributors to HF in the elderly, namely, hypertension [106] and myocardial infarction [16, 17]. However, while the guidelines for hypertension in elderly patients were based on data from randomized clinical trials that included older age groups, this was not the case for myocardial infarction and HF. Pending more evidence-based data in elderly HF patients, the principles for secondary prevention of HF in adults can be adapted to the elderly provided specific issues are addressed, including multisystem aging, comorbidities, polypharmacy, frailty, and psychosocial factors, especially in the oldest old [10, 11, 65, 139]. While guideline-driven management of hypertension decreased HF in the elderly [140], including the oldest old [141, 142], caution is prudent with other therapies in that group. Thus, adverse drug events account for most emergency hospitalizations for HF among elderly Americans (aged 65 to ≥85 years), especially involving warfarin, insulins, oral antiplatelet agents, and oral hypoglycemic agents [143], suggesting the need for improved management of antithrombotic and antidiabetic drugs in the elderly.

As for primary prevention of CV diseases that lead to HF, the AHA guidelines address mainly adults, aged ≥40 years. They recommend early risk intervention and emphasize smoking cessation, blood pressure control, healthy diet, aspirin, blood lipid management, physical activity, weight management, diabetes management, and management of chronic atrial fibrillation [134]. All guidelines have emphasized lifestyle management, especially smoking cessation, physical activity, and healthy diet with caloric restriction in adults and the elderly [137], and its benefits were evident when implemented in adults [144]. Although evidence supports caloric restriction for healthy CV aging [145] prolonged longevity [146], this is not aggressively implemented. Ideally, primary prevention should begin in early childhood and include adults aged <40 years before the appearance of overt CV disease.

Role of Education in Prevention

Education is key in prevention. The HF prevention guideline emphasizes the value of physician education for increasing awareness [137]. The US education program for hypertension started in the 1970s was very successful [147]. A Canadian healthcare professional education program started in the mid-1970s increased the diagnosis and treatment of hypertension [148], reduced the gender gap in treatment [148], and encouraged more aggressive hypertension management in the elderly [149]. However, even with tight blood pressure control, hypertensive patients remained at increased risk for stroke and myocardial infarction due to undertreatment of other CV risk factors [150]. Education reinforcing comprehensive management of CV risk factors using risk scores and biomarkers is therefore needed.

Despite a worldwide decrease in systolic blood pressure through education and therapies since 1980, systolic blood pressure remains high among low-income and middle-income countries

[151], suggesting the need to target those groups via education programs and/or additional measures to decrease the global HF burden. Prevention guidelines have emphasized ethnic differences and higher prevalence of adverse CV risk factors, including smoking, sedentary lifestyle, and high saturated fat diets [137], suggesting that those groups also need to be targeted in education programs. In a Canadian study of HF hospitalizations, Chinese patients were older and had the highest rates of renal disease and higher 1-year mortality than white patients, whereas East Indian patients were youngest and had the highest rates of ischemic heart disease and diabetes and similar mortality as white patients [152]. Education can be a powerful tool for primary prevention. Simply providing understandable calorie information via posted signs to low-income black adolescents resulted in a decrease in purchases of sugar-containing beverages, thereby reducing calorie intake [153].

Conclusions

The elderly population is increasing worldwide and the burden of HF is greatest in the elderly. Morbidity and mortality from CVD and comorbidities in the elderly and related healthcare costs are increasing at an alarming pace. Several biological markers correlate with the aging phenotype and HF. Low telomerase activity and telomere shortening may be early markers of aging-related CVD and can be used to guide preventive strategies. It is important to appreciate that CV aging is a continuous lifelong and risky process because concomitant lifelong exposure to adverse CV risk factors throughout the process fuels the march to HF (Fig. 2.1).

There is urgent need for identifying new therapeutic targets through translational research for optimizing HF therapy in the elderly as well as delay and/or retard CV aging. Efforts need to be directed on promoting healthy aging and preventing development of CVDs that contribute to HF. Legislation is needed to reduce lifelong exposure to CV risk factors, including toxins and pollutants we inhale, ingest, or are exposed to from our external environment and transfer to our internal environment. For secondary prevention, more clinical trial data is needed to identify optimal HF therapies for different aging subgroups ranging from young adults to the elderly and very old based on the new advances in the pathobiology of aging-related HF and use of biomarkers of biological aging. Education programs should reinforce comprehensive management of CV risk factors using risk scores and biomarkers. For primary prevention, programs should target all age groups including children, adolescents and young adults, and older age groups. In its broadest sense, education programs should be aimed not only at physicians and healthcare personnel but also at the public of all age and ethnic groups, both genders, and teachers as well as children, adolescents, and young adults in schools and universities. Education can be a most powerful tool for both primary and secondary prevention. Strong emphasis should be placed on education from early childhood and adolescence about the role of exposure to adverse CV risk factors in the march to HF and how this can be halted and thereby promote healthy aging.

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3 Hypertension and Prevention of Diastolic Heart Failure in the Aging Population

Wilbert S. Aronow, Maciej Banach, and Ali Ahmed

Introduction

In older Americans, hypertension is the most important risk factor for cardiovascular disease (CVD) and is present in nearly two-thirds of patients with incident heart failure (HF) [1, 2]. In 5,143 persons in the Framingham Heart Study and Framingham Offspring Study followed for a mean duration of 14.1 years, hypertension was the most common risk factor for HF and accounted for 39 % of cases of HF in men and for 59 % of cases for HF in women [3]. In 2,562 community-dwelling older adults with hypertension in the Cardiovascular Health Study, presence of isolated systolic hypertension was associated with a significant 26 % ($p=0.016$) increase in risk incident HF [4]. Also, in the Cardiovascular Health Study, those with uncontrolled hypertension had a significant 39 % ($p=0.003$) increased risk of new-onset HF compared with those with controlled hypertension, which was more pronounced in those with a systolic blood pressure (BP) ≥160 mmHg (a significant 58 % higher risk; $p<0.0001$) [5]. This chapter will discuss hypertension and prevention of diastolic HF (DHF) or HF with preserved left ventricular (LV) ejection fraction (EF) in the aging population.

Data from Olmsted County suggest that the prevalence of mild and moderate to severe preclinical LV diastolic dysfunction was 21 % and 7 % in the general population and 48 % and 17 % in older adults with hypertension or coronary artery disease, respectively [6]. Data on pulse and tissue Doppler echocardiographic estimates of resting early (E) and atrial (A) transmitral peak inflow and early (Em) mitral annular velocities were collected from 89 community-dwelling older adults (mean age, 74; range, 65–93 years; 54 % women) in Birmingham, Alabama [7]. In that study, 47 % had cardiovascular morbidity, 37 % had hypertension, but none had HF at baseline, and 60 % had normal diastolic function (E/A 0.75–1.5 and E:Em < 10) [7]. Among those with LV diastolic dysfunction, 83 %, 14 %, and 3 % had grade I [E/A < 0.75, regardless of E/E(m)], II (E/A 0.75–1.5 and E/E(m) ≥ 10), and III (E/A > 1.5 and E/E(m) ≥ 10) diastolic dysfunction, respectively [7].

W.S. Aronow, MD (✉)
Department of Medicine, Westchester Medical Center/New York Medical College, Valhalla, NY, USA

Cardiology Division, New York Medical College, Macy Pavilion, Room 138, Valhalla, NY 10595, USA
e-mail: wsaronow@aol.com

M. Banach, MD, FAHA, FESC
Department of Hypertension, Medical University of Lodz, Lodz, Poland

A. Ahmed, MD, MPH
Department of Medicine, University of Alabama School of Medicine at Birmingham, Birmingham, AL, USA

Department of Medicine, Veterans Affairs Medical Center, Birmingham, AL, USA

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The prevalence of a normal LVEF associated with DHF increases with age and is higher in older women than in older men [8–10]. The prevalence of DHF in 572 older patients with HF was 37 % in men and 56 % in women [8], in 674 older patients with HF was 38 % in men and 57 % in women [9], in 73 older patients in the Framingham Heart Study was 51 % [10], in 269 older patients in the Cardiovascular Health Study was 63 % [11], and was 55 % in older community-dwelling adults in Olmstead County, Minnesota [12]. In 674 older patients with HF, hypertension was a significant independent risk factor for the development of HF with a risk ratio (RR) of 2.5 ($p=0.0001$) [9]. Hypertension is more common in patients with DHF than in patients with systolic HF or HF with low LVEF [8, 13].

Pathophysiology of Hypertension in Older Adults

An increase in systolic BP in elderly persons is related to an age-associated increase in arterial stiffness due to structural changes within the arterial media (a change in the amount or nature of collagen, interstitial fibrosis, and calcification, and degradation of elastin fibers) [14]. The increased wall stiffness and tortuosity of the aorta and large arteries with aging is often reflected by an increased systolic BP, widened pulse pressure, and decreased diastolic BP. In older adults, the presence of isolated diastolic hypotension is associated with an increase in the risk of incident HF by a significant 33 %, which is similar to the association with isolated systolic hypertension [4, 15]. Older persons with hypertension are more likely to have increased LV mass, increased peripheral resistance, reduced baroreceptor sensitivity, increased characteristic aortic impedance at rest, decreased LV early diastolic filling rate, decreased LV early diastolic filling volume, increased left atrial dimension, and decreased cardiovascular response to catecholamines [14].

Flow-mediated arterial dilation, primarily mediated by endothelium-derived nitric oxide, decreases markedly with aging [2]. The neurohormonal profile of older adults is characterized by increased plasma norepinephrine, low renin, and low aldosterone levels [2]. Many so-called normal aging changes in arterial structure and function are blunted or absent in populations not chronically exposed to high sodium/calorie diets, low physical activity levels, and high rates of obesity [2].

The reduction in baroreflex sensitivity with age and with hypertension leads to impaired baroreflex-mediated increase in total systemic vascular resistance and to an inability to increase heart rate in response to decreased BP [16]. Therefore, older persons with hypertension have a greater impairment in baroreflex sensitivity and are more likely to develop orthostatic and postprandial hypotension on antihypertensive drug therapy [17].

Hypertension in the elderly also increases the age-dependent decline in renal function. Of 143 older persons, mean age 73 years, with hypertension in an academic nursing home, 60 (42 %) had moderate (33 %) or severe (9 %) renal insufficiency with an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 [18]. Renal artery stenosis is also an important cause of secondary hypertension in the elderly [19].

The Framingham Heart Study showed that higher aortic stiffness, forward wave amplitude, and augmentation index examined over a 7-year period in 1,759 persons, mean age 60 years, were associated with a higher risk of incident hypertension [20]. This study has three clinical implications [20, 21]. First, lifestyle changes such as a low sodium diet, aerobic exercise, weight management, and treatment with statins may improve endothelial function and vascular stiffness and possibly prevent development of hypertension [21]. Second, noninvasive measures of vascular stiffness and endothelial dysfunction may be used to optimize therapeutic strategies to try to prevent hypertension [21]. Third, vascular stiffness should be targeted by drugs to try to prevent hypertension [21]. Prospective studies are needed to validate whether lifestyle measures plus drugs in persons with vascular stiffness, endothelial dysfunction, or both will prevent hypertension and reduce CV events [21, 22]. In hypertensive patients, DHF was associated with the inflammatory markers

interleukin (IL) 6, IL-8, and monocyte chemoattractant protein 1, with the fibrotic markers amino-terminal propeptide of collagen 3 and carboxy-terminal telopeptide of collagen 1, and the extracellular matrix turnover markers of matrix metalloproteinase (MMP) 2 and MMP9 [23]. These biomarkers need to be tested in a prospective study to investigate whether patients with asymptomatic hypertension and increased levels of these biomarkers are at increased risk for developing DHF.

Left Ventricular Diastolic Dysfunction

Numerous studies have demonstrated that hypertension is associated with LV diastolic dysfunction [24–36]. LV diastolic dysfunction is the first clinical manifestation of heart disease in patients with hypertension [24]. In the community, the prevalence of LV diastolic dysfunction is more common than LV systolic dysfunction. In the Olmsted County, overall prevalence of mild, moderate, and severe LV diastolic dysfunction was 21 %, 7 %, and 1 %, respectively, while that of systolic dysfunction (LVEF <40 %) was 2 % [6]. LV diastolic dysfunction leads more often to HF in patients with hypertension than does LV systolic dysfunction [24]. Patients with DHF have an exaggerated hypertensive response to exercise which can be partly suppressed by blocking angiotensin II [26]. LV relaxation was more prolonged in hypertensive DHF patients than in non-hypertensive DHF patients, partly because of the different loading sequence [27]. LV diastolic function is worse in hypertensive patients of African-Caribbean origin than in hypertensive patients in white Europeans [28]. Early BP control offers the greatest promise for reducing the incidence of DHF in patients with hypertension [29, 31–33]. High visit-to-visit variability of systolic BP was associated with LV diastolic dysfunction and may constitute a high risk for hypertensive patients to develop DHF [35]. In the Losartan Intervention For Endpoint reduction (LIFE) study, antihypertensive treatment in patients with electrocardiographic LV hypertrophy caused improvement in transmitral flow patterns [34]. A normal transmitral flow pattern in the LIFE study was associated with a 78 % less risk for HF ($p=0.048$) [34]. Of 3,336 older patients with hypertension seen in 107 clinics in Italy, 23 % had signs of HF [36]. Of 2,545 patients, mean age 70 years, with hypertension without HF in this study, 46 % had LV diastolic dysfunction [36].

Progression from Hypertension to Diastolic HF

Hypertension can progress to HF through different pathways [2, 37–39]. These include development of LV hypertrophy, impaired LV filling, and increased wall thickness [2]. DHF in the elderly is probably related to progressive fibrosis and myocardial stiffening associated with coronary artery disease, diabetes mellitus, and age plus LV hypertrophy caused by hypertension [2]. It has been suggested that pathogenesis of progression from hypertension to DHF may vary by sex, which may also explain the higher prevalence of DHF in women. Findings from animal models of chronic pressure overload that male rats are more prone to develop eccentric hypertrophy (LV dilation and modest wall thickening, with resultant increased wall stress and low LVEF), while female rats are more prone to develop concentric hypertrophy (increased LV wall thickness and normal chamber size, with normal or near-normal wall stress and LVEF) [40]. Findings from the Hypertension Genetic Epidemiology Network (HyperGEN) demonstrated that in humans, the deceleration time and the isovolumic relaxation time were longer in men than in women, suggesting that men had slower early diastolic LV filling than women [41].

Left Ventricular Hypertrophy

Patients with LV hypertrophy have an increase in size of the cardiomyocyte, alterations in the extracellular matrix with accumulation of fibrosis, and abnormalities of the intramyocardial

coronary vasculature, including medial hypertrophy and perivascular fibrosis [39]. Aging and hypertension-related aortic and conduit artery stiffening increase LV loading leading to LV hypertrophy [2]. Hypertensive LV hypertrophy is associated with cardiomyocyte hypertrophy and increased myocardial collagen [42]. Myocardial fibrosis and LV diastolic dysfunction precede development of LV hypertrophy in patients with hypertension [42].

LV hypertrophy is an increase in LV mass index [43]. Concentric LV hypertrophy is an increased LV mass index with a relative wall thickness ≥0.45 [43]. Eccentric LV hypertrophy is an increased LV mass index with a relative wall thickness <0.45 [43]. Concentric LV remodeling is a relative wall thickness ≥0.45 with a normal LV mass index [43]. Factors influencing LV geometry in hypertensive patients include (1) the severity, duration, and rapidity of onset of pressure load; (2) volume load; (3) age, race/ethnicity, and gender; (4) comorbidities coronary artery disease, diabetes mellitus, obesity, and valvular heart disease; (5) the neurohormonal milieu; (6) alterations of the extracellular matrix; and (7) genetic factors [39]. Increased afterload causes an increase in LV systolic stress and the addition of sarcomeres in parallel [44]. This results in increased LV wall thickness with a normal or decreased LV chamber size and an increased relative wall thickness. This pattern of LV hypertrophy is called concentric LV hypertrophy and is likely to develop in persons with LV pressure overload as in hypertension with increased systemic vascular resistance or in valvular aortic stenosis [44]. Increased preload causes an increase in LV diastolic stress and the addition of sarcomeres in series [37]. This results in an increase in the ratio of LV chamber size to wall thickness. This pattern of LV hypertrophy is called eccentric LV hypertrophy and is likely to develop in persons with LV volume overload as with obesity, aortic regurgitation, or mitral regurgitation [44].

In the Cardiovascular Health Study of the 1,871 community-dwelling adults, 65 years of age or older, without baseline HF, 59 % hypertensive, with data on baseline and 7-year echocardiograms, 343 (18 %) had concentric LV geometry at baseline (83 % had concentric remodeling and 17 % had concentric LV hypertrophy or LVH) [45]. After 7 years of follow-up, LV geometry normalized in 57 %, remained unchanged in 35 %, and transitioned to eccentric hypertrophy in 7 % of participants [45]. Incident eccentric hypertrophy occurred in 25 and 4 % of those with baseline LVH and concentric remodeling, and those with incident eccentric hypertrophy at year 7 also had higher LV end-diastolic volume and lower LVEF at year 7 [45].

In 84 African Americans, mean age 78 years, with hypertension and in 326 whites, mean age 82 years, with hypertension, echocardiographic LV hypertrophy was present in 71 % of hypertensive blacks versus 56 % of hypertensive whites ($p<0.02$) [43]. Electrocardiographic LV hypertrophy was present in 20 % of hypertensive blacks versus 15 % of hypertensive whites ($p=$ns) [43]. Concentric LV hypertrophy was present in 60 % of hypertensive blacks versus 40 % of hypertensive whites ($p<0.001$) [43]. Eccentric LV hypertrophy was present in 12 % of hypertensive blacks versus 17 % of hypertensive whites ($p=$ns) [43]. Among African Americans with hypertension, HF developed at 37-month follow-up in 48 % of those with echocardiographic LV hypertrophy versus 13 % of those with a normal LV mass index ($p<0.005$) [43]. Among hypertensive whites, HF developed at 43-month follow-up in 52 % of those with echocardiographic LV hypertrophy versus 15 % of those with a normal LV mass index ($p<0.005$) [43]. Using 15 variables in a multiple logistic regression model for the 410 older hypertensive patients, significant independent prognostic variables for development of HF were prior HF (odds ratio {OR} 41.31, $p<0.001$), concentric LV hypertrophy (OR 2.44, $p=0.018$), and echocardiographic LV hypertrophy (OR 2.57, $p=0.022$) [43].

LV hypertrophy in patients with hypertension is more closely related to BP during stressful situations than to basal BP [46]. In older persons in the Cardiovascular Health Study, LV hypertrophy was an independent predictor of incident HF not related to prevalent or incident myocardial infarction [47]. At 42-month follow-up of 2,638 patients, mean age 81 years, patients with persistent or new electrocardiographic LV hypertrophy

had a higher incidence of new HF and an earlier time to the development of HF than older persons without electrocardiographic LV hypertrophy ($p=0.001$) [48]. At 4.7-year follow-up in the LIFE study, regression of electrocardiographic LV hypertrophy was associated with a 36 % reduction of new HF ($p<0.001$) [49]. Lowering BP improved LV diastolic function irrespective of the type of antihypertensive drug used [50]. In the LIFE study, regression of electrocardiographic LV hypertrophy was associated with similar reductions in risk of new-onset HF in patients with systolic and diastolic hypertension or with isolated systolic hypertension [51]. Antihypertensive drugs such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, and alpha-methyldopa have been shown to reduce LV mass in hypertensive patients [44, 52]. A meta-analysis of 109 treatment studies showed that angiotensin-converting enzyme inhibitors were more effective than other antihypertensive drugs in reducing LV mass [53]. The alpha-adrenergic blocker trimazosin did not reduce LV mass after 18 months of treatment [54]. The direct-acting vasodilator minoxidil also did not reduce LCV mass after 6 months of treatment [55]. Future research needs to understand the mechanisms for progression of asymptomatic LV concentric hypertrophy to DHF and how to prevent this occurrence. Presently, this transition seems to be associated with progressive adverse remodeling of the extracellular matrix and increase in LV filling pressures [39].

Prevention of HF by Antihypertensive Drug Therapy in Older Adults

Large-scale, prospective, double-blind, placebo-controlled trials have demonstrated that antihypertensive drug therapy reduces the incidence of HF in elderly hypertensive patients [2, 56–58]. The European Working Party on High BP in the Elderly trial demonstrated in 840 patients with systolic plus diastolic hypertension, mean age 72 years, randomized to placebo or to hydrochlorothiazide plus triamterene plus methyldopa if needed that at 4.7-year follow-up, antihypertensive drug therapy reduced the incidence of HF by 63 % ($p=0.014$) [56]. The Systolic Hypertension in the Elderly Program (SHEP) demonstrated in 4,736 patients, mean age 72 years, with isolated systolic hypertension randomized to placebo or to chlorthalidone plus atenolol if needed that at 4.5-year follow-up, antihypertensive drug therapy reduced the incidence of HF by 49 % ($p<0.001$) (number needed to treat to prevent one HF event = 48) [57]. The Hypertension in the Very Elderly Trial (HYVET) demonstrated in 3,845 patients with a systolic BP of 160 mmHg or higher aged 80 years and older, mean age 83.6 years, randomized to placebo or to indapamide plus perindopril if needed that at 1.8-year median follow-up, antihypertensive drug therapy reduced the incidence of HF by 64 % ($p<0.001$) [58]. A meta-analysis of 147 randomized trials of use of blood pressure lowering drugs in the prevention of CVD in 464,000 patients with hypertension showed that diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers with cardioselective or alpha blocking properties, and calcium channel blockers all reduced development of HF in hypertensive patients [59]. Beta-blockers were the most effective antihypertensive drugs in preventing recurrent coronary events in patients with a history of coronary artery disease [59].

Although the optimal blood treatment goal in elderly patients with hypertension has not been determined, a therapeutic BP target of <140/90 mmHg in persons aged 65–79 years and a systolic BP of 140–145 mmHg if tolerated in persons aged 80 years and older is reasonable [2, 60–65]. We should also be careful to avoid intensive lowering of the BP in elderly persons, especially those with diabetes and coronary artery disease, as this might be poorly tolerated and might increase CV events (the J-curve phenomenon).

A propensity-matched study of 7,785 ambulatory patients, mean age 64 years, with mild to moderate HF showed that HF hospitalizations during 5-year follow-up in patients with a systolic BP of 120 mmHg or lower were increased by 21 % compared to those with a systolic BP higher than 120 mmHg ($p=0.002$) [66].

Diastolic HF

The progression of LV diastolic dysfunction plays a major role in the development of HF in persons with hypertension [67]. The prevalence of hypertension in patients with DHF varies between 55 and 88 % [68]. In 745 patients in the Irbesartan in HF With Preserved Ejection Fraction trial (I-PRESERVE), LV hypertrophy or concentric remodeling was present in 59 % of patients, left atrial enlargement in 66 % of patients, and LV diastolic dysfunction in 69 % of patients [69]. Multivariable analyses showed that increased LV mass, LV mass/LV volume ratio, and left atrial sized were independently associated with an increased risk of morbidity and mortality [69]. The great majority of patients with DHF have a normal LV diastolic volume supporting that progressive LV diastolic dysfunction predisposes to DHF [70, 71]. Patients with DHF have a higher prevalence of comorbidities including hypertension, anemia, obesity, renal dysfunction, and chronic obstructive pulmonary disease that may contribute to volume overload than patients with systolic HF [70, 72]. Patients with acute pulmonary edema associated with hypertension have a normal LV ejection fraction during the acute episode [73]. Patients with acute hypertensive pulmonary edema have worse ventricular-arterial coupling, estimated diastolic stiffness, and filling pressures than asymptomatic hypertensive patients [74]. Data suggesting that LV stiffness modulates cardiac function in DHF patients suggest that LV diastolic dysfunction with increased LV stiffness is a target for DHF therapy [75].

Prevention of Diastolic HF in Older Adults with Hypertension

Older adults with hypertension should be treated with antihypertensive drug therapy to reduce HF development [2, 76]. A therapeutic BP target of <140/90 mmHg in persons aged 65–79 years and a systolic BP of 140–145 mmHg if tolerated in persons aged 80 years and older is reasonable [60–65]. Elderly persons with hypertension should be treated with a low sodium diet [2, 77]. Lifestyle modification should be used in older persons to prevent mild hypertension and to reduce the dose levels of drugs needed to control hypertension. Weight reduction; consuming a diet rich in fruits, vegetables, and low-fat dairy products with a reduced amount of saturated fat and total fat; sodium reduction to not exceed 1.5 g daily; smoking cessation; regular aerobic physical activity; avoidance of excessive alcohol intake; avoidance of excessive caffeine; and avoidance of drugs which can increase BP, including nonsteroidal anti-inflammatory drugs, glucocorticoids, and sympathomimetics, are recommended [2]. Implementing a national salt reduction program is likely a simple and cost-effective way of improving public health [77, 78].

Dyslipidemia, myocardial ischemia, and comorbidities such as coronary artery disease, obesity, diabetes mellitus, chronic kidney disease, anemia, and atrial fibrillation should be treated [2, 76]. The ventricular rate should be controlled in patients with supraventricular tachyarrhythmias [2, 76]. Angiotensin-converting enzyme inhibitors should be used in patients with atherosclerotic vascular disease, diabetes mellitus, or hypertension [76]. Patients with asymptomatic LV systolic dysfunction should be treated with angiotensin-converting enzyme inhibitors and beta-blockers [76]. Valve replacement or repair should be considered in patients with severe valvular stenosis or regurgitation [76]. The prevalence of DHF in patients with unoperated severe aortic stenosis and HF was 30 of 48 patients (63 %) [79]. The prevalence of DHF in patients with unoperated severe aortic regurgitation and HF was 17 of 25 patients (68 %) [80]. Further research needs to be performed to try to prevent DHF from developing in elderly persons with hypertension.

Treatment of Diastolic HF in Elderly Patients with Hypertension

The treatment of DHF in elderly patients is discussed extensively elsewhere [81]. The primary cause of DHF should be searched for and treated. Precipitating causes of HF should be treated if

possible. Avoid using of inappropriate drugs which may precipitate HF such as nonsteroidal anti-inflammatory drugs. Hypertension must be adequately controlled and is the most important single treatment strategy for DHF. Daily sodium intake should be reduced to 1.5 g daily. Loop diuretics should be used cautiously. Myocardial ischemia should be treated with beta-blockers plus nitrates with calcium channel blockers added if needed. Coronary revascularization should be considered in patients with myocardial ischemia despite optimal medical management, especially in patients who have chest pain or flash pulmonary edema. Sinus rhythm should be maintained if possible. A rapid ventricular rate in patients with atrial fibrillation should be slowed by beta-blockers. Verapamil, diltiazem, and digoxin may also be used to slow the rapid ventricular rate. Comorbidities should be treated. An exercise training program improves exercise tolerance. In elderly patients with stable compensated DHF, peak arterial-venous oxygen difference was higher after exercise training and was the primary reason for improved peak VO_2 [82]. This suggests that peripheral mechanisms (improved microvascular and/or skeletal muscle function) contribute to improved exercise capacity after exercise training in patients with DHF [82].

Beta-blockers may be used in the treatment of patients with DHF who have a prior myocardial infarction, angina pectoris, myocardial ischemia, hypertension, complex ventricular arrhythmias, or supraventricular tachyarrhythmias. At 32-month follow-up of 158 patients, mean age 81 years, with prior myocardial infarction (67 % with hypertension) and DHF, patients randomized to propranolol treatment had by multivariate Cox regression analysis a 35 % reduction in mortality ($p=0.030$) and a 37 % reduction in mortality plus nonfatal myocardial infarction ($p=0.018$) [83]. At 1-year follow-up in this study, patients randomized to propranolol had a reduction in LV mass from 312 g to 278 g ($p=0.0001$) [83]. In the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With HF (SENIORS) of 2,111 patients, mean age 76 years, with systolic or DHF, nebivolol was equally effective in improving at 21-month follow-up the primary outcome of all-cause mortality or CV hospitalizations in patients with systolic HF or DHF [84].

Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may be used in the treatment of DHF in patients who have hypertension, atherosclerotic vascular disease, left ventricular hypertrophy, diabetes mellitus, or chronic kidney disease. At 3-month follow-up, older persons with HF due to prior myocardial infarction with normal LVEF treated with diuretics who were randomized to receive enalapril had significant improvements in New York Heart Association (NYHA) functional class, in treadmill exercise time, in LVEF, and in LV diastolic function assessed by Doppler echocardiography [85]. In addition, enalapril significantly reduced cardiothoracic ratio measured from chest x-rays and echocardiographic LV mass [85].

At 1-year follow-up of 850 patients, mean age 76 years, with DHF in the perindopril in elderly people with chronic HF (PEP-CHF) study, compared with double-blind placebo, patients randomized to treatment with perindopril had a 31 % reduction in all-cause mortality and unplanned HF-related hospitalization ($p=0.055$), a 33 % reduction in HF hospitalization ($p=0.033$), an improvement in NYHA functional class ($p<0.030$), and an improvement in 6-min corridor walk distance ($p=0.011$) [86]. In the Candesartan in HF: Assessment of Reduction in Mortality and Morbidity (CHARM) preserved study, 3,023 patients, mean age 67 years, with DHF were randomized to candesartan 32 mg daily or to placebo [87]. At 37-month median follow-up, candesartan insignificantly reduced CV death or HF hospitalization by 11 % but reduced hospitalization for HF by 16 % ($p=0.017$) [87]. However, at 49.5-month follow-up of 4,128 older patients with DHF compared to placebo, irbesartan 300 mg daily did not improve clinical outcomes [88]. Similar results were observed in a propensity-matched study of real-world DHF patients [89].

Aldosterone antagonists need investigation in the treatment of DHF because modulation of the renin-angiotensin-aldosterone pathway may affect fibroblast activity, interstitial fibrosis, intracellular calcium handling, and myocardial stiffness. In 202 patients with hypertension and

LV hypertrophy, at 9-month follow-up, eplerenone was as effective as enalapril in LV hypertrophy regression and BP control [90]. The combination of eplerenone plus enalapril was more effective in decreasing LV mass and systolic BP than eplerenone alone [90]. At 6-month follow-up of 44 patients with DHF and a history of hypertension, compared with placebo, patients randomized to eplerenone had a similar improvement in 6-min walking distance but a reduction in serum markers of collagen turnover (procollagen type 1 amino-terminal peptide, $p=0.009$, and carboxy-terminal telopeptide of collagen type 1, $p=0.026$) and improvement in echocardiographic measure of LV diastolic function (E/E′, $p=0.01$) [91]. Preliminary findings from a propensity-matched study of real-world older DHF patients suggest that aldosterone antagonists had no effect on clinical outcomes in these patients [92]. We are awaiting the clinical outcomes/results from the National Heart, Lung, and Blood Institute-funded study—Treatment Of Preserved Cardiac function HF with an Aldosterone anTagonist (TOPCAT)—in which 3,445 adults with DHF were randomized to spironolactone (target dose 30 mg daily) or placebo [93]. Novel agents reducing vascular and myocardial stiffness need to be investigated since the prevalence of DHF is increasing as our population increases in age.

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Aging and Optimal Therapy of Systolic Heart Failure in the Elderly

4

Nakul Chander Sharma and Bodh I. Jugdutt

Introduction

Aging is a biological process that affects everyone with the passage of time. Several factors affect the rate of cardiovascular aging such as genes, environment, healthcare facilities, and economics. Cardiovascular changes that occur during aging [1–4] may predispose elderly (age ≥65 years) people to diastolic and systolic dysfunction with heart failure (HF). In developed countries, the number of elderly people has been increasing and this trend is expected to continue [5, 6]. Concurrently, the number of elderly patients with systolic HF (SHF) and diastolic HF (DHF) is expected to increase [7–9]. This growth of cardiac systolic dysfunction in the elderly population has been driven primarily by an increasing incidence of coronary artery disease (CAD) and other major cardiovascular disease (CVD) risk factors such as hypertension (HTN), diabetes mellitus (DM), and dyslipidemia [7–12]. Although several management guidelines have been proposed for the use of a wide range of existing pharmacotherapies to optimize the treatment of systolic heart failure (SHF), none of them specifically address the elderly population, the impact of the aging process, or related issues [7, 9, 13–15]. In fact, the majority of therapeutic drugs for treating SHF were tested in younger population cohorts, without recognizing that the potential aging process may alter the response to several of them [13–16]. As cardiologists and other allied physicians will be seeing more and more elderly patients with SHF and/or DHF [17] in their practices and follow patients with CVD as they age, it is imperative that they have a clear understanding of the changes in physiology and pathophysiology that occur with aging and are prepared to adjust the existing medical therapies accordingly. This chapter addresses strategies for optimizing therapy of SHF in the elderly using existing and novel pharmacological agents.

N.C. Sharma, MD, FRCP (✉)
Division of Cardiology, Department of Medicine, Mazankowski Heart Institute, WMC 2C2 8440-112 Street, Edmonton, AB, Canada T6G 2B7
e-mail: ncsharma@ualberta.ca

B.I. Jugdutt, MD, MSc, DM, FRCPC
2C2 W.C. Mackenzie Health Sciences Centre, Division of Cardiology, Department of Medicine, Mazankowski Alberta Heart Institute, University of Alberta and Hospitals, 727, Todd Landing NW, Edmonton, AB, Canada T6G 2B7
e-mail: bjugdutt@ualberta.ca

Demographics and Epidemiology

The changing demographics and implications for therapy of HF in the elderly have been reviewed [10]. Heart failure in the elderly is a growing, global, healthcare problem. In the USA, the number of patients diagnosed with HF (SHF and DHF) is greater than six million [8], with the overall world incidence exceeding 23 million [7, 9]. The elderly population has been steadily

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increasing over the last 30 years [1]. Population studies in the USA, Europe, and other developed countries suggest that this trend will very likely continue [5, 6]. In the Framingham Study, Ho et al. showed that even two decades ago, the prevalence of HF was increasing in both men and women and suggested that this trend was likely to continue unabated with current medication regimens as the population aged further [18].

More recent population studies revealed that HF prevalence was approximately 8 per 1,000 in men and women and increased to a staggering 66/1,000 in men and 79/1,000 in women patients aged 80 years [7]. Of note, the majority of patients admitted with HF are elderly, and the increase in the number of hospitalizations in that population segment leads to higher levels of morbidity and mortality [8, 17]. Ultimately this trend will result in an increase in resource utilization and, if left unchecked, has the potential to cost taxpayers many billions of dollars [8, 19]. In the Heart Disease and Stroke Update of the American Heart Association (AHA), data from the National Health and Nutrition Examination Survey (NHANES) clearly showed that the increase in HF prevalence is age dependent and the prevalence is highest in elderly men and women [8]. Similar trends as in the USA [7] were found in Canada [20]. It is therefore imperative that new therapies and strategies (such as mechanical support, cardiac resynchronization therapy or CRT) and therapeutics (such as medications, exercise programs) be developed for this continuously increasing and higher risk population.

In addition, more clinical studies need to be carried out in the older population in order to find the best strategy for optimizing the therapy of SHF in the elderly using existing therapeutic drugs and algorithms developed for younger patients, something that has been slow to come about [18]. Furthermore, more translational research is needed to develop novel therapies specifically targeting the growing elderly population.

With respect to future studies for optimizing therapy, it is important to recognize that the aging process is progressive and the elderly population is fairly heterogeneous. The conventional socio-economic-driven threshold age of 65 years has little meaning in the context of an aging continuum [21]; it is also too low for developed countries that are already experiencing increased life expectancy of >85 years. Several studies have used 3 or more elderly subsets that may be more appropriate in efforts to optimize therapy [22–27].

Definitions

Since general practitioners, generalists, and geriatricians rather than cardiologists currently manage the majority of elderly patients with HF, it is important to have an understanding of the often-varied clinical presentations. In general, the definition of HF as a *clinical syndrome associated with heart dysfunction that results in failure to pump blood at a rate adequate to support metabolizing tissues* based on pathophysiology still applies in the elderly. The terminology in the guidelines of the AHA/American College of Cardiology (ACC) [7] and the European Society of Cardiology (ESC) [9] based on symptoms as outlined in the New York Heart Association (NYHA) classification provides a sound reference base. Acute HF refers to sudden onset of pulmonary edema as in acute myocardial infarction, while chronic HF refers to the presence of signs and symptoms for some time. Congestive HF refers to presence of congestion due to salt and water retention and may be acute or chronic. Most clinical trials of SHF select patients based on the objective evaluation of the left ventricular (LV) ejection fraction (EF) by radionuclide or echocardiographic techniques and enrolled those with EF ≤35 %. More recent trials enrolled patients with DHF and EF >40–45 % or >50 %; these patients represent a group without major systolic dysfunction. Thus, patients with EF between 35 % and 50 % are considered to be in a *grey zone* with mild systolic dysfunction. Cardiogenic shock generally refers to SHF patients characterized by severe hypotension and hypoperfusion, low blood pressure (systolic <90 mmHg), oliguria (due to renal failure), and circulatory failure with cold extremities, mental confusion, weakness, and fatigue.

Pathophysiological Considerations

There are three key factors that may explain the increasing incidence/prevalence of HF in the elderly population: (1) prolonged exposure to risk factors for CVD, (2) aging-related cardiovascular changes, and (3) comorbidities in the aging population that impact the cardiovascular system and therapy.

Prolonged Exposure to CVD Risk Factors

The effects of aging on the cardiovascular system predispose the elderly to the development of congestive HF. The prevalence of risk factors of CVD that increase with age (such as HTN, CAD, dyslipidemia, DM) is likely the antecedent cause of congestive HF in this subpopulation [8]. Several trials have shown that the prevalence of congestive HF in octogenarians can be as high as 1 in 10. The two most common risk factors in the elderly population are HTN and CAD, as high as 80 %, and both of these conditions are on the rise [8]. In general, patients with HTN tend to develop concentric LV hypertrophy and remodeling and HF with preserved systolic function (HFPSF) or preserved EF (HFPEF) [11]. On the other hand, patients with predominant CAD and/or previous histories of myocardial infarction develop HF with predominantly reduced systolic function (HFRSF) or reduced EF (HFREF) and likely some diastolic dysfunction and dilative LV remodeling with eccentric hypertrophy [11].

Several studies suggest that advanced age may be an independent predictor of poor outcome in patients with acute [28, 29] and chronic [30] HF. As individuals age, the likelihood of patients having a combination of both pathophysiologies increases and generally results in a mixed picture when assessing LV systolic/diastolic function and hemodynamics in the elderly [11].

Despite knowledge of the underlying cardiovascular pathophysiology among most physicians, it has become quite clear that with regard to the treatment of HF in the elderly, the use of mortality-benefiting medications such as beta-blockers (BBs), angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and aldosterone or mineralocorticoid receptor antagonists (MRAs) were less when looking at the recent EuroHeart Failure Survey II conducted in 2009 [16]. In that study, the average age of the elderly group was 83.7 years compared to 68.4 years in the younger cohort [16]. This trend of underutilization of evidence-based medications among physicians may be related in part to awareness of underrepresentation of elderly patients in major HF trials as well as the unique issues of tolerance to medications and compliance.

Aging-Related Cardiovascular Changes

Hearts of elderly HF patients show special pathophysiological features that may result in more complex morbidity profiles. Biological changes that are independent of conventional CVD risk factors occur with aging [1–4, 11, 12, 31]. Increasing knowledge of the biology of aging [11, 12, 31] and aging-related changes in cardiovascular structure and function [1–4] suggest that aging predisposes the heart to CV disease including HF. Evidence indicates that aging is a continuous biological process, and the progressive structural, physiological, and biochemical changes in the aging heart can negatively impact cardiac function and contribute to HF [11, 12, 31]. It is reasonable to hypothesize that targeting these aging-related changes might prevent HF.

With progression of aging, increased collagen deposition and collagen cross-linking in the arterial walls coupled with degradation of elastin fibers over time produces stiffness that may be essentially irreversible. This pathology, as one can predict, results in a slow rise in blood pressure (hence HTN) over time and negatively affect the heart by increasing the afterload it has to overcome [32].

Fibrosis is a hallmark of cardiovascular aging. The aging heart develops increased collagen deposition in the myocardial interstitium with

fibrosis and myocyte hypertrophy associated with increased afterload and myocardial oxygen demand. The end result is aging-related apoptosis and necrosis [32–34]. Myocyte loss and dysfunction have been well documented in aging hearts [35, 36], and this is one major mechanism for DHF (also called HFPSF or HFPEF). In addition, myocardial fibrosis associated with aging and comorbidities (such as HTN and CAD) itself is another mechanism for diastolic dysfunction and DHF [37]. Several studies have shown that elderly patients develop DHF or HFPEF [26, 38, 39], which has been reported in as many as 53 % [40]. Fibrosis in the aging heart has been linked to increased angiotensin II and reactive oxygen species (ROS), an upregulated renin–angiotensin–aldosterone system (RAAS), and enhanced inflammation [41, 42].

Aging-Related Cellular and Subcellular Changes

Aging leads to a host of defects at cellular and subcellular levels, which collectively negatively impact systolic and diastolic function in the elderly [43–45]. Aging leads to a lack of β-adrenergic receptor (β-AR) signaling and response to stimuli, and this ultimately results in reduced contractility [41]. This pathology is also associated with impaired β2-mediated peripheral arterial vasodilation [43, 44]. Diminished adenosine triphosphate (ATP) production in response to cardiac demand and inefficient utilization lead to impaired contractility in the aging heart [43, 44]. Aging-related deficits in β-AR signaling, increased generation of ROS, altered excitation–contraction (EC) coupling, and altered sarcoplasmic reticulum (SR) Ca^{2+} cycling (i.e., uptake, storage, release) contribute to systolic and diastolic dysfunction [44]. Depressed Ca^{2+} pump ATPase (SERCA2a) in the aging heart contributes to dysfunction [45]. Aging also results in changes in contractile proteins themselves [3]. An association between telomere shortening, a marker of biological aging, and HF has also been documented [36, 46].

Aging also negatively affects endothelial function and its role in vasodilation. This results in diminished peak coronary flow and likely accelerated atherosclerosis [1–4, 47]. Both of these effects (i.e., decreased vascular reserve and coronary flow) are known to accelerate the onset of HF especially in the elderly population with systolic dysfunction [4, 47, 48].

Clinical Implications of Aging-Related Changes

In the elderly patient, it is important to understand the contribution of the multiple pathophysiological pathways to SHF before making a concerted effort to treat it effectively. Not only are common CVD risk factors more prevalent in the elderly but the progressive changes that occur during aging makes treating the elderly population more difficult and complex. An example is with the use of beta-blockers. As described above, its use is ubiquitous in the HF population, but, as we know, aging can cause a lack of cardiac contractility through poor β-2 adrenergic responsiveness [43]. This suggests that there is a potential for more harm in the elderly as currently used drugs may amplify the preexisting pathophysiology. This conundrum is seen again in this population when treating hypertension and its relation to SHF. Whereas arterial stiffness in the elderly can be overcome with the use of ACEIs and ARBs, we have come to learn that its treatment does not necessarily improve mortality when looked at as a primary outcome [47].

Comorbidities

Population studies have established the role of genetic, environmental, and lifestyle factors in the development of HTN, CAD, and HF [5–8]. Lifelong exposure to CVD risk factors can lead to pathophysiological alterations that contribute to HF [11, 21] and end-organ damage [49]. In this context, interactions among CVD risk factors, comorbidities (such as type 2 diabetes, metabolic

syndrome, and obesity), and the aging cardiovascular system can act in concert and lead to progression of vascular disease and contribute in the march to HF [21]. For example, several CV risk factors that lead to HTN can in turn interact with other risk factors and comorbidities, resulting in complications and end-organ pathologies, including stroke, myocardial infarction, HF, and renal failure [49]. Not surprisingly, the risk of HF increases steeply in the presence of antecedent HTN and myocardial infarction [8]. In a population study that spanned two decades (1975–1995), the risk of myocardial infarction increased progressively across three elderly subgroups: the younger elderly aged 65–74 years, the older elderly aged 75–84 years, and the very elderly aged >85 years [22]. In the INTERHEART study that ranked potentially modifiable CVD risk factors for myocardial infarction in five age groups ranging from younger adults to the older elderly (<45, 46–55, 56–65, 66–70, and >70 years), a similar trend was found [23].

Whereas increased myocardial and vascular stiffness usually lead to HF with preserved contractility and EF (HFPEF), precipitating factors (such as ischemia, hypertension, tachycardia) may lead to increased end-diastolic pressure and acute (flash) pulmonary edema. HFPEF in the elderly is typically associated with LV hypertrophy, left atrial dilatation, and hypertrophy, and can progress over time to dilative LV remodeling and dysfunction [49]. Atrial fibrillation often precipitates HF in the elderly [50]. Of note, elderly patients hospitalized with acute HF usually have HFPEF with higher EF and are usually female [16, 25, 27].

Aging-Related Changes in Other Organ Systems

Besides cardiovascular changes with aging, changes in other organ systems can contribute to the suboptimal treatment of elderly patients with SHF and underutilization of recommended therapies (Table 4.1). Orthostatic/postural changes as a result of poor autonomic function limit the titration and even the use of certain medications; this is especially the case with therapeutic drugs that lower blood pressure, reduce afterload, and/or decrease heart rate, thereby reducing cardiac output and leading to symptoms [18]. Changes in the renal system, including reduction in glomerular filtration rate (GFR) secondary to poor cardiac function [51], can lead to reduced clearance of medications and increased drug levels. Reduced gastrointestinal absorption and hepatic conversion can also affect the pharmacodynamics and pharmacokinetics of widely used cardiovascular medications such as amiodarone, digoxin, and calcium channel blockers [16].

Table 4.1 Common issues that occur when treating elderly patients with systolic heart failure

Issue	Complicating factor
Hepatic	Decreased metabolism results in low bioavailability of medications and potential side effects
Renal	Ineffective clearance and toxic buildup of drug metabolites
Polypharmacy	Increased number of medications resulting in more side effects
Mobility	More pronounced effect on vasodilator tone—especially with nitrates
Eye sight	Difficulty in adjusting medications on their own—more risk for over/underdosing
Cognitive impairment	Decreases judgment, increased confusion, and risk for delirium
Frailty	Increased side effects from medications (i.e., anticoagulation, BBs, and ACEI)

Other comorbidities in the hemopoietic and pulmonary systems, such as anemia and pulmonary disease, have been shown to be intimately tied to the increasing prevalence of HF in the elderly [52–54]. Pulmonary disease with elevated LV filling pressure and/or use of potential pulmonary toxic medications (such as amiodarone) can lead to increased hospitalizations for worsening HF symptoms and thereby increasing the overall morbidity/mortality [55]. Approximately 40 % of HF patients have associated anemia likely due to chronic disease, but if not they should be treated similarly to patients without HF. The presence of anemia increases the overall morbidity/mortality [54]. Cognitive decline, which also increases with age, may decrease compliance,

follow-up, and therefore effectiveness of the desired medical therapy [56]. It has been shown that overall, elderly patients respond less effectively to ACEIs [56], inotropic agents [57], and diuretics when compared to the younger populations. As mentioned before, underrepresentation of elderly patients in most clinical trials may have been driven by fear of noncompliance and/or worse outcomes.

Current Management of Systolic Heart Failure and Caveats

In the absence of evidence-based data from randomized clinical trials conducted in the elderly population, current recommendations represent extrapolations from data on therapeutic drugs tested in mostly non-elderly patients. As a result, the current treatment of SHF in the elderly patient is largely the same as that for the younger population. The rationale for this approach is that the overall goals of therapy in both groups are similar with respect to maintaining and/or improving systolic function. The goals of treatment include medication titration and compliance, relief of symptoms, both acute and chronic, and reduction in morbidity (i.e., hospitalizations) and mortality if and when possible [52, 58]. Risk factors need to be managed and controlled according to management guidelines [7, 9, 13, 14]. Restriction of fluid (<1.5 L/day) and salt (<2 g/day) is essential. Education is the cornerstone of treatment in the HF patient, and weight management through the use of home diuretics should be taught and enforced. Exercise is imperative, but patients should be counseled through a physiotherapist before proceeding.

It is possible to optimize therapy of SHF in elderly patients through the establishment of HF clinics with specialized multidisciplinary management teams for seeing and following elderly patients [59]. The management team may include cardiologists, geriatricians, internists, generalists, nursing practitioners, pharmacists, social workers, physical therapists, psychologists, and case managers.

Pharmacotherapy

In this pragmatic approach, all patients with SHF should be treated with ACEIs or ARBs, BBs, and aldosterone/MRA antagonists given their mortality benefit, with digoxin, diuretics, and other vasodilators being reserved for control and improvement of symptoms. Elderly patients can thus derive the benefits of existing therapies while awaiting results of future trials focusing on elderly subsets and development of specific drug therapies for the elderly.

Angiotensin Converting Enzyme Inhibitors

Any patient with/without symptomatic HF and an LV systolic dysfunction with EF <40 % should be on an ACEI, as recommended by the ACC/AHA/ESC [7, 9, 13, 14] and Canadian Cardiovascular Society (CCS) [60] guidelines. Their use is essential as they confer a morbidity benefit (decreased hospitalization) and mortality benefit [61]. In the elderly with HF, the use of ACEI can sometimes be difficult as this group of patients tends to experience symptoms to a greater degree than younger patients [11]. In view of this, orthostatic hypotension seems to be the limiting factor in titrating ACEIs as most elderly patients with LV ejection fraction between 10 and 15 % are prone to this, especially as they generally have some degree of autonomic dysfunction due to other comorbidities [15]. Decreasing the dose of the diuretic and occasionally using fluids to improve preload can be tried to allow the elderly patient to tolerate ACEIs better [7]. Other strategies include staggering the doses or using them before bedtime, as ACEIs are better tolerated when patients are supine [7]. The rationale is that these strategies allow an otherwise undertreated population to derive mortality and morbidity benefits they might not see otherwise.

As renal function tends to decrease with aging, a real risk of renal under-perfusion exists with the

use of ACEI therapy. A modest proportion of patients with markedly reduced LV systolic function (ejection fraction <15 %) may experience a rise in their creatinine of >0.3 mg/dL [62]. Other risk factors more prevalent in the elderly are renal artery stenosis, the concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDS) and other renal toxic medications [61]. When using NSAIDS, the renal function should be monitored very carefully especially in the elderly [7]. Additional attention to ACEI dose is warranted when higher than average dose of diuretics is used in patients with refractory fluid retention [7]. This is because intravascular dehydration and eventual renal under-perfusion can cause exacerbated rises in creatinine, forcing a treating physician to either reduce the dose of ACEI or stop it altogether, thereby negating any previous benefit derived from the ACEI. Hyperkalemia (serum potassium level >5.5 mmol/L) is another known side effect. The potassium level should be monitored carefully especially in elderly patients with abnormal renal function [7]. When initiating ACEI therapy, creatinine and electrolytes should be checked within 2 weeks.

There are two other uncommon drug side effects that are seen with ACEI therapy and should be noted as alternative medications can be used. First, a dry nonproductive cough that develops upon initiation of an ACEI generally impairs the patient's quality of life, and switching to an ARB can be helpful. It is seen in <10 % of Caucasians and some reports suggest as high as 50 % in oriental descent [63]. Second, angioedema is a potential life-threatening side effect that occurs in <1 % [63] of patients on ACEIs, and substituting the ACEI for an ARB should be done very cautiously in this case, if not using a totally different class of medication [7].

In theory, all ACEIs should be titrated to the target therapeutic dose as outlined in the respective clinical trials. Unfortunately, 80 % of elderly patients are underdosed, leading to less benefit and likely more potential hospitalizations [64]. If target doses cannot be achieved, then the highest possible dose tolerable should be utilized [7]. As to efficacy of different ACEIs, the effect on mortality and morbidity appears to be a class effect [7]. The biggest concern is that most elderly patients are excluded from treatment because of the high prevalence of comorbidities. However, evidence suggests that there is still a mortality benefit in these patients. One such population is that with moderate to severe aortic stenosis. Other populations include those with modest elevation of serum potassium levels and depressed renal clearance [65].

In summary, elderly patients should not be denied the mortality benefit derived from this class of medication. However, an understanding of the interplay between the physiology/pharmacodynamics in the elderly and a slightly different side effect profile compared to younger patients will likely improve its use and titration to target doses. Additionally, elderly patients with other comorbidities should also be looked at in the same light as even low-dose therapy has its benefits.

Angiotensin Receptor Blockers

There are fewer trials with ARBs than with ACEIs; however, the ACC/AHA/ESC recommends their use in patients intolerant to ACEI therapy [7]. In the CHARM-Alternative trial, mortality benefit was achieved in patients who could not tolerate the prescribed ACEI and were switched to the ARB candesartan [66]. The same benefit was seen in the Val-HeFT (Valsartan Heart Failure Trial), suggesting a class effect of the drugs [67]. Besides symptoms, there are no specific contraindications (similar to those with ACEIs) to the use of ARB therapy, which should be used whenever ACEI therapy is not tolerated.

Aldosterone Antagonists

Once the patient is stable on an ACEI and/or a BB therapy, the ACC/AHA/ESC guidelines suggest that an aldosterone antagonist (spironolactone or eplerenone) should be added in those with depressed LV systolic function (ejection

fraction <30 %) provided their electrolytes (potassium in particular) and creatinine can be carefully monitored [7, 9]. This is irrespective of chronological age. In the RALES trial (Randomized Aldactone Evaluation Study), patients with stable NYHA class 3 HF were enrolled whose median age was 67 years [68]. Two other trials [69, 70] that looked specifically at the use of an aldosterone antagonist in HF patients were EMPHASIS-HF (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms) and EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study). The mean ages of enrolment were 69 and 64 years, respectively. Both trials showed significant mortality and morbidity benefits in patients with LV systolic dysfunction and even in those with only mild symptoms, indicating that in stable patients on effective ACEI and BB therapy (unless contraindicated) that aldosterone antagonist should be added unless the renal function and/or electrolytes are prohibitive [69, 70].

When using this class of medication, one must be aware of the fact that in the elderly patient there is potential for more side effects as renal perfusion is generally lower and the risk of hyperkalemia is markedly increased when the patient is already on high-doses ACEI or ARB. The ACC/AHA/ESC recommends that creatinine and electrolytes be checked one week after initiation, then monthly for the first 3 months, and then every 3 months, with reinitiation of the schedule whenever medical therapy changes [7]. Although the elderly population was not looked at specifically, it can be extrapolated that the benefit is clear and when tolerated should be initiated in the elderly under the guidance of an HF clinic.

Beta-Blockers

The use of BBs is mandated through the ACC/AHA/ESC guidelines, which suggest that every patient with depressed LV systolic function should be on this form of therapy unless there are contraindications. There are three BBs, namely, bisoprolol, carvedilol, and sustained release (CR) metoprolol, that have been found to be effective in the treatment of HF in the elderly [71]. In a meta-analysis of over 12,000 patients, no difference was found in the derived benefit between elderly and non-elderly patients with respect to mortality or morbidity. The reduction in mortality is quite clear regardless of age. In the SENIORS trial (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with HF) and the MERIT-HF trial (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure), patients aged >70 years compared with a younger cohort did not show any statistical difference in mortality, confirming the importance of BB therapy in the elderly [72, 73]. The same effect was seen in patients aged >75 years [73].

The use of BBs is contraindicated in patients with severe decompensated HF (low cardio output), inotropic dependence, and complete or high-grade heart block. Interestingly the use of nonselective BB therapy in patients with well-controlled chronic obstructive lung disease showed a mortality benefit regardless of age suggesting that BB therapy can be applied to patients with reactive airway disease provided it is not severe and is well controlled [74]. Potential side effects of BB therapy include bradycardia and possible hypotension, which predisposes the elderly to more falls and potentially other sequelae [15]. A more common side effect is fatigue, which generally improves with time. However, when the patient is either taking sleeping medications or has other comorbidities (anemia, osteoarthritis, polymyalgia rheumatica, etc.), differentiating the cause of fatigue can be difficult. Therapy should be titrated carefully as the potential for hypotension exists to a greater degree in the elderly. The use of adequate volume can minimize this but needs to be balanced with the fluid status of the patient and should be stopped if there is evidence of hypoperfusion [9]. Additionally when patients already on BB therapy are admitted to hospital with HF, evidence suggests that there is an increased risk of mortality if the BB is stopped. Instead, the BB should be

continued at the same dose or the dose cut by half rather than discontinuing it altogether [9].

In patients with sinus rhythm, LV ejection fraction <35 %, heart rate >70 bpm, and NYHA class 2–4 symptoms, the use of ivabradine has been shown to decrease hospitalization for HF. This is irrespective of whether the patient is already on evidence-based treatment with a BB. The latest review at the ESC also concluded that there is evidence to support starting ivabradine in patients who are intolerant to BBs, with a view to decrease morbidity. As per the SHIFT trial, this effect was seen in patients >65 years of age [9, 75].

Diuretics

It is recommended that the patients adhere to a strict salt restricted diet (<2 g/day) and make use of judicious amounts of diuretics [7]. Loop diuretics are very good at helping the kidney to excrete free water even when the creatinine clearance is markedly reduced [60]. The combination of thiazide diuretics and loop diuretics has a synergistic effect and can be an effective combination when dealing with patients who are fluid overloaded [76]. There are no long-term trials to date to indicate that diuretics have any mortality benefit [15]. When using diuretics, one must be cognizant of the fact that with too low a dose, the effectiveness of ACEI is limited due to fluid retention and poor renal perfusion; in contrast, with too high a dose, adequate ACEI may not be possible due to postural hypotension and intolerance to the medication [76]. One must also monitor electrolytes and creatinine very carefully when administering diuretics especially in the elderly [7]. Recently the new diuretic, tolvaptan, a selective V_2 vasopressin antagonist, has been studied in the SALT-1 and SALT-2 trials and has been shown to improve hyponatremia and symptoms (based on the SF-12) when compared to placebo. The average age in both of these trials was 62 years. The benefit in the elderly still needs to be worked out [9, 77].

Vasodilators: Nitrates/Hydralazine/Nesiritide

Vasodilators

These agents are one of the mainstay therapy tools for acute exacerbation or chronic therapy of systolic HF, especially if patients cannot tolerate ARBs or ACEI. Additionally the ACC/AHA recommends that the use of vasodilators is reasonable in patients with persistent symptoms of HF and at maximal therapy with BB and ACEI or ARBs [7]. It may also be considered in patients with hyperkalemia and/or intolerance to ACEIs. In patients of African descent, the addition of vasodilators (nitrates and hydralazine) instead of ACEIs is beneficial [7, 78].

Vasodilators can affect both sides of the circulation, the venous and arteriolar. By affecting the arteriolar side of the circulation, vasodilators decrease the vascular resistance against which the left ventricle has to pump against, leading to a better cardiac output. This in turn helps in reducing the LV size and systolic pressure, thereby reducing the myocardial oxygen demand. An unexpected overdrop in the arterial pressure can be detrimental. However, this is less likely with somewhat abnormal LV systolic function. On the other hand, venodilators cause venous pooling and thereby a drop in venous blood pressure. It is important to normalize preload in an HF patient and thus improve the cardiac output. This is particularly beneficial in ischemia-driven HF. The decrease in preload helps in decreasing ventricular size as well as wall stress, thereby improving myocardial oxygenation/utilization. Headache, hypotension/dizziness, and nausea were the most common side effects. Hence, hypotension is a contraindication to the administration of vasodilators.

Most of the vasodilators affect both the arteriolar side and the venous side with different degrees of effectiveness. Some agents are selectively venodilators (i.e., organic nitrates). Currently available vasodilators cause vasodilatation by increasing intracellular cGMP.

Organic Nitrates

The organic nitrates are one of the oldest agents available for acute HF. These are predominant venodilators that help in treatment of pulmonary edema. Their rapid effect helps decrease pulmonary venous and ventricular filling pressures. This results in improvement of symptoms (dyspnea) and signs (pulmonary congestion) of acute HF. Organic nitrates can also be arteriolar vasodilator at higher doses. They improve blood flow in the epicardial coronaries—rather than intramyocardial coronaries—due to their selective nature [79]. This is important in patients with active myocardial ischemia leading to HF or vice versa. Availability of oral, sublingual, or spray formulation helps in administration of such agents in patients without peripheral access in the emergency department. Treatment can be started sooner than later [7]. The initial starting dose for intravenous nitrates (or nitroglycerin) is 20 mcg/min, with fast uptitration possible in as early as 5 min. The goal of therapy is the relief of symptoms or a drop in mean blood pressure by 10 mmHg, while keeping systolic blood pressure above 100 mmHg. If the systolic blood pressure drops under 100 mmHg, the dose of infusion should be cut in half or the infusion even discontinued if symptomatic hypotension develops [80]. The use of nitrates in the elderly is less clear as it has not been studied extensively in this population [15].

Organic nitrates are proven to improve exercise capacity as well as ventricular function when administered with hydralazine in patients with decompensated HF irrespective of age. These agents also reduce hospital admission rates for worsening heart failure. Majority of the evidence comes from V-HeFT-I [81] and A-HeFT [78]. In the former study, 1,600 men were either given placebo, prazosin, or hydralazine with isosorbide dinitrate [81]. Over 2 years of follow-up, there was evidence of increased exercise tolerance as well as improvement of LV ejection fraction when compared to placebo. A trend towards reduction of all-cause mortality was also noticed. In the later study, more than 1,000 African-American with advanced heart failure (NYHA III–IV) were randomized to placebo or nitrates with hydralazine [78]. This patient population was on better medical therapy including diuretics, digoxin, ACEI, BBs, aldosterone antagonists, and ARBs. After follow-up of 10 months, this study was stopped due to significant mortality reduction. However, improvement of quality of life and drop in hospitalization risk were also noted [78]. The mean age of the patients in that study was 56.7 ± 12.7 years.

Sodium Nitroprusside

Sodium nitroprusside is most effective in hypertensive acute HF. It has a half-life of a few minutes. That makes it an ideal agent for hypertensive emergencies as well as moderate to severe aortic/mitral insufficiency cases presenting with acute HF. A prodrug, nitroprusside is metabolized to nitric oxide and cyanide. It is a potent vasodilator with immediate action, hence the usage in hypertensive patients. It can be discontinued abruptly without tapering down and with little risk of rebound hypertension. Despite its strong properties, it is not used commonly (1 % in patients with acute HF) [15]. This may be due to the requirement of invasive blood pressure monitoring via an arterial line as well as its vasodilatory effect on intramyocardial coronaries resulting in "steal phenomenon," inducing myocardial ischemia [15].

Side effects of sodium nitroprusside include nausea, dysphoria, and abdominal discomfort. These are related to cyanide metabolites. Cyanide poisoning potentially can occur if more than 1.5 mg/kg is administered over a few hours or more than 4 μg/kg a minute for more than 12 h. An exposure of more than 2 days may also expose patients to cyanide poisoning. In case of such an event, the treatment is intravenous sodium thiosulfate [15].

Nesiritide

Nesiritide is a recombinant human brain natriuretic peptide (BNP) that is a strong vasodilator (both veno- and arteriolar vasodilator), producing significant drop in venous and LV filling pressures. This in turn improves the clinical

features of HF (relief of shortness of breath and some increase in cardiac output). It also has natriuretic and diuretic effects primarily mediated via the natriuretic peptide receptor A on the vascular smooth muscle, endothelium, kidneys, and adrenals. However, this "natriuretic" effect is not a substitute for diuretic agents in acute HF [82].

Nesiritide has no direct inotropic effect. When administered intravenously, its effect is seen within minutes. It is reserved mostly for patients with decompensated HF and symptoms on minimal exertion or at rest (NYHA III–IV). It reduces preload by reducing the pulmonary capillary wedge pressure and right atrial pressure almost immediately. It also improves cardiac output by reducing afterload. Its effectiveness is similar to nitrates—but lower than dobutamine—for 6-month mortality. It causes fewer headaches than nitrates. Hypotension is a contraindication for nesiritide usage. Unfortunately it did not have a mortality benefit but did improve symptoms. The mean age of enrolment was 67 years, and therefore the trial results can be applied to the elderly population.

Inotropes

The use of digoxin after careful titration of BB, ACEI, and diuretic therapy is supported by the ACC/AHA [7]. Unfortunately despite a great enrolment in the only trial looking at digoxin (the DIG trial), which included 27 % of patients over the age of 70 years, there was no mortality benefit [83]. However, there was a decrease in hospitalizations. Generally, it is recommended that patients who tolerate digoxin remain on them, as discontinuation leads to more ER visits [7]. The use of digoxin is limited in the elderly by its narrow therapeutic window and its many drug interactions [15]. The starting dose in the elderly with normal renal function is 0.125 mg daily or every other day with target levels of digoxin being 0.5–1.0 ng/L [15]. Levels greater than 1 ng/L are associated with greater risk of toxicity and mortality from hyperkalemia [83]. Signs of digoxin toxicity include visual disturbances, nausea, emesis, and arrhythmias of which should be monitored very carefully especially in the elderly. To be safe, when starting digoxin in the elderly patient who is already on medications known to interact with digoxin (amiodarone, verapamil, quinidine, etc.), doses should be reduced and drug levels monitored more closely along with clinical review [7].

As a general rule inotropic medications have not been used for any length of time because of the risk of increased mortality [84]. This includes both phosphodiesterase inhibitors and other inotropic medications such as dopamine, dobutamine, and alpha-agonists [84]. Even with oral forms, the recommendation is not to use them long term [84]. These medications can be used in refractory HF cases as a method of improving cardiac output to improve diuresis or in palliative cases [7]. The only other area of use is in patients who are considered cardiac transplant candidates and cannot leave the hospital on conventional oral therapy [7]. Another option is for outpatient inotropic support, much like dialysis; however, this method is very resource intensive [85].

Anticoagulation

In general, HF patients with depressed LV systolic heart function are at an increased risk of thromboembolism from the left ventricle. Warfarin and aspirin are often given to these patients. However, until the WARCEF [86] and WATCH [87] trials, they had not been compared to each other in a randomized fashion. One should keep in mind that patients with atrial fibrillation were excluded as they already have a primary indication for anticoagulation [9, 86].

WARCEF enrolled 2,305 patients from 176 sites in 11 countries with an LVEF of less than 35 % in sinus rhythm. This double-blind trial studied the results of warfarin treatment with a target INR of 2–3.5 versus aspirin given as 325 mg daily [9, 86]. As expected, the number of ischemic strokes was reduced (0.72 events versus 1.36 events per 100 patient-years; HR 0.52,

95 % CI 0.33–0.82; $p=0.005$), but was offset by the increased risk of major bleeding (0.27 and 0.22 events per 100 patient-years, respectively; $p=0.82$) [86]. Based on this data, there is no concrete evidence to suggest that patients with systolic dysfunction in sinus rhythm benefit from anticoagulation unless there is another primary indication such as ischemia, previous stroke, and atrial fibrillation [86].

Device Therapy

The ACC/AHA/ESC recommends the use of ICDs (implantable cardioverter-defibrillators) in all patients with a low systolic function (LVEF <35 %) 40 days post myocardial infarction and in individuals with a low EF and NYHA 2 to 3 symptoms and expectant life span greater than a year [9, 88]. The use of ICDs is also indicated in patients with cardiac arrest or sustained ventricular tachycardia [88]. The use of ICD therapy in those aged >80 years has also been verified, indicating that age should not be a restriction to their implantation [89]. In elderly patients with a widened QRS (>120 ms), CRT should be considered [88]. Several studies have confirmed the reduction of morbidity with CRT; however, recently, the use of CRT on top of ICDs has been shown to reduce all-cause and specifically cardiovascular death. This was illustrated in the RAFT (Resynchronization–Defibrillation for Ambulatory Heart Failure Trial), which had a mean age of enrolment of 66 years [90].

Mechanical support and cardiac transplantation are therapies rarely considered in the elderly. The current culture suggests that patients over 65 years of age should not be considered for cardiac transplant; however, there have been small center trials which have shown good outcomes in those aged >70 years when controlled for comorbidities [91]. In a large Scientific Registry of Transplant Recipients, the 10-year survival after transplantation for patients aged >65 years was 44.4 % versus 57.2 % for those recipients aged 35 to 47 years [91]. This has led to increasing numbers of elderly patients being considered for mechanical support. There is both short-term and long-term mechanical support (ventricular assist device or VAD). They may also be implanted in the left and right side. In elderly patients, it may be used for bridge to decision, bridge to recovery, bridge to destination, or bridge to possible transplantation. In patients aged >70 years, the *HeartMate 2* VAD has shown good overall functional recovery, survival, and quality of life at 2 years, and thus advanced age should not be used as an independent contraindication when selecting a patient for VAD [92, 93].

Diastolic Heart Failure

Specific therapy for diastolic dysfunction is lacking. Fibrosis is a major cause of diastolic dysfunction in the elderly. As the RAAS inhibitors are powerful antifibrotic agents, elderly patients may benefit from them [41]. Several experimental studies suggested that dual inhibition of ACE and neural endopeptidase (NEP) pathways in a single molecule such as omapatrilat (OMA) may provide added benefits in that regard for SHF after myocardial infarction and DHF in HTN. However, despite the superior antihypertensive efficacy of OMA over ACEI [94] and equal anti-remodeling efficacy in HF patients [95], the Food and Drug Administration (FDA) bureau did not approve OMA for patients with hypertension because of angioedema. Recently, the concept of dual-action molecules was revived with LCZ696, which combines neprilysin (NEP) and the angiotensin receptor blocker valsartan; this has been shown to be beneficial in HFPEF patients [96] and is being evaluated in HFREF patients [96, 97].

Other Issues

A significant knowledge gap exists with regard to the treatment of SHF as well as DHF in the elderly. Evidence-based treatments are lacking

due to underrepresentation in randomized clinical trials. While several HF trials focused on the elderly [98–102], more knowledge and studies are needed. Most trials systematically excluded the elderly. There is marked heterogeneity in the elderly population. Many elderly HF patients have different clinical profiles and atypical symptoms. The prognostic significance of low EF has been questioned as many elderly patients have HFPEF. Symptoms such as dyspnea are often nonspecific. Real issues such as cognitive impairment, dementia, frailty, reduced mobility, and osteoarthritis affect compliance. Multiple comorbidities, aging-related effects on multiple organs, altered pharmacokinetics and pharmacodynamics, and polypharmacy complicate management. As elderly HF patients tend to be seen and followed by general practitioners with limited access to resources rather than cardiologists and specialized teams, HF management may be suboptimal with poor adherence to guidelines and poor use of diagnostic tests to guide management.

Conclusion

In the elderly population, there is little randomized trial data that has looked at efficacy and safety in the elderly population with LV SHF. With a few exceptions, most of the guidelines for the elderly come from extrapolation of data from existing trials and community registries (Table 4.2). There have been advances in the field of mechanical support and CRT/ICDs, which are very promising. It is also quite clear that the elderly benefit equally from HF therapies in comparison to their younger cohort, but that they are not treated to effect due to many reasons (renal disease, orthostatic hypotension, drug interactions, and lack of knowledge of the physiology in the elderly). The hope is that, with an increasing elderly population, more evidence-based research can be conducted to help treat this cohort to the same degree as the younger population has already been.

Table 4.2 Therapy for systolic heart failure in the elderly compared to younger patients

Therapy	Specific recommendations in the elderly population
ACE inhibitors/ARBs	No difference than in younger patients—concern with renal disease/postural hypotension
Ivabradine[a]	Concern with symptomatic bradycardia—more pronounced in the elderly
Beta blockers	No difference than in younger patients—concern with postural hypotension/reactive airway disease and symptomatic bradycardia
Aldosterone antagonists	No difference than in younger patients—concern over renal disease and hyperkalemia
Tolvaptan[a]	Need to watch sodium level carefully in the elderly
Diuretics	No difference than in younger patient
Vasodilators	More likely to have postural hypotension in elderly
IV inotropes	Not recommended for long-term use
Digoxin	No difference than in younger patients
ICD/CRT	No difference than in younger patients
Transplant	Unlikely to be a transplant candidate—few small centers have done transplants in patients aged >70 y with limited success
VAD	Need to evaluate comorbidities more stringently

[a]Newer agents

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Atrial Fibrillation and Heart Failure in the Aging Population

5

Pedram Kazemian and Bodh I. Jugdutt

Epidemiology

Atrial fibrillation (AF) is considered a disease of the elderly with cardiovascular conditions, among which heart failure (HF) is a primary comorbid condition (Table 5.1) [1]. The median age of patients with AF was 75 years in pre-1995 studies [2]. The prevalence of AF in the USA is more than 2.2 million, with approximately 70 % of patients being aged between 65 and 85 years [2]. In parallel with the expected increase in the number of Americans aged >65, the number of individuals with AF is projected to exceed 12 million by 2050 [3–5]. Combining the major epidemiological studies of AF, the point prevalence of AF increases dramatically from less than 0.1 % in those younger than 40 to 6.8–12 % in those older than 75 years [5–11]. Given that about 25 % of cases of AF are asymptomatic and many cases of paroxysmal AF were not detected in these studies, the prevalence of AF is likely underestimated [12]. Similar to prevalence, the incidence of AF increases with age, doubling with every decade after age 50 [13]. Aging and HF are independent predictors of AF progression and are incorporated into the HATCH score (HTN, Age > 75, History of TIA/Stroke, COPD, CHF) for prediction of AF progression [14].

Pathophysiology

The exact explanation for increased prevalence of AF in the elderly is unknown (Fig. 5.1). Conditions that predispose to AF (such as hypertension, HF and ischemic heart disease) are more prevalent in the elderly, partly because aging involves longer exposure to those factors. However, in the Framingham study, the incidence of AF doubled with each decade of age independent of the increased prevalence of known predisposing conditions [13], suggesting that the aging process itself might predispose to the development of AF. Thus, aging deleteriously affects atrial tissue through atrial dilation due to decreased left ventricular (LV) compliance, dilation of the pulmonary veins, fibrosis of atrial tissue, gradual loss of nodal fibres and accumulation of genetic mutations in atrial mitochondrial DNA [15–18]. Importantly, aging-related abnormal changes in atrial electrophysiologic measurements such as prolonged and fractionated electrograms are detectable in patients with paroxysmal AF [19].

P. Kazemian, MD, MSc (✉)
Department of Cardiac Electrophysiology, Brigham and Women's Hospital/Harvard,
65 Jefferson St, Suite 5, Newton, MA 02458, USA
e-mail: pedram.kazemian@utoronto.ca

B.I. Jugdutt, MD, MSc, DM, FRCPC
2C2 W.C. Mackenzie Health Sciences Centre,
Division of Cardiology, Department of Medicine,
Mazankowski Alberta Heart Institute,
University of Alberta and Hospitals, 727, Todd Landing NW, Edmonton, AB, Canada T6G 2B7
e-mail: bjugdutt@ualberta.ca

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Table 5.1 Demographic and comorbid conditions associated with AF in large cross-sectional studies

Study	West of Australia [8]	PAFTA [10]	ATRIA [6]	Olmstad [5]	Rotterdam [11]
Year	1989	1999	2001	2006	2006
Number of patients	1,770	729	4,618	4,618	6,808
Age (years)	72.1[a]	74.8	71.2	73.1	69.2
Age and AF frequency (%)	<60 (n/a)	n/a	n/a	<55 (0.62)[b]	
	60–64 (1.7)[c]	n/a	n/a	55–64 (4.34)	55–64 (1.9)[b]
	65–69 (3)	n/a	n/a	65–74 (12.91)	65–74 (8.8)
	70–74 (7)	n/a	n/a	75–84 (24.5)	75–84 (18.6)
	≥75 (11.6)	n/a	n/a	≥85 (39.7)	≥85(20.8)
Systemic hypertension (%)	11.5	42.6[d]	49.3	80	21.4
History of CHF (%)	n/a	n/a	29.2	28.7[e]	2.5
Stroke (%)	n/a	11.8[f]	8.9	9.5	n/a
History of CAD (%)	18.3[g]	11.5[g]	34.6	38	12.8[g]
Diabetes mellitus (%)	n/a	16.5	17.1	18	10.5
Dyslipidemia (%)	n/a	24[h]	n/a	37	n/a
Smoking (%)	28	10	n/a	13	22.8
Valvular heart disease (%)	n/a	n/a	4.9	24	n/a
Hyperthyroidism (%)	n/a	5.4	n/a	1	n/a

n/a not available, *AF* atrial fibrillation, *CAD* coronary artery disease, *CHD* congestive heart failure, *TIA* transient ischemic attack. Prevalence of comorbidities is estimated from available data for individuals between 50 and 89 years

[a] Estimated from available data

[b] Incidence per 1,000 person year

[c] Percentage of patients with AF in the studied population

[d] BP > 160/95 mmHg

[e] Prior or concurrent CHF

[f] Previous stroke and TIA

[g] History of myocardial infarction

[h] Total cholesterol >6.5 mmol/L

AF, Stroke and Aging

There is a clear association between AF and increased mortality, although a causal relationship has not yet been established [20]. AF in the elderly is also associated with more complications such as stroke and HF. AF independently increases the risk of ischemic stroke by fourfold to fivefold [7]. The risk of stroke attributable to all cardiovascular risk factors decreases with age except for AF, for which the attributable risk of stroke increases from 1.5 % for those aged 50–59 years to 23.5 % for those aged 80–89 years [7]. Strokes associated with AF tend to recur and be more severe and fatal than non-AF strokes [21].

The traditional view of thromboembolism in AF that involves embolization of clot formed during relative stagnation of blood in fibrillating atrium cannot adequately explain the spectrum of clinical observations from the very low risk of stroke in patients with lone AF and occurrence of strokes in patients with brief episodes of subclinical AF to the large number of cases of clinical AF and stroke without the presence of atrial arrhythmia at the time or prior to their strokes.

Subclinical AF is implicated in 25 % of strokes of unknown cause [22]. New subclinical AF occurs in 10 % of patients (≥65 with hypertension) within only 3 months of follow-up and is associated with ischemic stroke (HR = 2.52; CI 1.25–5.08) [23]. Moreover, the analysis of TRENDS study has shown that of patients with AF who had stroke or systemic embolism 45 and 70 % did not have any AT (atrial tachycardia)/AF

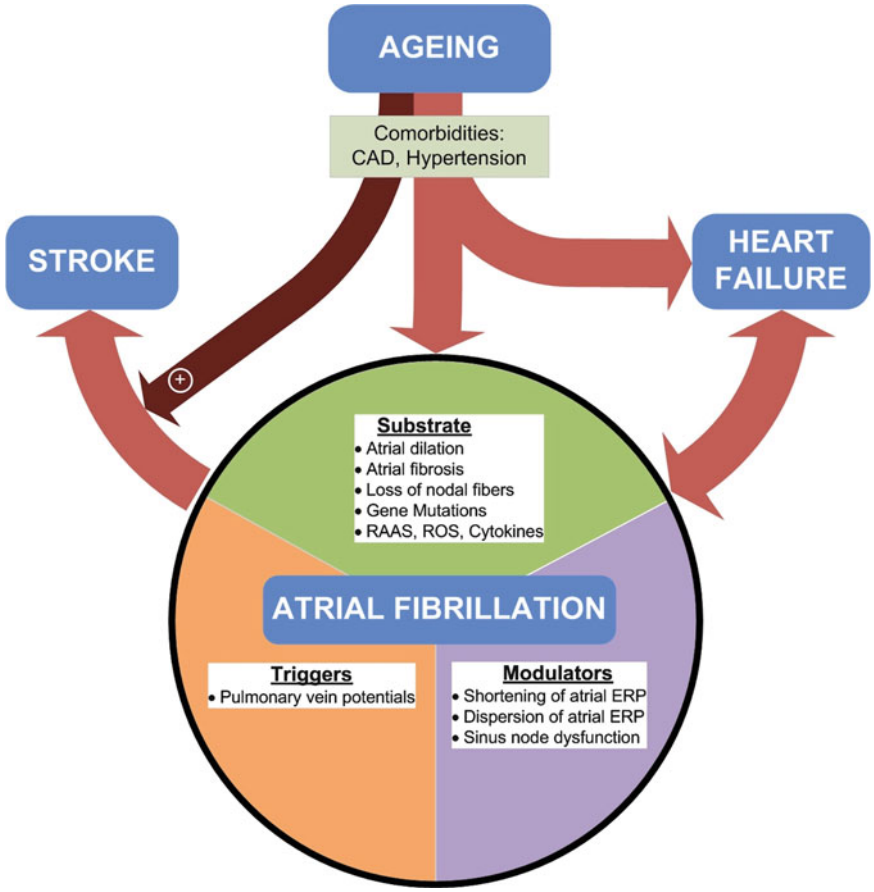

Fig. 5.1 Schematic showing pathophysiology of AF with aging. Aging is associated with progression of processes that are involved in the pathogenesis of AF. These include triggers, modulators and substrates of AF. Aging is also associated with increased prevalence of comorbid conditions such as HF that contribute to these processes. Aging is considered a major risk factor for cardioembolic stroke in patients with AF. *IHD* ischemic heart disease, *CHF* congestive heart failure, *ERP* effective refractory period, *PV* pulmonary vein

episodes within 30 days prior to and at the time of their event, respectively [24]. Therefore, AF, along with other known risk factors of stroke such as those summarized in CHADS2VASc, is likely a marker of a more fundamental mechanism for thromboembolic stroke such as endothelial dysfunction, hypercoagulability and inflammation. This may explain why restoration of sinus rhythm by pharmacological or ablation methods has not eliminated the risk of stroke in AF patients.

Recent data also suggest that AF is independently associated with all forms of dementias [25]. The mechanism of this relationship is not entirely clear and is very difficult to ascertain due to the significant overlap between risk factors for dementia and AF. Hypothesized mechanisms by which AF may cause dementia include embolic strokes (including silent recurrent embolic strokes) [26], reduced cerebral blood flow [27] and systemic inflammation [28].

AF, Heart Failure and Aging

One of the most important comorbid conditions associated with AF is congestive HF, which has the highest burden in the elderly [29]. Evidence suggests that HF begets AF and AF begets HF (Fig. 5.1).

The prevalence of AF increases from 5 to 50 % as the severity of HF increases from New York Heart Association (NYHA) classes I–IV, and coexistence of AF portends higher mortality in HF patients regardless of the severity of symptoms [30–32].

From a pathopysiological perspective, AF adversely affects HF through multiple mechanisms. First, loss of atrial contribution to ventricular filling (the so-called atrial kick) and irregular and often rapid heart rate result in decreased and irregular ventricular filling [33, 34]. The loss of "atrial kick" results in 20–30 % decline in stroke volume in normal subjects and even greater decrease in HF patients [33, 34]. The combination of rapid and irregular heart rate in AF represents double jeopardy in the elderly heart that is already burdened by increased angiotensin II, reactive oxygen species (ROS) and fibrosis [35]. Even in HF patients aged <65, the onset of AF results in clinical and hemodynamic deterioration and heralds a poorer prognosis while reversible AF predicts chronic AF [36].

Second, evidence suggests that persistently rapid AF leads to HF through mechanisms similar to those with tachycardia-induced HF [37–42]. Thus, rapid ventricular pacing has been shown to result in the up-regulation of neurohormones, cytokines, extracellular matrix (ECM) proteolytic and fibrosis pathways [37–42]. In dog models of HF induced by rapid right ventricular pacing, several markers of HF (i.e. norepinephrine, renin, aldosterone and atrial natriuretic peptides) increased before development of symptoms and normalized after cessation of pacing [37–39]. In patients with rapid AF or supraventricular tachycardia without HF, levels of natriuretic peptides also rose during tachycardia and declined thereafter [43]. Although restoration of sinus rhythm in dogs with rapid AF and HF is associated with improvement [44], recovery is rarely complete [45]. In the dog model of AF, Nattel's group showed that conversion to sinus rhythm restores electrical remodeling, but structural abnormalities and vulnerability to AF persist [46]. Thus, HF from ventricular tachypacing in dogs is associated with atrial fibrosis [46, 47] and electrical remodeling with slow conduction [47]; however, the electrical remodelling is quite different from that associated with HF secondary to rapid atrial pacing [47–49]. Atrial tachypacing with controlled ventricular rate also increases atrial ECM [49, 50], suggesting that increased atrial ECM promotes AF [49] and rapid AF promotes atrial fibrosis [50]. The mechanism for AF-induced fibrosis appears to be linked to increased angiotensin II-dependent signalling and antagonistic regulation between angiotensin-converting enzyme (ACE) and ACE2 [50]. Moreover, HF due to ventricular tachypacing in dogs was shown to increase atrial angiotensin II and MAPK and alter signalling that contributes to arrhythmogenic atrial remodeling, and these changes are attenuated by ACE inhibition [51]. However, data on aging animals is lacking.

Diastolic HF or heart failure with preserved ejection fraction (HF-PEF) [52] accounts for more than 53 % of cases of HF in individuals over 65 years [53]. Myocardial fibrosis and pathological hypertrophy associated with aging and comorbid conditions (i.e. hypertension, coronary artery disease) result in increased myocardial stiffness that leads to diastolic dysfunction and diastolic HF [54]. Recently, tachycardia was shown to induce diastolic dysfunction associated with increased LV mass, left atrial volumes, increased calcium loads and resting tone in patients with normal ejection fraction. Left atrial enlargement which parallels the development of diastolic dysfunction [55] results in atrial structural and electrical remodeling that involves stretching of the left atrium and pulmonary veins, shortening of the atrial refractory period and neurohormonal dysregulation that initiate and maintain AF (Fig. 5.1).

In addition, aging-related increase in angiotensin II, oxidative stress and inflammation can contribute to AF via atrial fibrosis as well as through ventricular fibrosis and diastolic dysfunction [56–58]. Accordingly, pharmacological strategies for prevention of AF, the so-called upstream therapies, with agents that target the renin-angiotensin system (RAS), inflammation, oxidative injury and atrial fibrosis such as ACE inhibitors, angiotensin type 1 receptor blockers (ARBs), statins and polyunsaturated fatty acids (PUFAs), have attracted attention.

ACE inhibitors, which have previously been shown to decrease collagen synthesis and fibrosis

after myocardial infarction as well as myocardial overload hypertrophy [59, 60], can also decrease atrial fibrosis [61]. Multiple meta-analyses of >80,000 patients enrolled in randomized controlled trials have demonstrated that RAS inhibition with ACE inhibitors or ARBs is effective in prevention of AF (Relative Risk Reduction ≈ 50–60 %) and the greatest benefit is achieved in those with HF [61–63]. However, the available studies are heterogeneous with regard to the outcomes of interest and patient population, and more definitive trials are underway to address this question. The largest evidence for RAS inhibition in AF is in primary prevention, and it seems that once atrial fibrosis and remodelling is established, their effect is limited in secondary prevention of AF.

Statins could prevent AF by exerting their pleiotropic anti-inflammatory effect especially in cases of AF that are associated with increased ROS and inflammation such as seen with aging and postoperatively [64, 65]. Currently, contradictory clinical evidence exists for the role of statins in reducing the recurrence of AF [66, 67], but four randomized clinical trials are underway to address this question [68].

PUFAs are ubiquitously found in cell membranes and known to alter membrane fluidity [69], modulate ion channels and have anti-inflammatory that could prevent AF [69]. However, the results of clinical studies on the effect of PUFAs for primary and secondary prevention of AF have been conflicting, and a major clinical trial was negative [70].

Pharmacological Treatment of AF in the Elderly

Strategies for treatment of AF include cardioversion and long-term pharmacotherapy for maintenance of sinus rhythm, rate control and anticoagulation. These treatments often need to be modified to accommodate special needs, preferences and coexisting medical conditions of elderly patients.

One major treatment decision is the choice between rate and rhythm control. Six major trials have attempted to clarify the optimal treatment strategy in AF patients (mean age 61–70 years) [71–79]. Whereas AFFIRM and HOT CAFE trials hinted at a benefit of the rate control over the rhythm control strategy, STAF showed an opposite trend, and PIAF and RACE showed no difference. A meta-analysis of the first five trials found no differences in all-cause mortality and incidence of ischemic strokes between the rate and rhythm control strategies [80]. This apparent lack of mortality benefit with the rhythm control strategy was likely due to the suboptimal efficacy in maintaining sinus rhythm and the extensive side effect profile of antiarrhythmic drugs (AADs). The AF–congestive heart failure (CHF) and CAFE-II trials showed that even in the HF population, rhythm control does not confer a mortality benefit over rate control, even when only those who were successfully maintained in sinus rhythm were included [78, 79, 81]. However, CAFE-II demonstrated that rhythm control could improve quality of life and LV function compared with rate control alone in patients with AF and HF, especially those who were successfully maintained in sinus rhythm [81].

Given these results, a predominant view in treatment of AF, including in the elderly and in those with HF, is to use the rate control strategy for the majority of patients who have no or minor symptoms and to reserve the rhythm control strategy for those who have significant symptoms and have failed rate control or catheter-based ablation (CBA) therapies.

Antiarrhythmic Medications for AF in the Elderly

The choice of AADs is of paramount importance in the elderly patient who requires consideration of their comorbidities, such as coexisting structural heart disease, HF, varying degrees of renal and hepatic failure as well as drug interactions with other commonly used drugs.

Class IA Antiarrhythmic Drugs

Quinidine, as a prototype of class IA AADs, has been shown to maintain sinus rhythm after cardioversion in about 50 % of patients with AF at 1 year but has been associated with increased

mortality (OR ≈ 3) [82] especially in patients with HF (RR = 4.7) [83]. Because of increased mortality and arrhythmogenicity associated with class IA AADs, most notably torsades de pointes; today, it is rarely used in clinical practice. However, the Prevention of Atrial Fibrillation after Cardioversion Trial (PAFAC) and the Suppression of Paroxysmal Atrial Tachyarrhythmias Trial (SOPAT) examined the efficiency of a fixed-dose combination of quinidine and verapamil in patients with AF in comparison with sotalol and found that the combination of quinidine and verapamil was as effective as sotalol in maintaining sinus rhythm without increasing the risk of torsades de point [84, 85].

Class 1C Antiarrhythmic Drugs

Flecainide and propafenone have similar efficacy in maintaining sinus rhythm in up to 68 % of patients at 6 months [86, 87]. The main concern with class 1C drugs is the observed increase in mortality in patients after myocardial infarction as observed in the Cardiac Arrhythmia Suppression Trial (CAST) [88, 89]. A review of data from CAST I and II trials showed that older age is an independent predictor of adverse events, including death, with a relative risk of 1.30 per decade of age with this group of AADs [90]. Accordingly, the use of class 1C drugs is limited to patients with structurally normal hearts.

Class III Antiarrhythmic Drugs

Amiodarone, which has been shown to be effective and safe in HF, after bypass surgery, in post-myocardial infarction patients and elderly [91–94] is more efficient in maintaining sinus rhythm than sotalol and propafenone [92]. However, amiodarone is associated with potentially dangerous adverse effects that are mostly dose dependent, and some appear to be more common in elderly patients. Thus, there is an increased risk of bradycardia requiring a permanent pacemaker after amiodarone therapy in elderly patients with AF [95]. Nonetheless, low-dose amiodarone is safe and organ-specific side effects happen in less than 5 % of patients after 1 year [96]. Given the fact that many elderly patients would require only very low doses of amiodarone (e.g. ≤200 mg/day) for control of their AF, the risk of developing significant side effects is relatively small.

Sotalol is also effective for maintenance of sinus rhythm in patients with AF but is associated with unacceptably high rate of torsades de pointes in patients with HF (5.0 versus 1.7 % without HF) and is therefore not recommended by the ACC/AHA guidelines [97, 98]. Elderly women in particular have a greater risk of QT prolongation after exposure to sotalol (OR = 3) [99–101].

Other class III AADs are ibutilide and dofetilide. The main concern with ibutilide, which is only used for cardioversion, and dofetilide is the increased incidence of ventricular tachycardia of up to 8 % during acute administration [102, 103]. However, chronic administration of dofetilide in patients with AF and HF has been shown to be safe and effective [104].

New AADs and the Elderly with AF

Dronedarone for the treatment of AF received FDA (Federal Drugs Administration) approval in July of 2009. It is pharmacologically related to amiodarone with the important exception that it lacks the iodine moiety associated with thyroid and pulmonary side effects [105]. It has a shorter half-life of 13–19 h (compared with 30 to 55 days for amiodarone), which allows achievement of steady-state plasma concentration in only 4–8 days [106]. Dronedarone increases digoxin levels by 1.7- to 2.5-fold but does not alter the INR when administered concomitantly with Coumadin [107]. It also inhibits renal excretion of creatinine without affecting the glomerular filtration rate [107]. Five major placebo-controlled randomized clinical trials have assessed the safety and efficacy of dronedarone in controlling AF [108–111]. EURIDIS (European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm) and ADONIS (American–Australian–African Trial

with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm) trials showed that dronedarone was effective in preventing the recurrence of AF compared to placebo (64.1 versus 75.2 %) in relatively young patients (mean age 63 years) without HF [108]. ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease) and ATHENA (Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter) assessed the primary end point of mortality and hospitalization in patients treated with dronedarone or placebo [109, 110]. ANDROMEDA enrolled patients with severe HF and median age of 71.5 years; it was prematurely terminated because of excess mortality and hospitalization that was mostly related to the worsening of HF in the dronedarone arm [109]. ATHENA enrolled high-risk patients with AF including those older than 71.6 years but excluded patients with severe HF such as those with NYHA class IV or recent decompensated HF [110]. Only 12 % of patients had an LVEF <45 %, and dronedarone significantly reduced the risk of hospitalization due to cardiovascular events or death in patients with AF or flutter compared to placebo (31.9 versus 39.4 %) [110]. The DIONYSOS (Efficacy and Safety of Dronedarone versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation) trial enrolled patients with mean age 64 years and excluded those with severe HF (NYHA classes III and IV) [111]. During the 7-month follow-up period, the recurrence rate of AF in dronedarone group was higher than amiodarone group (63.5 versus 42 %), but dronedarone was associated with lower rates of neurologic, skin, ocular and thyroid side effects [111]. The DIONYSOS trial included patients with mean age 64, and 18.8 % of patients were older than 75; however, those with severe HF (NYHA III/IV) were excluded [111].

From a pharmacologic perspective, the major side effects of dronedarone include bradycardia, QT prolongation with reported cases of torsades de pointes and liver toxicity [110] although cases of acute liver failure requiring transplantation have also been reported [http://www.fda.gov/drugs/drugsafety/ucm240011.htm]. In the PALLAS (Permanent Atrial fibriLLAtion Outcome Study Using Dronedarone on Top of Standard Therapy) trial, dronedarone was associated with increased rates of HF, stroke and death from cardiovascular causes in patients with permanent AF and at least one other cardiovascular disease risk factor (HR = 2.3) [112].

Considering the available evidence, three conclusions can be reached about the therapeutic role of dronedarone: (1) Dronedarone is more effective than placebo in reducing the recurrence of AF and the incidence of hospitalization in patients with non-permanent AF. (2) Dronedarone is less effective than amiodarone and likely also flecainide, propafenone and sotalol in reducing the risk of AF recurrence but is associated with less side effects and withdrawal rate. (3) Dronedarone is associated with increased mortality in patients with severe HF or permanent AF. The 2011 ACCF/AHA/HRS focused update on the management of AF suggested dronedarone as a first-line therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent AF except those with hypertension and substantial LV hypertrophy (LVH) or with HF [113].

Efficacy and Safety of AADs in the Elderly

The physiologic changes associated with aging, concomitant diseases and drug interactions affect the pharmacodynamics and pharmacokinetics of AADs. Sotalol, dofetilide and procainamide are primarily excreted renally. Given the higher prevalence of renal dysfunction in the elderly population, either these medications should be avoided or their dosages adjusted according to the degree of renal dysfunction [114]. Amiodarone is a lipophilic drug that is distributed into adipose tissue. Because of the age-related increase in body fat, amiodarone has a larger volume of distribution, lower clearance and prolonged elimination

half-life in the elderly [115]. There are several important drug interactions involving amiodarone and warfarin, digoxin or quinidine, especially in the context of AF in the elderly, increasing their plasma levels and potential for toxicity. Amiodarone augments the anticoagulant effect of warfarin requiring a reduction in warfarin dose [116]. Serum digoxin concentration is elevated in the elderly, due to decreased total body water and muscle mass and increased total body fat. There is also a decline in renal elimination of digoxin due to age-related decline in the glomerular filtration rate that results in an increase in its half-life [114]. Digoxin levels are also increased due to concomitant use of other commonly prescribed drugs in the elderly such as verapamil, warfarin, diuretics and quinidine [117].

Anticoagulation in AF and the Elderly

AF is associated with increased risk of stroke especially in elderly patients, which is independent of the increased prevalence of other stroke risk factors in this age group [7, 118]. The risk of stroke increases by age in a continuous manner (Relative Risk = 1.4 % for every decade) [119, 120]. Congestive HF, hypertension, age >75 years, diabetes and prior cerebral ischemia which were previously identified as independent risk factors for stroke have been incorporated into the CHADS2 stroke risk index formula [118, 121, 122]. The CHADS2 score stratifies patients with AF into low-, intermediate- and high-risk groups for stroke, which correspond to 1.9, 2.8 % and more than 4 % adjusted annual stroke rate, respectively [122]. The relatively high risk of stroke in the so-called intermediate risk category creates difficulty in deciding the need for anticoagulation in this group of patients. Furthermore, it fails to incorporate other validated risk factors for stroke in AF patients such as female gender and age between 65 and 75 years [123, 124].

A new validated scoring system based on the Euro Heart Survey on Atrial Fibrillation, known as CHADS2VASc, incorporated new stroke risk factors, namely, vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque), age (between 65 and 74) and sex category (i.e. female gender). It further increased the weighted score attributed to age >74 from 1 to 2 [124]. Low-, intermediate- and high-risk categories are defined as CHADS2VASc score of 0, 1 and ≥2, respectively, which correspond to adjusted annual stroke risk of 0, 0.7 % and >1.9 % [124]. Patients with AF and CHADS2 scores in the low and intermediate range still have a non-negligible risk of stroke of up to 3.56 per 100 person years. Using CHADS2VASc score, the intermediate risk patients according to the CHADS2 scoring are mostly reclassified to a higher risk category. The remaining patients in the low-risk category according to CHADS2VASc have truly low risks of stroke and can be safely managed without anticoagulation therapy. According to this new scoring system, elderly patients aged >75 years with AF will be considered high risk for stroke and would require oral anticoagulation (OAC) therapy even without the presence of other risk factors.

Risk of Bleeding

Although OACs are highly effective at reducing stroke risk in the older population, their use is also associated with an increased risk of intracranial and other serious bleeding complications [119, 125]. The incidence rate of major bleeding associated with OAC increases from 1.5 per 100 patient-years for patients younger than 60 years to 4.2 per 100 patient-years for patients older than 80 years [126]. Intracranial haemorrhage causes 88 % of mortality and 95 % of major functional disability cases due to Coumadin-associated major bleeding and roughly constitutes 20–25 % of all cases of major bleeding [127]. Therefore, bleeding risk must be taken into consideration in clinical decision-making prior to initiation of therapy in the elderly. Among the various bleeding risk scores that has been developed such as HEMORR2HAGES [128] and ATRIA [129], the newly developed HASBLED score (acronym HASBLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding

history or predisposition, Labile INR (<60 % in the therapeutic range of INR 2–3), Elderly (age >65), Drugs/alcohol (1 point each and includes NSAIDS and antiplatelet agents)) has better prediction accuracy for OAC-associated bleeding [130]. As is evident from this scoring system, the increased risk of bleeding in the elderly is likely multifactorial and stems from not only their age but also the presence of other comorbidities such as hypertension and abnormal liver and kidney function.

To minimize the risk of bleeding, several studies investigated the alternative use of antiplatelet therapy instead of OAC for management of patients with non-valvular AF [122]. Multiple trials have demonstrated the superiority of oral anticoagulants over aspirin [131] or combined therapy with clopidogrel (75 mg/day) and aspirin (75–100 mg/day) [132]. Unlike OACs, the relative benefit of antiplatelet medication for preventing stroke and cardiovascular outcomes decreases significantly with advancing age and seems not to be effective in stroke prevention after the age of 80 [119]. This is likely due to the fact that OACs are primarily preventing cardioembolic strokes whereas antiplatelet agents are mostly protective against non-cardioembolic causes of stroke which constitute 24 % of stroke cases in AF patients [22]. In the elderly with AF, the proportion of strokes due to non-cardioembolic causes decline resulting in significant decrease in the protective effect of antiplatelet agents against strokes. As a result, OACs are more effective than antiplatelet agents at reducing stroke risk in patients with AF and more so in the elderly. Therefore, in patients who are appropriately risk stratified for stroke and bleeding risk, age alone should not prevent prescription of OAC therapy.

New Oral Anticoagulants

Several new oral anticoagulation medications including the direct thrombin inhibitor, dabigatran, and the activated factor X inhibitors, rivaroxaban, apixaban and edoxaban, have been developed for the prevention of thromboembolism in AF.

Dabigatran is a new OAC prodrug that is converted by a serum esterase to an active reversible direct thrombin inhibitor. The pharmacokinetic of dabigatran allows for a fixed-dose regimen without the need for routine coagulation monitoring [133]. Dabigatran has a predictable pharmacokinetic, pharmacodynamic and safety profile in elderly patients [134]. The RE-LY trial was a multicentre, randomized controlled trial that enrolled more than 18,000 patients to compare the effects of fixed doses of dabigatran to adjusted-dose warfarin in patients with AF and risk of thromboembolism [135]. Dabigatran at a dose of 110 mg was as effective as adjusted-dose warfarin in preventing thromboembolic complications and lowered rates of major bleeding complications (2.71 versus 3.36 %/year, $P=0.003$) [135]. Dabigatran at a higher dose of 150 mg was more effective than adjusted-dose warfarin for prevention of thromboembolism and had similar rates of bleeding complications [135]. The analysis of RE-LY trial showed significant treatment by age interaction in terms of major bleeding complications [136]. Although dabigatran compared with warfarin was associated with a lower risk of major bleeding in patients aged <75 years (1.89 versus 3.04 %; $P<0.001$ for 110 mg bid dose and 2.12 versus 3.04 %; $P<0.001$ for 150 mg bid dose), in patients >75 years, it was associated with either similar risk or a trend towards increased risk of major bleeding (4.43 versus 4.37 %; $P=0.89$ for 110 mg bid dose and 2.12 versus 3.04 %; $P<0.001$ for 150 mg bid dose) [136]. However, regardless of age, the risk of intracranial bleeding was consistently lower in patients receiving dabigatran compared to warfarin, which is postulated to be due to the lack of interference with tissue factor-dependent coagulation process of dabigatran [136]. The FDA recently approved dabigatran at a dose of 150 mg for the prevention of stroke and systemic embolism in patients with AF regardless of age. However, older patients are also at higher risk of bleeding complications, and both the Canadian Cardiovascular Society and European Society of Cardiology suggest using dabigatran at the lower dose of 110 mg for patients older than 75 years [137, 138].

Although the routine monitoring of anticoagulation status is not necessary, it has an important clinical role in cases of emergency bleeding and during transitioning of anticoagulation especially in elderly patients with higher bleeding risk. The HEMOCLOT (HYPHEN BioMed, France) thrombin inhibitor assay can accurately and quickly assess the dabigatran's anticoagulant activity [139]. Other tests of anticoagulation status such as thrombin clotting time, aPTT, activated clotting time (ACT) and ecarin clotting time (ECT) are affected by dabigatran, but their clinical utility has been restricted due to their non-uniform dose–response curve, or lack of standardization or validation for dabigatran [133].

Rivaroxaban is an oral, direct, reversible factor Xa inhibitor with a short half-life (7–11 h) that exerts rapid onset (1–4 h) of anticoagulation that is primarily renally excreted [140]. The ROCKET-AF trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) was a double-blind randomized trial that enrolled 14264 patients (median age of 73 years) with non-valvular AF and CHADS2 score ≥ 2 to receive either rivaroxaban (at a daily dose of 20 mg or 15 mg if CrCl = 15–30 mL/min) or dose-adjusted warfarin. Rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism (HR, 0.79; 95 % CI, 0.66–0.96; $P < 0.001$) and the risk of bleeding (HR, 1.03; 95 % CI, 0.96–1.11; $P = 0.44$), although intracranial (HR, 0.67; 95 % CI, 0.47– 0.93; $P = 0.02$) and fatal bleeding (HR, 0.50; 95 % CI, 0.31–0.79; $P = 0.003$) occurred less frequently in the rivaroxaban group [141]. The efficacy and safety of rivaroxaban seemed to be independent of age. FDA approved rivaroxaban for prevention of stroke and systemic embolism in non-valvular AF in 2011.

Apixaban is an oral, direct, factor Xa inhibitor with a half-life of ~8–15 h that has both hepatic (75 %) and renal (25 %) elimination [142]. The ARISTOTLE trial that involved 18,201 patients with AF and at least one risk factor for stroke found significant reduction in the rate of stroke or systemic embolism by 21 % ($P = 0.01$), rates of major bleeding by 31 % ($P < 0.001$), intracranial haemorrhage by 58 % ($P < 0.001$) and all-cause mortality by 11 % ($P = 0.047$) with apixaban compared with warfarin [143]. Apixaban dose was reduced from 5 to 2.5 mg twice daily in elderly patients (>80 years) with a body weight of less than 60 kg, or a serum creatinine level of 1.5 mg per decilitre (133 μmol per litre) or more [143]. The AVERROES trial ($n = 5599$) compared apixaban with ASA in patients who had failed or were unsuitable for Coumadin [144]. The trial was terminated prematurely when early analysis revealed that apixaban was more effective than ASA in reducing the risk of stroke and systemic embolism (HR, 0.45; 95 % CI 0.32–0.62; $P < 0.001$) without increasing the risk of major bleeding [144]. In both trials of apixaban, no interaction with age was observed indicating that apixaban is superior to both Coumadin and ASA in terms of safety and efficacy in elderly patients. Apixaban was approved for stroke prevention in non-valvular AF in January of 2013. The labelling for Apixaban includes a boxed warning about the increased risk of stroke in patients who stop the medication without bridging anticoagulation.

Lastly, edoxaban, a selective and direct factor Xa inhibitor, is currently being investigated in a phase 3 trial (ENGAGE AF-TIMI 48) in comparison to warfarin for prevention of thromboembolism in patients with AF. The improved efficacy and reduced risk of bleeding of newer oral anticoagulants has resulted in more favourable net risk margin which offers more treatment options for elderly with higher risk of bleeding. Other important factors in choosing the most appropriate anticoagulant include cost and patients' preferences regarding the acceptable level of trade-off between bleeding risk and stroke prevention [145].

Given the higher risk of bleeding complications in the elderly, the availability of reversal agents for the new oral anticoagulants is of particular importance. The administration of coagulation factors such as prothrombin complex concentrates (PCC) and fresh frozen plasma (FFP) has little effect in correcting aPTT, TT or

ECT [146]; however, in animal bleeding models, administration of high-dose PCC, FFP and recombinant activated factor VII (raFVII) has been shown to reduce bleeding due to dabigatran [147]. The limited data for rivaroxaban suggest that high doses raFVII and PCC (activated 4-factor) could reverse the anticoagulation effect of rivaroxaban by varying degrees [147], but there are no human studies evaluating the effect of either of these agents on bleeding.

Catheter-based Ablation Therapy for AF

Over the past decade, CBA for AF has emerged as an important treatment option for patients with AF. The 2012 HRS/EHRA/ECAS expert consensus statement gave a classes I and IIa recommendation to CBA for maintaining sinus rhythm in symptomatic patients with paroxysmal AF who have failed therapy with a class I or III AAD and those who have not received AAD, respectively [148]. Multiple studies that included more than 6,000 patients investigated safety and efficacy of CBA for AF [113, 149]. However, there is a paucity of randomized trials comparing CBA with AADs, and none has studied older patients with HF. A single centre observational study of CBA ($n=1165$) found that the success and major complication rates were comparable between the three age categories (<65, 56–75, >75) although older patients required AADs more frequently to achieve the same outcome as younger patients [150].

In a non-randomized prospective study of patients with systolic HF (LVEF ≤ 45%) and AF that were resistant to at least two AADs, CBA resulted in improvement of LVEF (by 16–24 % in the subgroups), symptoms, quality of life and exercise capacity [151]. The magnitude of improvement was more pronounced in patients with inadequate rate control prior to ablation and without structural heart disease [151].

In the ThermoCool trial, which is one of the largest randomized trials comparing CBA versus AADs in paroxysmal AF, more than 5,500 patients were screened, and 167 were selected and randomized to either treatment with AAD or CBA. They excluded all the patients with LVEF < 40 %, moderate to severe symptomatic HF (NYHA II and III) and those with left atrial size larger than 50 mm [152]. Although they did not exclude older patients, partly as a result of its selection process, the average age of enrolled patients in ThermoCool trial was only 55.7 (95 % CI, 54.1–57.4) years. It showed that among these relatively young patients with paroxysmal AF and no significant HF who had failed at least one AAD, CBA resulted in longer time to treatment failure [152]. At the end of the 9-month follow-up, 66 % of patients in the CBA group remained free from protocol-defined treatment failure compared with 16 % treated with AADs [152].

Meta-analysis of the prospective studies of CBA and AADs for treatment of AF that included a total of 97 studies indirectly reported on efficacy of CBA compared to AADs [149]. The single-procedure success rate of CBA off AADs was 57 % (95 % CI, 50–64 %); the multiple procedure success rate off AAD was 71 % (95 % CI, 65–77 %); the multiple procedure success rate on AAD or with unknown AAD usage was 77 % (95 % CI, 73–81 %). The success rates for AAD therapy and placebo were 52 % (95 % CI, 47–57 %) and 24.9 % (95 % CI, 15–34 %), respectively [149]. However, as was the case in the ThermoCool trial, the mean age of patients in these studies and mean LVEF were 55.5 years and 57.7 %, respectively, preventing extrapolation of these results to older patients or those with HF [149]. Of note, peri-procedural dabigatran use has been associated with increased risk of bleeding or thromboembolic complications (OR, 2.76; 95 % CI, 1.22–6.25; $P=0.01$) compared with uninterrupted warfarin therapy especially in patients older than 75 (OR: 3.82; 95 % CI: 1.09–13.35; $P=0.04$) [153].

Radiofrequency ablation of atrioventricular node (AVN) and permanent pacing, the so-called ablate and pace strategy, is another non-pharmacological treatment option for patients with medically refractory AF. There are many small, uncontrolled trials that have assessed the efficacy of this method and have showed variable results [154, 155]. Meta-analysis of more than 21

such studies found that the ablate and pace strategy was associated with improvement in many clinical outcomes such as exercise duration and quality of life as well as modest improvement in ventricular function with an average increase in LVEF of about 4 % [156]. Right ventricular pacing, however, can result in ventricular dyssynchrony and adverse hemodynamic alteration that in turn can result in adverse clinical outcomes in patients with CHF [157, 158]. The PAVE trial evaluated the outcome of ablate and pace strategy in patients with symptomatic, medically refractory AF using biventricular pacing in comparison to right ventricular pacing. It found that biventricular pacing provided superior results in terms of clinical outcomes and measures of LV function compared to right ventricular pacing during the 6-month follow-up period [159]. It included older patients (mean age 69 ± 10 years) and those with HF (mean EF 0.46 ± 0.16) and found that those with systolic dysfunction (LVEF ≤ 45%) or symptomatic HF (NYHA class II/III) derived the most benefit from biventricular pacing [159]. It should be noted that according to the PAVE trial, right ventricular pacing was associated with small decline in LVEF, and there was no absolute improvement in LVEF after biventricular pacing [159].

A recent trial (PABA-CHF) compared ablate and pace strategy using biventricular pacing with pulmonary vein isolation (PVI) in patients with medically refractory AF and symptomatic systolic dysfunction. The composite primary end point that included a 6-minute walk distance, ejection fraction and symptoms favoured the group that underwent PVI [160]. At the end of the 6-month follow-up period, the mean absolute increases in LVEF were by 8 ± 8 and 1 ± 4 % in PVI and ablate and pace groups, respectively ($P < 0.001$) [160].

Many questions regarding CBA remain to be answered such as whether it can halt the progression of AF, reduce thromboembolic complications, improve HF outcomes, and be used efficiently and safely in elderly population.

Taken together, current limited data suggests that CBA could be an effective treatment option for medically refractory AF in patients with HF and possibly the elderly. However, there is a need for multicentre randomized trials with longer follow-up that include elderly patients with HF to more definitively address this issue.

Conclusion

AF is a prevalent disease in elderly patients that is associated with HF and thromboembolic complications with devastating consequences. The cornerstone of AF therapy is anticoagulation and pharmacological rate control. With the introduction of safer and more effective anticoagulation options, the choice of the medication requires adequate assessment of bleeding risk as well as patients preferences, cost and comorbidities. For elderly patients with severe symptoms, pharmacological rhythm management and CBA need to be considered. However, this is often challenging in elderly patients due to other coexisting medical conditions, increased drug–drug interactions and altered drug metabolism. With the introduction of new pharmacological and non-pharmacological treatment options, the management of AF in the elderly is evolving rapidly. In order to develop treatment guidelines that specifically address the elderly patients and those with HF, more multicentre randomized trials that include these groups of patients are needed.

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Optimizing Therapy of Heart Failure in the Aging Population with Monitoring in Clinics

6

John R. Dimitry and Justin A. Ezekowitz

Introduction

In recent years, the incidence and prevalence of heart failure (HF) has risen to epidemic proportions [1, 2]. In Canada, HF affects over 500,000 people, and each year 50,000 new cases are diagnosed [3, 4]. The burden of HF has a direct correlation with aging; HF affects <1 % of adults under 50 years of age. However, in patients over 80, the prevalence exceeds 10 %. In 1999, nearly 80 % of HF hospitalizations occurred in patients over the age of 65, with nearly 50 % of older HF patients requiring readmission within 6 months of discharge [5, 6]. Optimizing HF therapy in clinics under the guidance of multidisciplinary management teams has been shown to reduce readmission rates and mortality [7, 8]. Such teams consist of a physician (often a cardiologist but in many cases a general internist), nurse, pharmacist, dietitian, social worker, physical therapist, and a case manager [1, 9] (Fig. 6.1). Several contemporary randomized trials have shown up to 50 % fewer hospital readmissions with multidisciplinary HF intervention teams versus usual care [8].

J.R. Dimitry, MD, MPH, FRCPC
Division of Cardiology, Department of Medicine, University of Alberta and Mazankowski Alberta Heart Institute, Edmonton, AB, Canada

J.A. Ezekowitz, MBBCh, MSc (✉)
Division of Cardiology, Department of Medicine, University of Alberta, 8440-112 Street, Edmonton, AB, Canada T6G 2B7
e-mail: jae2@ualberta.ca

Specialized multidisciplinary HF teams are uniquely equipped to provide early identification of worsening symptoms and disease progression, optimize evidence-based pharmacotherapy while minimizing adverse drug events (ADEs), identify and eliminate detrimental medication use and dietary practices, discuss end-of-life preferences, and resolve psychosocial and financial barriers to adherence through ongoing education and a proactive monitoring system. In addition to ambulatory care office visits, multidisciplinary teams maintain close follow-up through telephone contacts, home visits, and ongoing collaboration with primary care physicians. The overall objective is to improve clinical outcomes, enhance quality of life, and improve functional capacity.

HF in the aging population poses unique challenges in management. Although the vast majority of major randomized trials in ACE inhibitor, beta-blocker, implantable cardioverter-defibrillator (ICD), and cardiac resynchronization therapy (CRT) included many elderly patients, the median age was 60, and many patients were excluded on the basis of comorbidities [10–12]. Aging is strongly associated with increased prevalence of comorbid illnesses, and optimal management demands a thorough understanding of the interactions between HF and important age-related illnesses such as frailty, renal failure, cognitive impairment, and functional decline. A multidisciplinary approach and a thorough understanding of cardiology, geriatrics, and internal medicine are necessary (Fig. 6.1). An important consideration often overlooked by healthcare

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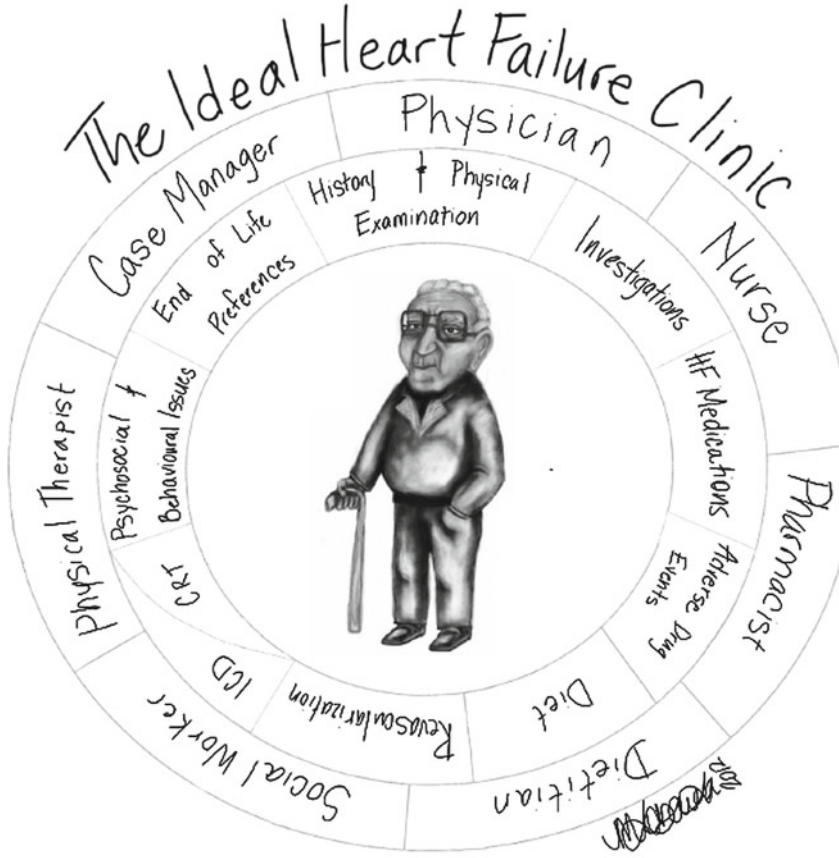

Fig. 6.1 The ideal heart failure clinic setup: all healthcare professionals should consider each aspect of care as appropriate for the patient. For example, the dietician may need to know if there are recurrent heart failure exacerbations to direct counseling accordingly. Similarly, a social worker and pharmacist may need to be aware of a new or change in medications that may impact the adherence or ability to afford medications (courtesy of Marissa Kobewka, BSc)

professionals is that HF interventions may further contribute to patient frailty and complicate management.

Evaluation of Symptoms

Early diagnosis and identification of symptom progression by specialized HF teams may help reduce HF hospitalizations and readmissions. Elderly patients often present in an atypical manner, and the standard HF history and physical examination may need interpretation in the context of normal aging [13, 14]. It is important to identify the baseline functional status of elderly patients, but functional status may mean considering the normal healthy age-matched control's exercise capacity. A normal aging patient may experience shortness of breath on mild exertion due to deconditioning and leg swelling due to chronic venous insufficiency [15, 16]. It may not be relevant to ask a frail elderly patient about the number of blocks walked or flights of stairs climbed before dyspnea occurs because these patients may be deconditioned or easily fatigued in the absence of HF. Orthopedic limitations may further aggravate the situation. Conditions such as depression, chronic lung disease, renal failure, and anemia may lead to similar states of functional decline and obscure the diagnosis. It is more useful to inquire about changes noticed while performing usual day-to-day activities, such as

making the bed, walking to the bathroom, or dressing themselves in the morning. Orthopnea and paroxysmal nocturnal dyspnea may not be identified if the patient sleeps upright in a chair. Weight gain may be due to an increasingly sedentary lifestyle and obesity rather than fluid retention. Indeed the body composition of a patient with HF and that of a frail elderly patient may be similar with significant sarcopenia [17, 18]. Although cognitive decline is very common in chronic HF, it is also a manifestation of age-related vascular and Alzheimer's dementia [19–21]. Chronic lung disease may lead to cough and pulmonary crackles, two common manifestations of HF. The jugular venous pressure may be elevated in worsening HF, but may also be elevated in patients with pulmonary hypertension due to COPD or chronic pulmonary embolism. In summary, traditional symptoms and signs of HF are far less specific in the aging population, and healthcare providers must be familiar with the individual patient's comorbid illnesses and baseline functional status. Collateral information from family and caregivers should be sought out if atypical symptoms and geriatric syndromes continue to obscure the diagnosis.

The New York Heart Association (NYHA) classification system is commonly used to characterize a patient's functional capacity once HF is diagnosed [3, 22, 23]. However, given the preexisting functional limitations of many elderly patients with or without HF, the NYHA classification may be difficult to apply, but should be attempted considering what a healthy, age-matched individual may be able to do. The Resident Assessment Instrument (RAI) 2.0 may provide more useful information in elderly HF patients [24]. It may also be beneficial to screen patients for cognitive impairment and frailty using the MoCA and the Canadian Study of Health and Aging (CSHA) frailty scales, respectively [25, 26].

Investigations

Although HF is a clinical diagnosis, investigations are often required to support the diagnosis, rule out other cardiac causes of signs and symptoms, and monitor the course of the disease. Transthoracic echocardiography (TTE) is the imaging modality of choice to assess left ventricular (LV) function and differentiate between systolic and diastolic dysfunction. TTE also enables determination of abnormalities of valves, myocardium, and pericardium. Subsequent TTE imaging also monitors progression of disease and response to pharmacologic therapy. A chest radiograph is another standard imaging modality that provides crucial diagnostic and prognostic information. However, similar to the history and physical examination, specificity decreases with advancing age as chronic lung disease and spinal deformities may obscure accurate interpretation. Routine blood work such as a complete blood count, renal function, electrolytes, and TSH should be obtained in all patients at diagnosis, and repeated when necessary to identify any confounding variables that may explain a patient's worsening clinical presentation. Anemia, renal failure, and hypothyroidism are common geriatric syndromes that may manifest as identical symptoms to HF and also contribute to HF progression. Many adverse drug events (ADEs) involve metabolic derangements and mandate prompt adjustment in a patient's HF pharmacologic profile. The combined use of ACE inhibitors and loop diuretics may significantly decrease renal perfusion and amplify the risk of hyperkalemia in elderly patients treated with spironolactone.

N-terminal brain natriuretic peptide (N-BNP) has emerged as a very useful diagnostic and prognostic blood test in HF and deserves careful consideration in the elderly. Normal BNP levels can be useful to rule out HF, while abnormal BNP levels may assist the healthcare team to rule-in HF if the diagnosis is in doubt [23, 27]. BNP is less specific in the aging population, and elevated levels may simply reflect advancing age. Common geriatric illnesses such as renal failure, COPD, and pulmonary embolism may also increase serum levels of BNP [28, 29].

More recently, BNP levels have been utilized to guide HF therapy. Serial BNP measurement is valuable in monitoring patients already diagnosed with HF and is much more important than one isolated measurement. Comparing BNP

measurements at each follow-up visit to a baseline value obtained during a euvolemic state provides important information on volume status and guides dose adjustments of diuretic and other therapy [30]. In patients presumed to be on optimal pharmacotherapy and an appropriately restricted diet, persistently abnormal BNP levels may suggest nonadherence as it reflects ongoing volume overload perhaps due to excess salt intake and/or noncompliance with diuretic and other heart failure medications. Recent evidence has compared BNP-guided HF therapy to symptom-guided HF therapy. Although BNP-guided therapy has been shown to decrease HF hospitalizations in patients 60–75 years of age, it has no such advantage in patients over 75 and may even increase serious adverse events such as renal failure and hypotension due to age-associated impairments in thirst mechanisms and pharmacokinetic processes [31].

Pharmacotherapy

Evidence-based pharmacologic therapy improves clinical outcomes and quality of life for patients with systolic HF. Although frail older patients are not well represented in clinical trials, the medical management of HF remains very similar to younger patients. There is a paucity of evidence regarding management of HF with preserved LV systolic function. However, the fundamental principle is improvement in ventricular relaxation through optimal blood pressure control. Age-related changes in pharmacokinetics must be carefully considered in order to minimize the risk of ADEs. Advancing age is directly associated with reduced lean body mass and total body water. This results in lower volumes of distribution and leads to higher plasma concentrations of hydrophilic drugs such as angiotensin-converting enzyme (ACE) inhibitors and digoxin. Conversely, body fat increases with advancing age and leads to increased plasma concentrations of lipophilic agents such as beta-blockers. Albumin concentrations decrease with advancing age, and as a result, drug-free concentrations of protein-bound compounds such as warfarin and salicylates increase. In addition, decreased hepatic and renal blood flow in older patients lead to increases in serum drug concentrations metabolized and excreted by the liver and kidney, respectively. These pharmacokinetic abnormalities demand medications be initiated at low doses and titrated slowly thereafter. Comorbid illnesses in the geriatric patient often require pharmacologic therapy, and the addition of HF medications to a patient's preexisting profile may increase the risk of drug–drug and drug–disease interactions.

Although loop diuretic therapy has not been evaluated in major clinical trials for mortality or re-hospitalization versus placebo, it remains an essential component of chronic HF symptom management. Older patients are more susceptible to dehydration due to impaired thirst mechanisms, and a careful fluid status assessment should be made prior to prescribing, and frequent reevaluation of the dose is critical [6]. Higher doses of loop diuretic therapy (median of 80 mg/day furosemide) are associated with worsening renal function and mortality [32]. Consider reducing or stopping diuretic therapy when fluid retention is not present to avoid dehydration, and careful observation during intercurrent illness can prevent complications. Obtaining a detailed history on fatigue, dizziness, and syncope is required with each visit. Orthostatic hypotension is a common finding in elderly patients and is defined as a fall of greater than 20 mmHg in systolic blood pressure or greater than 10 mmHg in diastolic blood pressure on standing [33, 34]. Electrolytes and renal function should be monitored regularly, and potassium, magnesium, or calcium supplements prescribed as necessary. However, there is limited safety or efficacy data on these supplements, and polypharmacy should be avoided where possible.

ACE inhibitors are the cornerstone of drug therapy in LV systolic dysfunction, although they are also important to consider in diastolic dysfunction for the prevention and regression of hypertension-induced ventricular hypertrophy [3, 22, 23]. They improve symptoms and heart function, prevent remodeling, and reduce morbidity and mortality. A systematic review of 34 double-blind RCTs involving ACE inhibitor treatment in HF

with LVEF < 40 % found a statistically significant reduction in mortality (OR = 0.77, 95 % CI, 0.67–0.88) [35]. These trials did enroll elderly patients; however it is important to note that many patients were excluded based on comorbidities, and the mean age enrolled was 60. Nevertheless, there is an abundance of observational data in the literature that strongly suggests similar benefits of ACE inhibitors in the elderly population. They should be prescribed early in the course of HF at a low dose and titrated slowly to the highest tolerable dose up to the target dose tested in large RCTs. Monitoring include symptomatic hypotension, renal insufficiency, angioedema, hyperkalemia, and persistent cough. Hyponatremia, hyperkalemia, and volume depletion should be corrected prior to prescribing. An increase in serum creatinine of 30 % or less is a normal response to ACE inhibitor initiation and should not prompt cessation of therapy. Symptomatic hypotension should also not prompt cessation of the ACE inhibitor; however, a reduction in dose may be necessary, or a reduction in diuretic dose is also an acceptable strategy. Angiotensin receptor blockers (ARBs) are a second-line therapy compared with ACE inhibitors; however, the evidence for ARBs is less established than with ACE inhibitors and should only be substituted in cases of clear ACE inhibitor intolerance. Patients unable to tolerate either an ACEI or ARB should be considered for combination of nitrate and hydralazine therapy.

Beta-blockers have also been shown to reduce morbidity and mortality in HF [36]. They improve symptoms, decrease heart rate, and increase the ejection fraction. They should be started early in the course of treatment and after initiation of ACE inhibitor or ARB. Similarly to ACE inhibitors, they should also be started at a low dose and titrated slowly to target or highest tolerable dose. Patients should be initiated on beta-blockers in a euvolemic state. Anecdotal evidence suggests beta-blockers can be particularly problematic in the geriatric population due to potential exacerbation of COPD. However, in 2006 a large cohort study published by Hogg and McMurray comparing heart failure in preserved versus reduced ejection fraction showed COPD to be a stronger predictor of adverse outcomes in patients with preserved systolic function compared to patients with reduced systolic function, a population where beta-blockers are far more commonly used [37]. Degenerative conduction system disease is far more common in the elderly, and beta-blocker therapy may worsen this condition. Frequent electrocardiographic surveillance for significant bradycardia or high-grade AV block is required. Sudden major dose reductions or abrupt withdrawal of beta-blockers should be avoided, as this may trigger reflex tachycardia and lead to rapid decompensation of the frail older patient.

Aldosterone antagonists may lead to life-threatening complications of hyperkalemia, especially in older patients with reduced renal function, on ACE inhibitors or ARBs, and during acute dehydrating illnesses [38]. In a post hoc analysis of TIME-CHF, spironolactone use in elderly HF patients was associated with worsening renal function and increased mortality [32]. However, given the mortality benefit in patients NYHA II–IV, these should be attempted with close monitoring of renal function, electrolytes, and blood pressure [39].

Digoxin is recommended in patients with persistent symptoms despite optimized HF medical therapy. Digoxin should be used with extreme caution in advancing age. Digoxin has a narrow therapeutic index, and older patients with decreased muscle mass and renal function are particularly susceptible to potentially fatal toxicity.

In addition to ensuring patients are prescribed evidence-based HF drugs, healthcare providers must also be diligent in identifying and eliminating drugs with potentially hazardous complications in HF. Osteoarthritis and chronic pain are very common comorbid illnesses in the elderly population leading to a high prevalence of NSAID use. A recent study has shown that greater than 20 % of patients age 60 years or older with HF take NSAIDs [40]. There is substantial evidence to suggest that NSAID use is potentially hazardous in HF and may increase the prevalence of HF hospitalizations. Unfortunately, many healthcare providers fail to identify HF patients using NSAIDs. Studies have shown that a focused analgesic medication history was superior to a usual

medication history to detect patients taking NSAIDs. In fact, a recent trial has shown that healthcare providers with appropriate training in obtaining a focused analgesic history reduced NSAID intake from 22 % to 7 % [40]. Overall, patients are willing to stop taking NSAIDs if educated appropriately and suitable replacements exist, including acetaminophen-based and low-dose opiate-based therapies.

Implantable Cardiac Devices

Coronary artery disease, valvular pathology, and conduction system abnormalities are more prevalent in older patients and contribute significantly to HF morbidity and mortality. While little evidence supports further active intervention strictly for coronary artery disease (such as PCI or CABG) or valvular dysfunction in this patient population, electrically related therapies should be considered carefully. Although interventional therapies are available to manage these issues, such invasive options should be presented to older patients on an individualized basis. Clinic visits provide a valuable opportunity to discuss these options; however the patient's frailty and physiologic reserve must be taken into careful consideration as these patients have a higher risk of surgical complications. Furthermore, ICDs for the primary and secondary prevention of sudden cardiac death may not be appropriate for patients more likely to die from a noncardiac cause [41, 42]. However, cardiac resynchronization therapy may be a practical consideration to achieve the goals of symptom management and hospitalization reduction. For example, in the CARE-HF study patients with heart failure and cardiac dyssynchrony receiving cardiac resynchronization therapy had significant improvement in symptoms and quality of life as well as a reduction in mortality compared with patients receiving medical therapy alone [43]. Not all patients require or desire an ICD, but many would consider a CRT device (without the "D") to improve symptoms at a lower resource cost. Healthcare providers must consider comorbid illnesses, frailty and physiologic reserve, and goals of care when presenting interventional therapy options to geriatric HF patients.

Dietary Considerations

Dietary restriction is another crucial element of optimal HF therapy in all patients. The elderly HF population is particularly susceptible to nonadherence with dietary restrictions due to cognitive and functional decline, as well as lower socioeconomic status. The outpatient clinic provides an ideal setting to discuss and reinforce the importance of strict dietary practices. According to the Canadian Cardiovascular Society, sodium intake should be restricted to 2–3 g/day in symptomatic patients, and those with more advanced HF and fluid retention may require even further restriction to 1–2 g/day [3]. Although fluid restriction is not necessary in many cases, patients with clear signs of edema and fluid retention should be advised to limit intake to 2 L/day [3]. Many elderly patients already suffer from poor oral intake, and as such, weight reduction through calorie restriction should be recommended in an individualized manner. In a recent study published by Arcand and colleagues, sodium restriction itself was found to be directly associated with reduced daily caloric intake [44]. As such, it may not be necessary to place additional restrictions on caloric intake. Arcand has also shown that elderly patients with and without heart failure are equally susceptible to inadequate intake of important vitamins and minerals which highlights the importance of nutrition counseling beyond sodium and fluid restriction alone. A randomized trial conducted by Arcand in 2005 highlights the importance of multidisciplinary HF care [45]. Dietitian-administered counseling was more effective than simply providing literature in reducing dietary sodium intake in HF patients.

Other Considerations

Socioeconomic factors play an important role in the management of HF in the elderly. The high cost of medications may contribute significantly to nonadherence, and it is important to identify and resolve any financial barriers early in the course of treatment. Ease of access to a social

worker during the outpatient encounter will assist in alleviating such challenges (Fig. 6.1).

Psychosocial and behavioral issues are common in the geriatric population. Aging often leads to social isolation, loss of independence, and difficulty getting to a physician's office. Further isolation with loss of a driver's license, loss of family or other support, and lack of appropriate means for rewarding activities can lead to substantial decline and difficulty in management of the other aspects of HF. A multidisciplinary conference involving the patient, family, and caregivers is an efficient and effective method of addressing such issues on an ongoing basis during outpatient visits. Prompt psychiatric evaluation and early aggressive pharmacologic therapy to treat depression will further improve compliance with HF therapy.

The clinic is perhaps the most ideal setting for discussion of end-of-life preferences of elderly patients with chronic heart failure. Recent evidence has shown that elderly HF patients are willing to address their end-of-life preferences. These issues are often inappropriately addressed during hospitalization when patients are acutely ill and lack the capacity to make informed decisions. Empathy, respect, and mutual understanding are the fundamental aspects of effective end-of-life counseling. Clinic visits provide a valuable opportunity to introduce the importance of advance directives regarding resuscitation preferences, life-sustaining interventions, and surrogate decision-makers. Elderly patients have traditionally been assumed to prefer improved quality of life to longevity. However, contemporary data actually suggests that the majority of these patients prefer longevity to quality of life, and greater than 50 % wish to be resuscitated if necessary [46].

Early discussions of palliative measures may help improve quality of life in patients with persistent advanced HF symptoms despite optimal therapy. Palliative care should be based on individual patient needs and symptoms rather than an estimate of remaining life expectancy [26]. The clinic provides an opportunity to assess patients for signs and symptoms of persistent advanced HF and to ensure all appropriate HF management strategies have been considered and optimized. Discussion of palliative therapeutic options may be initiated promptly thereafter while the patient is still capable of communicating his or wishes [47]. Mechanical circulatory support devices, positive inotropic agents, therapeutic pleural drainage devices, deactivation of ICDs, opioids, caffeine, and hospice care transfer may all be viable options in the palliation of such patients and should be individualized based on patient goals and comorbidities [26].

Conclusion

The median age of patients admitted to hospital for HF is increasing, and as the population ages and heart disease therapies advance, this will continue to rise. Optimizing and monitoring HF therapy in the outpatient setting will help reduce hospitalizations and the financial burden of this important epidemic. Although the principles of HF therapy are very similar in all patients, the aging population poses some unique challenges. Familiarity with atypical presentations, geriatric syndromes, age-related pharmacokinetic changes, social and behavioral issues, and end-of-life discussions will markedly improve HF management in clinics, leading to reduced hospital readmissions and overall mortality.

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Cardiac Alterations in Aging, Hypertension, and Diastolic Heart Failure

7

Edith Pituskin and D. Ian Paterson

Abbreviations

BP	Blood pressure
CVD	Cardiovascular disease
DHF	Diastolic heart failure
HF	Heart failure
HTN	Hypertension
LV	Left ventricle
MMPs	Matrix metalloproteinases
PICP	Procollagen type 1 carboxyl-terminal propeptide
PIIICP PIIINP	Carboxy-terminal and amino-terminal peptides of collagen type III
TIMPs	Tissue inhibitors of matrix metalloproteinases
ROS	Reactive oxygen species
SHF	Systolic heart failure

The authors have no industry relationship.

E. Pituskin, PhD(c)
Department of Oncology, University of Alberta,
Cross Cancer Institute, 11560 University Avenue,
Edmonton, AB, Canada T6G 1Z2
e-mail: pituskin@ualberta.ca

D.I. Paterson, MD, FRCPC (✉)
Department of Cardiology/Medicine,
Mazankowski Alberta Heart Institute,
University of Alberta, 8440 112 Street,
Room 2C2.43 WCM, Edmonton, AB, Canada T6G 2B7
e-mail: ip3@ualberta.ca

Introduction

As a result of longer life expectancy, the global proportion of individuals aged 60 or over is growing more rapidly than any other age group. While this phenomenon is the result of improvements in public health and socioeconomic development, it also presents challenges in terms of optimizing the ongoing health of older persons. Accordingly, an epidemiologic transition in the leading causes of death is observed from infectious disease and acute illness to chronic disease and degenerative illness [1]. Cardiovascular disease (CVD) is the leading cause of death globally, with an estimated 17.3 million people dying of CVDs in 2008 [2].

Age is a major independent risk factor of CVD [3], in part due to progressive exposure to a variety of insults including smoking, obesity, hypertension (HTN), and chronic diseases. Importantly, these exposures occur in the aging adult on a background of established, age-related decline in cardiovascular function due to progressive, negative changes to cardiovascular structure. The quest for a single culprit, a particular gene or body system, has increasingly been replaced by the view of progressive age as a complex, multifactorial process [4]. However, given the vital role of the cardiovascular system, negative changes upon this system impact the body as a whole.

Aging is associated with decreased aortic compliance [5], and population studies demonstrate linear increases in systolic blood pressure

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throughout each decade of life [6]. HTN, defined as a systolic blood pressure >140 mmHg and a diastolic blood pressure >90 mmHg, affects one third of Americans [7], and HTN prevalence rises to 55 % in those over the age of 65 [8]. HTN is the most commonly identified modifiable risk factor in CVD and most notably is present in 74 % of patients with heart failure (HF) [9]. The burden of HTN to society is high as direct US medical-related costs totaled $70 billion in 2010 and are expected to increase to $200 billion by 2030 [10]. At the level of the heart, HTN is associated with increased afterload and mechanical wall stress and may result in adverse cardiac remodeling. Left ventricular hypertrophy is found in 18 % of HTN patients [11] and is a strong predictor of cardiovascular events [12]. Cardiac remodeling is also an early manifestation of HF, and therapies aimed at reversing this process have been associated with clinical benefit [13].

HF is found in nearly 3 % of Americans and by 2030, its prevalence is expected to increase by 25 % [10] and hospital admissions by 55 % [14]. In the USA, direct treatment costs for HF totaled $25 billion in 2010 and is estimated to have caused $10 billion in lost productivity [10], confirming the excessive burden of this disease state on healthcare systems. Notably, age-adjusted incidence of HF has not declined substantially in the past 20–30 years in spite of improvements in control of causal factors [9, 15]. Furthermore, the relatively recent recognition of diastolic heart failure (DHF) as highly prevalent in the aging adult population has presented a new and additional challenge. DHF, also termed "heart failure with preserved ejection fraction," is now understood to account for 50 % of HF cases, with outcomes equally dismal as that of systolic heart failure (SHF) [16].

Only recently has the interaction of CVD and physiologic effects of aging attracted attention. Therefore, many aspects are yet to be elucidated. The aim of this chapter is to review key micro- and macroscopic cardiac alterations associated with aging, HTN, and DHF and discuss fundamental treatment strategies.

Microscopic Cardiac Changes

Improved laboratory methods and elegant studies have improved the understanding of pathologic remodeling, as well as the in interaction of CVDs such as HTN on the background of aging tissues. Progressive fibrosis associated with aging occurs in multiple organ systems including the heart, kidney, liver, pancreas, and lungs [17]. Increasing age, even in healthy individuals, is associated with progressive changes to myocardial tissues, including increased arterial and myocardial stiffness, decreased diastolic LV relaxation, decreased contractility, decreased coronary flow reserve, and decreased mitochondrial response to increased ATP demand [18, 19]. The aging heart exhibits a progressive increase in left ventricular mass, responding to peripheral vascular stiffening and increased hemodynamic load. These changes occur as a result of alterations to cardiac cellular composition, with a decrease in the number of cardiomyocytes and structural changes to collagen and extracellular matrix.

Myocardial Fibrosis

The cardiac interstitium is in an ongoing remodeling state, with continuous formation and degradation of collagen. The elastance of the extracellular matrix is determined by the total amount of collagen, the relative amounts of collagen type 1, and degree of collagen cross-linking [20]. Cross-linking increases tensile strength and limits degradation. Accumulation of cross-linked collagen has been proposed as a major mechanism in the pathogenesis of increased stiffness in the aging heart.

Collagen levels in the heart are determined by the balance between matrix-preserving and matrix-degrading signals; alterations in the normal synthesis/degradation activities result in alterations in composition. With increased synthesis, increased deposition of collagen type 1 occurs. Collagen type 1 has high tensile strength compared to the more compliant collagen III,

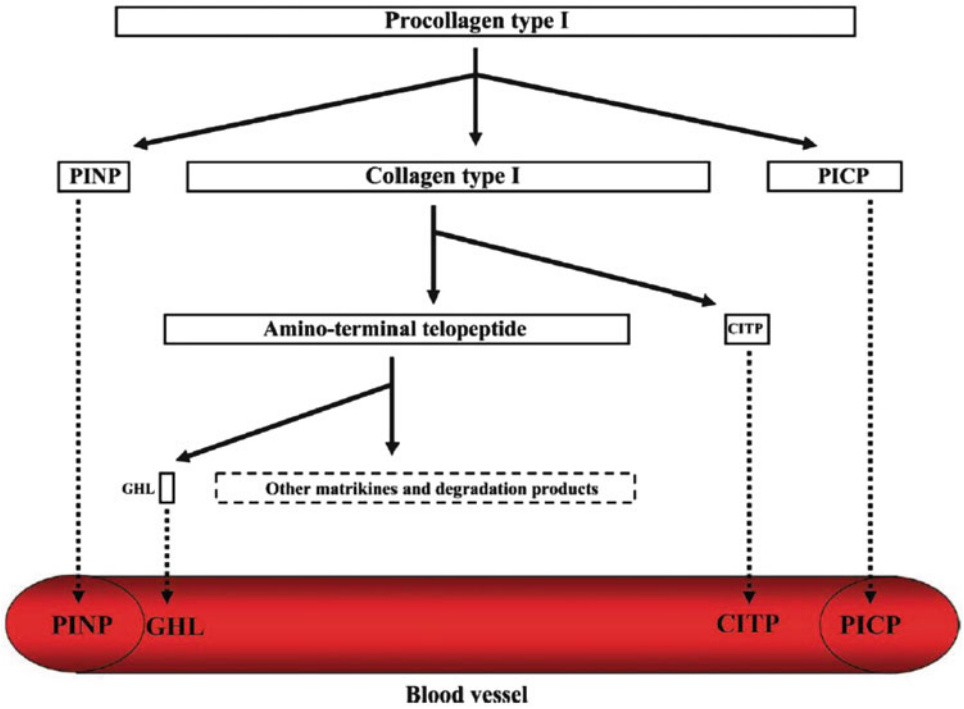

Fig. 7.1 Collagen type 1 metabolism with peptide product release into the bloodstream (reprinted from López B, González A, Díez J. Circulating Biomarkers of Collagen Metabolism in Cardiac Diseases. Circulation. 2010 April 13, 2010;121(14):1645–54. With permission from Wolter Kluwers Health)

contributing to increasing stiffness [21]. Importantly, as by-products of this interaction, multiple peptides are released into the bloodstream in varying number and proportions: procollagen type 1 carboxyl-terminal propeptide (PICP) and carboxy-terminal and amino-terminal peptides of collagen type III (PIIICP, PIIINP) [20, 22]. Increased collagen deposition also occurs as a result of decreased degradation activity. Matrix degradation is decreased due to downregulation of matrix metalloproteinases (MMPs) and upregulation of tissue inhibitors of matrix metalloproteinases (TIMPs) [20]. This imbalance therefore favors decreased collagen degradation and increased collagen accumulation (Fig. 7.1).

Such changes are documented to have significant impact on ventricular compliance and performance [19]. This balance is regulated by fibroblasts and myofibroblasts, which respond to stimuli including stretch, autocrine, and paracrine factors [22]. A major factor is angiotensin II, known to promote cardiomyocyte hypertrophy and stimulate fibroblast proliferation and expression of extracellular matrix proteins. Inflammatory markers such as TGF-β are believed to influence age-associated cardiac fibrosis, by enhancing matrix protein synthesis by cardiac fibroblasts [17]. In addition, TGF-β may exert potent matrix-preserving actions by suppressing the activity of MMPs and by inducing synthesis of protease inhibitors, such as PAI-1 and TIMPs.

Other inflammatory markers, such as TNF alpha, have been elevated in large portions of community-dwelling patients and implicated in shorter survival [23]. Collier performed a population-based study of 275 stable hypertensive patients; DHF patients were observed to have increased inflammatory biomarker signals (IL-6, IL-8, and MCP-1), increased fibrotic signal (PIIINP and CITP), and increased matrix turnover signal (MMP-2 and MMP-9). Alterations in MMP and TIMP enzymes were found to be significant indicators of greater degrees of asymptomatic left ventricular diastolic dysfunction.

Animal studies suggest increased collagen synthesis may not be the main culprit of fibrosis in the aging myocardium. In rodent models, aging was associated with reduced MMP-2 and MMP-1 expression and activity, whereas collagen I expression remained unchanged [24]. These findings imply that in normal aging, fibrosis may be primarily due to a reduction in the proteolytic activity of matrix MMPs and account for the excessive collagen deposition in the aging heart [17].

It is important to recognize that collagen biomarker data, while promising, remain in the exploratory phase. In the i-PRESERVE study, increased peripheral collagen turnover markers were not independently associated with increased mortality on multivariate analysis and however were associated on single-variable analysis. Collagen turnover in the entire body is a dynamic process; this is complicated by the fact that collagen is the most abundant protein in the body and that remodeling markers are not necessarily unique to the cardiovascular system [17]. Furthermore, multiple age-related disease processes are likely occurring simultaneously in the elderly, necessitating further careful study into mechanisms of pathologic fibrosis in human aging and DHF before conclusions can be drawn.

Cardiomyocyte Alterations

Stiffness

In addition to fibrosis, cardiomyocyte stiffness may contribute to diastolic dysfunction. Increased stiffness is related to titin, a giant elastic protein expressed in two main isoforms: N2B (stiffer spring) and N2BA (more compliant spring) [25]. With contraction, potential energy is stored with titin compression; titin provides elastic recoiling force to restore the myocyte to its resting length. Alterations in titin isoform expression have been shown to increase passive stiffness. Myocardial biopsy specimens from patients with DHF were observed to have a lower ratio of N2BA:N2B titin compared to SHF specimens, resulting in higher myocyte passive stiffness, suggesting that titin isoform switching and myofibrillar stiffness adjustment occur in opposite directions in systolic versus diastolic HF [26].

Relaxation

Aging is associated with prolonged relaxation and disturbed calcium homeostasis [27]. Slow relaxation may reduce stroke volume, particularly at higher heart rates. Myocardial relaxation is dependent on calcium reuptake; as calcium sequestration slows, relaxation time increases, resulting in greater proportion of LV filling occurring in late systole, explaining observations of E/A reversal in the elderly [28]. In an elegant study, Selby et al. examined human myocardial samples of 14 patients with DHF studying mechanisms of myocardial calcium homeostasis and the effect on passive and active myocardial properties [29]. They observed incomplete relaxation in preparations from patients with concentric left ventricular hypertrophy, coupled with increased cellular calcium load. In incomplete relaxation, the myocardium remains activated, in a state of diastolic contracture, suggesting abnormal calcium handling [29]. Relaxation is dependent on the reuptake of cytoplasmic calcium by the sarcoplasmic reticulum CA ATPase (SERCA2a) pump and to a lesser degree the sodium/calcium exchanger which transports calcium to the extracellular space [19]. This is highly relevant, for the increased energy required for calcium transport results in myocardial energy deficits, enhancing stress.

Myocyte Senescence

In the normal heart, cardiac myocytes occupy approximately 75 % of the myocardial tissue volume, but account only for 30–40 % of the total number of cells. With aging, a decrease in absolute number of cardiomyocytes occurs, due to increased apoptosis and necrosis and a decrease in repopulation of cardiomyocytes from cardiac stem cell reserves [18]. However, the rate of regeneration in the elderly may not be adequate to maintain cardiomyocyte numbers in response to cardiomyocyte loss.

With age, cardiomyocytes are more vulnerable to stressors, including oxidative stress [18]. Increase in reactive oxygen species (ROS) production results in an increased rate of cardiomyocyte

death. In cases when cardiomyocytes undergo necrosis, the release of cellular components can affect survival of neighboring cardiomyocytes, in addition to promoting the development of proinflammatory and profibrotic environments in the aging heart [17].

Macroscopic Cardiac Changes

Cardiac Alterations in Aging

Early cross-sectional autopsy [30] and echocardiographic [31] studies of left ventricular remodeling suggested that left ventricular mass increases with age in women but not in men. More recently, longitudinal observations in the Framingham Heart Study found increasing LV wall thickness, decreasing LV dimensions, and increasing fractional shortening with advancing age in both genders [32]. Age-related increases in arterial stiffness have been shown to promote LV hypertrophy and increase myocardial fibrosis and thus could account for the increasing LV wall thickness [18]. The increased fractional shortening with aging might be a compensatory mechanism for diminishing preload. Volumetric assessment of LV geometry on three-dimensional echocardiography has also shown that the left ventricular mass to volume ratio increases with age, particularly in women [33]. The accentuation of LV remodeling in aging women might be attributable to estrogen withdrawal following menopause. Estrogen receptors are expressed in the heart, and knockout mouse models of estrogen receptor beta have shown exaggerated LV hypertrophy, myocardial fibrosis, and cardiomyocyte apoptosis in pressure overload [34, 35].

Given the observed pattern of LV remodeling associated with aging (i.e. increased wall thickness and reduced cardiac volume), it is not surprising that healthy elderly individuals have reduced left ventricular compliance on invasive pressure-volume loops relative to healthy young controls [36]. Hence, for a given preload, elderly individuals have higher intracardiac filling pressures than younger controls. Interestingly, this same study found that exercise-trained elderly had LV compliance and mass that were indistinguishable from the young healthy group. Taken together, these findings suggest that chronic reductions in venous return from decades of inactivity lead to heart atrophy. Furthermore, sedentary elderly individuals have difficulty handling preload due to reduced myocardial viscoelasticity from increased interstitial fibrosis and increased cardiomyocyte stiffness as described earlier.

Cardiac Alterations in HTN and DHF

The typical phenotypic expression of HTN and DHF is left ventricular hypertrophy. Echocardiographic data from the Framingham Heart Study suggests that the presence of underlying cardiovascular risk factors tends to preserve left ventricular end-diastolic volume in the face of increasing wall thickness. Thus, overall ventricular mass increases in an aging hypertensive cohort [32]. Relative to healthy and hypertensive elderly, patients with DHF have further increases in left ventricular mass as well as an elevated left atrial volume reflecting high intracardiac filling pressures [37] (Fig. 7.2).

Pathologic changes in diastolic function are well documented in hypertensive and DHF patients. Diastolic function is defined by two processes: active myocardial relaxation and passive stiffness of the left ventricle. Relaxation is an energy-dependent process resulting in uncoupling of actin–myosin crossbridge bonds [38]. Ventricular stiffness is determined by the properties of the cells and extracellular matrix of the myocardium (myocardial stiffness), chamber geometry, and pericardial constraint [39]. Diastolic dysfunction is most commonly described in terms of impaired relaxation of the ventricle and/or increased stiffness [40]. Hypertensive patients typically have impaired relaxation characterized by a delay in the onset of filling and a related reduced rate of filling. In cases of impaired relaxation, heart rate is an important modulator of the effects on diastolic filling [41], where end-diastolic pressures remain normal at lower heart rates due to sufficient time

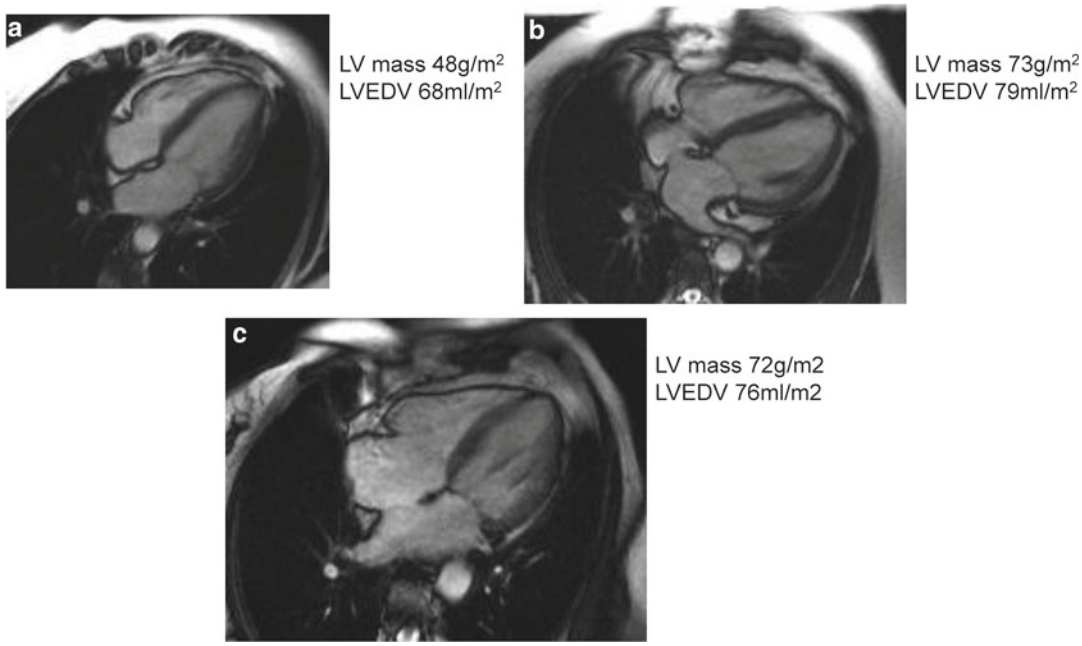

Fig. 7.2 Cardiac remodeling in elderly and hypertension and diastolic heart failure: representative cardiac magnetic resonance four chamber view with left ventricular measures. (**a**) Normal elderly control, female aged 63; (**b**) hypertensive elderly, female aged 63; and (**c**) diastolic heart failure patient, female aged 81. Note the increased mass and volume for (**b**) and (**c**) as well as the increased left atrial size in (**c**). *LV* left ventricle, *EDV* end-diastolic volume (Images courtesy of the Alberta HEART Study)

for filling [40]. Conversely, DHF patients operate at increased end-diastolic filling pressures during resting conditions due to increased ventricular stiffness in addition to impaired relaxation [40]. In a study of 70 patients with DHF, rapid pacing (120 BPM) or handgrip exercise resulted in increased diastolic pressures and reduced stroke volumes and was attributed to increased ventricular stiffness [42]. Measuring diastolic dysfunction in clinical practice is challenging. Surrogate measures of diastolic dysfunction are routinely obtained on Doppler echocardiography; however, a large clinical trial of DHF found that these echo measures were unable to identify HF cases majority (86 %) of the time [43]. Indeed, others have shown that these echocardiographic measures of diastolic dysfunction cannot reliably distinguish hypertensive patients with left ventricular hypertrophy from patients with DHF [37].

Loading conditions also strongly modulate diastolic function; therefore all measures of diastolic function have to be interpreted in the context of how the heart couples with the arterial and venous systems [44]. In a study of 17 patients with DHF, impaired arterial vascular reserve and blunted heart rate response were the primary mechanisms for poor exercise performance, whereas diastolic filling (diastolic function) was no different from hypertensive controls [45]. Furthermore, significant increases in afterload have been shown to impair relaxation in normal hearts and in HF [46].

The Challenge of Diagnosing DHF in the Elderly

Current guidelines recommend establishing the diagnosis of DHF based on the presence of symptoms and signs of HF as well as evidence for preserved ejection fraction (EF>50 %) [47, 48]. However, symptoms of low exercise tolerance are common in the elderly and likely reflect physiologic changes occurring with normal aging. Aging has been associated with a 10 % decline in peak VO2 max per decade [49]. This phenomenon

can be partly attributed to age-associated reductions of skeletal muscle mass and function [50] and lung function [51]. Indeed, in a clinical cohort of elderly patients presenting with dyspnea, impaired lung function was the main abnormality in over half of cases, whereas a primary cardiac cause was found in only 18 % [52]. In a recent study of 48 patients with DHF, the strongest correlates for reduced exercise tolerance were low cardiac output and low peripheral oxygen utilization (arterial-venous oxygen difference) [53]. The latter finding suggests that abnormalities in skeletal muscle perfusion and oxygen extraction are important mediators of the functional limitations in DHF.

The most commonly used biomarker for diagnosing DHF is B-type natriuretic peptide (BNP). BNP is a circulating peptide that is synthesized and released in response to left ventricular wall stretch. The European DHF guidelines recommend using BNP as laboratory evidence for raised intracardiac pressures. However, BNP levels in DHF are significantly lower than those seen in SHF, particularly in an outpatient setting [54], and do not always discriminate DHF from age-matched controls [55]. Newer serum biomarkers that are not dependent on the volume status are promising. As mentioned earlier, patients with DHF have been shown to have increased markers of inflammation (IL-6, IL-8, and MCP-1), myocardial fibrosis (PIIINP, CITP), and matrix remodeling proteins (MMP-2, MMP-9) [56]. Contrast-enhanced T1 mapping techniques on MRI have also been correlated to histologically proven myocardial fibrosis in a group of HF and transplant patients [57] and can detect subclinical myocardial disease in ischemic and nonischemic cardiomyopathy [58]. However, these load-independent blood and imaging biomarkers require more study before their widespread adoption in a clinical setting.

Treatment Strategies

As mentioned, age-adjusted incidence of HF has not declined substantially in the past 20–30 years in spite of enhanced control of causal factors. The Canadian EFFECT study examined consecutive HF patients, observing no significant difference in the 1-year survival between DHF and SHF [59]. However, pharmacotherapy aimed at reversing cardiac remodeling has been associated with clinical benefits. The treating professional also needs to be mindful of treatment goals in elderly patients, namely, symptom relief, improving functional capacity, quality of life, preventing acute exacerbations/hospital admissions, and potentially prolonging life.

Recent consensus documents recommend initiating drug therapy at the lowest possible dose and increasing gradually depending on blood pressure (BP) response. Of note, in the elderly "full dose" may not be the maximum recommended dosage applicable to the general adult population, and that treatment must be individualized [60] (Fig. 7.3). Careful consideration must also be applied to comorbid diseases, concomitant medications, and renal function. Target BP in the elderly, as in other adult populations with uncomplicated HTN, is 140/90 mmHg. However, significant reduction in BP may result in orthostatic hypotension in the elderly as well as other negative symptoms. Nonetheless, careful pharmacotherapy is warranted; in the LIFE study, reduction of LV hypertrophy was associated with a 36 % reduction in HF diagnosis and improved diastolic function [61].

While large-scale, well-designed studies have been undertaken in patients with DHF, to date, the results of pharmacotherapeutic management have been disappointing. Meta-analysis was recently undertaken of randomized studies examining effect of pharmacologic intervention on diastolic function, exercise tolerance, and mortality; while improvements in exercise capacity were shown, no improvement in diastolic function or mortality was observed [62].

These results raise the question of appropriate trial endpoints in such patient populations; outcomes including symptom relief, physical well-being, and quality of life may be more relevant and achievable. Therefore, health promotion and lifestyle modification should be the mainstay of care and may well be the only therapy required. Clinical assessments and interventions into regular

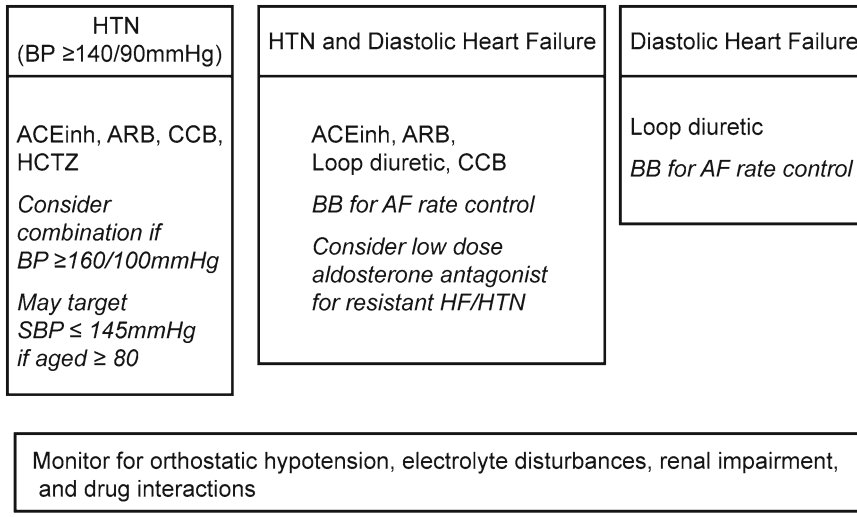

Fig. 7.3 Suggested pharmacotherapy for elderly with hypertension and/or diastolic heart failure. *BP* blood pressure, *SBP* systolic blood pressure, *ACEin* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker, *HCTZ* hydrochlorothiazide, *BB* beta-blocker, *AF* atrial fibrillation, *HF* heart failure, and *HTN* hypertension (adapted from Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, Brown AS, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. J Am Coll Cardiol. 2011 May 17;57(20):2037–114. PubMed PMID: 21524875 and Cheng JW, Nayar M. A review of heart failure management in the elderly population. Am J Geriatr Phamacother 2009 Oct,7(5):233–49)

physical exercise to influence weight reduction and improve mood; dietary modifications with attention to sodium, caloric, and alcohol intake; and smoking reduction should be a basic aspect of care. This is best undertaken by a multidisciplinary team of dieticians, pharmacists, exercise therapists, and other healthcare professionals, as regular assessments and interventions provided by these professionals have been shown to improve multiple outcomes [63–66]. Unfortunately, in the traditional model of care delivery, this is largely ignored; nutrition and exercise advice is offered to patients with HTN at only 35 and 26 % of clinic visits [67].

Future Directions

Certainly, improved understanding of the multiple effects of aging on the cardiovascular system is required in order to make meaningful differences in outcomes. Study of mechanistic targets associated with hypertrophy, antifibrotic agents, titin modification, and calcium homeostasis is urgently needed to move forward with appropriate clinical study. Randomized trials are currently underway, guided by the experiences of previous studies and basic science. PDE5 is markedly upregulated with oxidative stress and pressure overload hypertrophy both common in DHF. The PhosphodiesteRasE-5 Inhibition to Improve CLinical Status And EXercise Capacity in Diastolic Heart Failure (RELAX trial; clinicaltrials.gov NCT00763867) trial will examine the effect of 24 weeks of sildenafil versus placebo in patients with DHF, with the primary endpoint peak exercise oxygen consumption [68].

Sedentary lifestyles are widely prevalent in both developed and developing countries, leading to significant difficulties applying health promotion interventions such as regular exercise. Chronic exercise in humans has been convincingly

shown to convey beneficial effects on maximum oxygen consumption, cardiac function (diastolic filling, myocardial relaxation) compliance, and diastolic function [36, 69, 70] . Further, regular physical activity (2.5 h/week moderate–vigorous) is associated with lower inflammatory markers at 10 years follow-up. In 4,289 adults (mean age 49.2) from the Whitehall II cohort study, physically active participants at baseline had lower CRP and IL6 levels and this difference remained stable over time [70]. The authors concluded that regular exercise is beneficial in preventing this proinflammatory state, which may ultimately attenuate aging effects on the cardiovascular system.

Challenges may also arise with exercise interventions later in the aging and disease trajectory. Poor exercise tolerance and breathlessness, experienced by deconditioned and DHF patients, may present theoretical difficulties in tolerating even very mild forms of exercise [52, 53]. Hemodynamic disturbances worsened or elicited with exercise and inability to increase systolic and diastolic function with exercise (reduced rotation, delayed untwisting, reduced suction) compared to controls have been documented [71, 72]. However, Edelman reported a pilot study of 64 DHF patients (71 screened) randomized 2:1 to aerobic/resistance training; 86 % of participants adhered to greater than 70 % of the prescribed exercise sessions. No adverse events occurred, and the primary endpoint of improved VO2 peak at 3 months was observed (from 16.1 ± 4.9 to 18.8 ± 5.4 mL/kg/min) [73]. Here, quality of life was improved, as well as echocardiographic measures of LV diastolic function and atrial reverse remodeling. The contribution of systems other than cardiovascular must also be considered in this patient population. Haykowsky examined 40 elderly (69 ± 6 years) DHF patients after 4 months of supervised endurance training compared to controls, observing improved peak VO2 in trained versus controls (16.3 ± 2.6 vs. 13.1 ± 3.4 mL/kg/min) [74]. Importantly, improved peak A-VO2 Diff was improved while no significant improvements in peak EDV, stroke volume, or cardiac output were observed. This key finding indicates skeletal muscle adaptations as a result of exercise training, and other non-cardiac interventions to the oxygen cascade may prove to be the most worthwhile therapeutic approach to DHF. Future work should examine optimal timing of interventions, advantageous training approaches, prescribing exercise interventions in the setting of other comorbidities, and improved understanding of both cardiovascular and systemic effects of exercise interventions.

Recognizing the imminent burden of aging and CVD, the Center for Disease Control recommends five activities necessary to promote health and prevent disease in the elderly:

1. To provide high-quality health information and resources to public health professionals, consumers, healthcare providers, and aging experts.
2. To support healthcare providers and healthcare organizations in prevention efforts.
3. To integrate public health prevention expertise with the aging services network.
4. To identify and implement effective prevention efforts.
5. To monitor changes in the health of older adults [1].

These activities will require enthusiasm and involvement across multiple sectors as well as financial support. The special needs of older adults must be recognized and programs delivered in communities where older adults work, reside, and congregate. Ongoing evaluation of acceptability and short/long-term health outcomes will be necessary.

> "*If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health.*" *Hippocrates*

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8 Polypharmacy and Adverse Drug Reactions in the Aging Population with Heart Failure

Michael W. Rich and William J. Nienaber

Aging is associated with numerous alterations in body composition and organ function that result in substantial changes in the absorption, distribution, metabolism, and elimination of virtually all drugs (Table 8.1) [1, 2]. In addition, older patients with heart failure (HF) almost invariably have multiple coexisting medical conditions for which they are receiving medications [3, 4]. Taken together, these factors greatly increase the risk for adverse drug events and drug interactions among older HF patients. Adverse drug events are estimated to account for 5 % of all hospital admissions, and HF medications (digoxin, diuretics, calcium channel blockers) are among the most frequently cited medications [5]. This chapter reviews common adverse drug effects and drug interactions associated with HF therapy in older patients and discusses strategies for minimizing the risk of adverse drug events. In addition, the intersection between HF medications and common geriatric syndromes, including polypharmacy, falls and syncope, and fatigue and low energy, is briefly reviewed.

M.W. Rich, MD (✉)
Washington University School of Medicine,
660 S. Euclid Avenue, Campus Box 8086,
St. Louis, MO 63110, USA
e-mail: mrich@wustl.edu

W.J. Nienaber, MD
Cheyenne Cardiology Associates,
Cheyenne, WY, USA

Adverse Events from Heart Failure Medications

Diuretics

Renal function, as measured by the creatinine clearance or glomerular filtration rate (GFR), declines by 5–10 cc/min/decade [6–8]. As a result, the prevalence of chronic kidney disease (CKD), defined as an estimated GFR < 60 cc/min/1.73 m^2, increases with age. Due to decreased muscle mass, serum creatinine levels may not accurately reflect renal function in the geriatric patient, and a normal creatinine may accompany moderately impaired renal function. In addition, alterations in renal tubular function lead to reductions in concentrating and diluting capacity and impaired ability to maintain electrolyte homeostasis [8]. These changes increase the propensity of older patients to develop significant electrolyte disturbances, including hyponatremia, hypokalemia, and hypomagnesemia, in response to thiazide and "loop" diuretics. Furthermore, aging is associated with a reduction in the thirst mechanism, which predisposes older patients to dehydration during chronic diuretic therapy [9]. Not uncommonly, overdiuresis is manifested by relative hypotension, altered sensorium, and evidence for prerenal azotemia (i.e., an increase in the blood urea nitrogen (BUN) to serum creatinine ratio). Conversely, older patients may be less responsive to diuretics

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Table 8.1 Age-related changes in body composition and organ function

Alterations in body composition
Reduced lean body mass, especially muscle mass
Reduced total body water
Increased fat to lean body mass ratio
Alterations in organ function
Decreased intestinal absorption
Decreased hepatic metabolism and clearance
Decreased renal clearance

due to age-related alterations in renal function, and there is some empiric truth to the adage "age + BUN = Lasix dose" [10].

The implication of these changes is that older patients treated with diuretics may require more vigilant follow-up than younger patients, with more frequent assessments of renal function, serum electrolyte levels, and volume status in order to ensure that congestion and edema are adequately controlled without adversely impacting renal function or electrolytes. In many older patients with advanced HF and/or significant renal insufficiency, it may be difficult to balance the two interrelated disorders, and it may be necessary to accept a "happy medium" [11], i.e., some degree of residual volume overload in conjunction with slight worsening of renal function. With regard to managing hypokalemia and hypomagnesemia, increased dietary intake of these electrolytes should be encouraged, and supplemental potassium and magnesium should be prescribed as needed. However, since older patients are also at increased risk for hyperkalemia, dose requirements for potassium supplements are often lower in older than in younger patients, and serum potassium levels should be monitored more closely.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blockers

As with diuretics, age-related changes in renal function predispose older patients to increased risk of worsening renal function with both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs). In addition, older patients may be at increased risk for hypotension and hyperkalemia with these agents. Overdiuresis and intravascular volume contraction further increase the risk of both renal impairment and hypotension, and hypotension itself often adversely affects renal function. Although relatively rare, altered taste may also be more common in older patients treated with ACEIs; the mechanism for this association is unknown. Other side effects, such as allergic reactions and ACEI-associated cough, do not appear to differ in frequency between older and younger patients. Importantly, although ARBs are less likely to cause cough or allergic reactions than ACEIs in patients of all ages, the incidence rates of worsening renal function, hyperkalemia, and hypotension are similar with ACEIs and ARBs [12, 13].

Because of the potential for causing worsening renal function, ACEIs and ARBs should generally be avoided in elderly patients with stage IV or stage V CKD (i.e., estimated GFR < 30 cc/min/1.73 m^2 based on the Cockcroft-Gault [14] or modification of diet in renal disease (MDRD) [15] equation) who are not on dialysis. In patients with stage III CKD (30 cc/min/1.73 $m^2 \leq$ GFR < 60 cc/min/1.73 m^2), ACEI or ARB therapy should be initiated at a low dose with very gradual titration, monitoring renal function and serum potassium levels closely. Small increases in the serum creatinine level (< 0.5 mg/mL) do not mandate discontinuation of ACEIs or ARBs but should prompt careful assessment of volume status and consideration of a reduction in diuretic dosages. Importantly, the average age of patients enrolled in the ACEI and ARB clinical trials was approximately 60 years [16], whereas the median age of HF patients in the community is about 75 years, raising concerns about both the efficacy and dosing of these agents in the older adult population. Despite this caveat, target doses of ACEIs and ARBs are generally similar in older and younger patients, but older patients may be less likely to tolerate guideline-recommended doses [17], in part due to concomitant use of multiple other medications. Although low-dose ACEIs are less effective than

full doses, there is evidence that even very low doses are beneficial in patients with severe left ventricular (LV) systolic dysfunction [18].

Aldosterone Antagonists

Age-related alterations in renal function greatly increase the risk of hyperkalemia in older patients treated with spironolactone or eplerenone, and older patients are at increased risk for worsening renal function with these agents as well [19, 20]. Due to an age-associated decline in testosterone levels in older men, spironolactone-related gynecomastia may be more common in older than in younger patients [21].

Aldosterone antagonists are contraindicated in patients with stage IV or stage V CKD who are not on dialysis [22]. For older patients with stage III CKD, the starting dose of spironolactone and eplerenone should be 12.5 mg daily (or 25 mg every other day). If tolerated, the dose can be increased to 25 mg daily. For patients with preserved renal function (estimated GFR $\geq$ 60 mL/min/1.73 m^2), the starting dose is 25 mg daily and the dose can be increased to 50 mg daily if tolerated. In all patients, serum creatinine and potassium levels should be monitored closely.

Beta-Blockers

Aging is associated with a progressive decline in the number of functioning sinus node pacemaker cells as well as degenerative changes throughout the cardiac conduction system [23, 24]. As a result, older patients are at increased risk for sinus bradycardia and AV-nodal conduction disorders. Treatment with beta-blockers often potentiates age-related changes leading to symptomatic bradyarrhythmias. The incidence of other side effects from beta-blockers appears to be similar in older and younger patients.

As in younger HF patients, beta-blockers should be initiated at the lowest available dose and titrated gradually to guideline-recommended target dosages. As with ACEIs and ARBs, older patients may be less able to tolerate high doses of beta-blockers, but most patients respond adequately to intermediate dosages (e.g., carvedilol 12.5 mg BID or metoprolol 50–100 mg daily). An electrocardiogram (ECG) should be obtained after initiating beta-blocker therapy and after each dose escalation to assess AV conduction. In patients with clear indications for beta-blocker therapy (e.g., LV ejection fraction < 40 %) who develop symptomatic bradyarrhythmias, implantation of a permanent pacemaker should be considered.

Digoxin

Age-related declines in renal function and lean body mass lead to reductions in the clearance and volume of distribution of digoxin, respectively [25]. As a result, equivalent dosages of digoxin are associated with higher serum digoxin concentrations in older than in younger patients, and this difference appears to be more pronounced in women than in men [26]. However, with appropriate dosage adjustment for renal function and lean body mass, older patients do not appear to be at increased risk for clinically significant digoxin toxicity. In the Digitalis Investigation Group (DIG) trial, for example, hospitalizations for suspected digoxin toxicity increased progressively with age in both the digoxin and placebo arms, but there was no incremental increase in the absolute risk of digoxin toxicity with increasing age, even in octogenarians [27]. Despite these findings, older patients may still be at increased risk for digoxin toxicity due to higher prevalence of electrolyte abnormalities (i.e., hypokalemia, hypomagnesemia, and hypercalcemia), chronic lung disease, and possibly cardiac amyloid [25]. The most common and well-recognized side effects of digoxin include cardiac arrhythmias (both tachycardias and bradycardias), gastrointestinal disturbances (nausea, diarrhea, anorexia, abdominal discomfort), and central nervous system (CNS) disorders (visual disturbances, especially photopsia and chromatopsia, headache, weakness, and altered mental status). Older patients with underlying cognitive dysfunction, even if not clinically recognized, may be at

increased risk for cognitive decline, loss of memory, disorientation, irritability, and depression when receiving digoxin. Similarly, older patients with significant vascular disease may be at increased risk for abdominal discomfort and intestinal ischemia [28].

To minimize the risk of side effects and toxicity, the dose of digoxin should be adjusted based on renal function and lean body mass. Although current guidelines do not recommend routine measurement of the serum digoxin concentration, it seems reasonable to assess the serum digoxin level after initiating therapy and periodically thereafter to ensure that it is within the therapeutic range, especially in older patients with impaired or fluctuating renal function. Data from the DIG trial indicate that the optimal therapeutic range for digoxin is 0.5–0.9 ng/mL, with higher levels being associated with increased toxicity without additional benefit [26]. Serum electrolytes should also be monitored, especially potassium and magnesium, and levels of these electrolytes should be maintained within the normal range. Treatment of digoxin toxicity is similar in older and younger patients.

Hydralazine and Nitrates

Side effects from hydralazine (headache, gastrointestinal disturbances, palpitations, worsening angina) and nitrates (headache, dizziness, flushing) are relatively common, but there is no convincing evidence that older patients are at increased risk for side effects with these medications. As with other medications, treatment of older patients with hydralazine and nitrates should be initiated at low dosages (e.g., hydralazine 10–25 mg TID, isosorbide dinitrate 10 mg TID) and titrated gradually to the target dosages as tolerated. No specific monitoring is required.

Calcium Channel Blockers

Calcium channel blockers (CCBs) are generally contraindicated in patients with systolic HF but may be necessary for management of comorbid hypertension, angina, or atrial fibrillation [22]. As with beta-blockers, older patients are at increased risk for bradyarrhythmias with diltiazem or verapamil. Constipation is a common side effect in older patients during long-term therapy with verapamil; less commonly, diltiazem induces constipation. Although the vasodilatory effects of all CCBs may lead to non-pitting lower extremity edema, this side effect is more common with the dihydropyridines, and older patients are at greater risk due to age-related alterations in venous function and preexisting disease of the venous system.

Bradyarrhythmias associated with diltiazem or verapamil should prompt dose reduction or discontinuation, if feasible. Significant constipation impairs quality of life and may lead to bowel obstruction or ileus [29]. Physicians should be alert to this condition in patients receiving diltiazem or verapamil and consider alternative therapy. Edema associated with CCBs should be managed with support stockings, diuretics, and consideration of dose reduction or discontinuation.

HF with Preserved Ejection Fraction

The proportion of HF patients with preserved LV ejection fraction (HFPEF) increases with age, exceeding 40 % in men and 60 % in women after age 70 [22, 30, 31]. Although the potential for adverse drug events is generally similar in patients with HFPEF as in those with reduced ejection fraction, there are some significant differences. Most importantly, patients with HFPEF tend to be "preload dependent"; i.e., the LV filling pressure must be maintained in order to maximize stroke volume and cardiac output [22, 31]. As a result, such patients are often "volume sensitive" and susceptible to reduced cardiac output and worsening prerenal azotemia in response to overzealous diuresis [22, 31]. In addition, diminished renal perfusion predisposes to worsening renal function and hyperkalemia during treatment with ACEIs and ARBs. Patients with HFPEF are also reliant on atrial contraction to optimize LV end-diastolic volume and may be less tolerant of

atrial fibrillation with rapid ventricular response, a common disorder in this population [32]. It is therefore essential to monitor electrolytes, especially potassium and magnesium, during diuretic therapy. Impaired LV diastolic filling may lead to a relatively fixed LV end-diastolic volume and an associated failure to increase stroke volume in response to exercise. Since cardiac output is the product of heart rate and stroke volume, patients with HFPEF are often dependent on augmentation of heart rate in order to increase cardiac output. As a result, beta-blockers, especially at high doses, may aggravate rather than alleviate exercise intolerance. Moreover, the presence of chronotropic incompetence due to age-related sinus node dysfunction (sick sinus syndrome) or HF itself may potentiate the adverse effects of beta-blockers on exercise tolerance. Clinicians treating older patients with HFPEF should remain alert to the potential for adverse drug events with diuretics, ACEIs, ARBs, and beta-blockers and adjust medication dosages or consider alternative agents accordingly.

Drug Interactions

General Principles

Depending on symptoms and LV function, current HF guidelines recommend a minimum of 2 drugs and as many as 7 [22]. Additional medications are often needed to treat other cardiovascular conditions, such as hypertension, coronary artery disease (CAD), and atrial fibrillation. The prevalence of noncardiovascular comorbidities, including arthritis, osteoporosis, diabetes mellitus, chronic lung disease, gastrointestinal disorders, and neurological conditions, also increases with age. As a result, older patients with HF are commonly prescribed 5–15 medications (or more!). Not only does this place a high burden on the patient in terms of cost and adherence, but the risk of drug interactions increases exponentially as the number of medications increases, such that the likelihood of significant drug-drug interactions exceeds 90 % in patients taking 10 or more medications [32].

Common Drug Interactions

Given the diversity of medications prescribed and frequency of prevalent comorbidities in older HF patients, it is not possible to provide a comprehensive discussion of potential drug interactions. Instead, some of the most common and clinically important interactions involving HF medications will be reviewed.

Nonsteroidal anti-inflammatory drugs (NSAIDs) increase renal sodium and water retention and may worsen kidney function, especially in patients with preexisting renal impairment [33]. In addition, NSAIDs antagonize the salutary effects of ACEIs, ARBs, diuretics, and possibly beta-blockers in patients with HF [34]. These interactions are more common in older patients, who are both more likely to have CKD and more likely to be taking NSAIDs on a chronic basis for treatment of arthritis. Indeed, in one study, initiation of NSAIDs was shown to increase the risk of hospitalization for HF by a factor of 1.6 in older patients without prior cardiovascular disease (CVD) and by a factor of 10 in older patients with prior CVD [35].

Amiodarone is often used to treat atrial fibrillation or ventricular arrhythmias in HF patients. Amiodarone potentiates the effects of numerous drugs, including digoxin, beta-blockers, CCBs, warfarin, and dabigatran [36]. Dronedarone has similar but less potent interactions with these drug classes, with the exception of warfarin, for which there is no clinically significant interaction [37]. In general, downward dosage adjustment and close monitoring are essential when initiating amiodarone or dronedarone in patients receiving any of these other agents.

The combination of an ACEI or ARB with an aldosterone antagonist (or other potassium-sparing diuretic, e.g., triamterene) substantially increases the risk of hyperkalemia, and older patients are at greater risk than younger patients due to age-related changes in renal function [19, 20, 38]. For similar reasons, the combination of an ACEI with an ARB is more likely to induce worsening renal function and hyperkalemia in older patients.

Coadministration of digoxin with other AV-nodal blocking agents (beta-blockers, diltiazem,

verapamil, and amiodarone) increases the risk for bradyarrhythmias, to which the elderly may be particularly prone due to age-related slowing of AV conduction. Use of multiple vasodilators, such as hydralazine, nitrates, and ACEI or ARBs, predisposes older adults to orthostatic hypotension. Further, concomitant use of a beta-blocker may blunt the normal increase in heart that occurs in response to an orthostatic fall in blood pressure. Thus, it is important to routinely monitor orthostatic vital signs in older adults receiving multiple HF medications.

Nonprescription Drugs

Apart from prescription medications, older patients are frequent users of over-the-counter (OTC) medications and dietary supplements [39]. Several of these agents have the potential to interact with HF and/or HF medications. Decongestants in OTC cold preparations can increase heart rate and blood pressure and increase the risk for supraventricular and ventricular arrhythmias while reducing the efficacy of beta-blockers. A partial listing of potential interactions between commonly used dietary supplements and HF medications is provided in Table 8.2 [40].

Table 8.2 Potential interactions between dietary supplements and heart failure medications

Supplement	HF medication	Interaction
Aloe vera	Digoxin	Increased toxicity due to hypokalemia
Black cohosh	Diuretics	Decreased efficacy
Chaste tree	Beta-blockers	Increased effects
Dandelion	Diuretics	Increased effects
Ephedra, ma huang	Digoxin	Increased toxicity
	Beta-blockers	Decreased efficacy
Goldenseal	Digoxin	Increased effects
Hawthorn	Nitrates	Increased hypotensive effects
	Digoxin	Increased effects
Licorice	Digoxin	Increased toxicity due to hypokalemia
Nettle	Diuretics	Increased effects
Peppermint oil	Digoxin	Increased toxicity
Pumpkin seed	Diuretics	Increased effects
Senna	Digoxin	Increased toxicity due to hypokalemia
Siberian ginseng	Digoxin	Increased digoxin levels
St. John's wort	Digoxin	Increased effects

HF heart failure
Adapted from Cohen PA, Ernst E. Safety of herbal supplements: a guide for cardiologists. Cardiovasc Therapeutics 2010;28:246–253. With permission from John Wiley & Sons, Inc

Geriatric Syndromes

Polypharmacy

Polypharmacy, often defined as chronic use of 5 or more medications, is almost universal among older HF patients [39]. In a recent study, for example, the average number of medications taken by a population of older HF patients (mean age 74.5 years) was 10.2 ± 3.2 [41]. As noted above, the risk for adverse drug events and interactions increases with the number of medications prescribed, underscoring the importance of avoiding the use of all but the most essential drugs.

Management of polypharmacy starts with the acquisition of a complete and accurate list of all medications the patient is taking—both prescription drugs and OTC agents, including dietary supplements [11]. Periodic "brown-bag checks" (in which the patient brings all medication bottles to the appointment) are recommended and frequently reveal disparities between prescribed medications and what the patient is actually taking. Clinicians should routinely inquire about the use of OTC agents, herbal products, and dietary supplements. Often, practitioners do not question patients about the use of these agents, and patients commonly do not volunteer this information.

Drugs for which there is no clear indication for ongoing use should be discontinued and the medication regimen should be consolidated wherever feasible. However, experience demonstrates that clinicians are often reluctant to discontinue a medication, especially if they were not the original prescriber. There is also a paucity of data on how to best withdraw many medications, making clinicians more hesitant to do so.

Nonetheless, such reservations should not discourage the clinician from eliminating an unnecessary drug. Indeed, use of "inappropriate" medications is common in geriatric patients and is an important source of therapeutic mishaps [42]. Recently, the American Geriatrics Society published an updated list of medications considered "inappropriate" for use in geriatric patients in specific clinical situations [43]. This list, known as the Beers Criteria, is available at http://www.americangeriatrics.org/files/documents/beers/2012BeersCriteria_JAGS.pdf. It is also available on the free and searchable iPhone application entitled iGeriatrics.

Prescribing cascades are a well-described complication of polypharmacy [44]. This occurs when a new drug is prescribed in order to treat an unrecognized side effect of a current medication. Medication side effects are often vague and nonspecific in the geriatric population and may not be properly attributed to a current medication. An example is the inappropriate diagnosis of uncontrolled hypertension in a patient on high-dose NSAIDs for an arthritis flare. As a general rule, new symptoms should be considered drug-related until proven otherwise.

In an effort to maximize adherence, the regimen should be simplified, in terms of both the number of medications and the number of times during the course of the day that medications are taken (optimally no more than two or three discrete times). Age-related cognitive impairment increases the likelihood of nonadherence (often unintentional) with complex medication and dosing regimens [45]. Attention to potential drug interactions is crucial, with the goal of eliminating or reducing the dosage of any drugs likely to cause clinically relevant drug interactions. If available, the services of a clinical pharmacist with expertise in geriatric drug prescribing can facilitate optimization of the medication regimen [41]. Adoption of non-pharmacological treatment strategies whenever possible (such as compression stockings for edema) may aid in simplifying drug regimens. All changes to the regimen should be carefully reviewed with the patient (and caregiver, if available) to ensure understanding of what medications are to be taken and when, as well as which medications are no longer needed. Importantly, the patient should be educated on both generic and brand names. Not uncommonly, the older patient is taking twice the prescribed dose of a medication, believing that the brand medication and generic medication are different drugs. Medication aids, such as pillboxes, are effective in increasing the likelihood that patients will take medications as intended by the physician [11, 46].

Falls and Syncope

Age-related changes in the vasculature and carotid baroreceptors predispose older patients to orthostatic hypotension [47]. Additional changes in the central nervous system and musculoskeletal system further impair the older patient's ability to adapt rapidly to alterations in body position, thereby increasing the risk for falls. Moreover, due to age-related changes in autonomic function and sinus node function, the heart is less able to increase cardiac output in response to an abrupt fall in blood pressure (e.g., upon standing), as a result of which older patients are at increased risk for syncope [23, 47]. HF exacerbates many of these age-related changes, and, with the possible exception of digoxin, all of the standard HF medications further increase the older patient's risk for falls and syncope.

As noted above, in order to minimize the risk of medication-induced falls and syncope, it is important to routinely measure blood pressure (BP) in the sitting and standing positions to assess for orthostasis [48]. In patients who report marked light-headedness on standing, especially if associated with falls, near syncope, or syncope, or who have marked orthostatic hypotension (>30 mmHg decline in systolic BP with standing), it may be necessary to reduce the dosages of one or more HF medications. Such patients should also be educated on postural hygiene—i.e., to arise slowly, especially at night, and to use an assistive device, such as a cane, when ambulating. Support stockings and other non-pharmacological interventions may also be helpful [48].

Fatigue and Low Energy

Fatigue and low energy level are common symptoms in older patients [49]. Although these symptoms are usually multifactorial in origin, medications frequently contribute to or exacerbate them, leading to significant impairment in quality of life [50]. Beta-blockers may cause fatigue by reducing cardiac output and through direct effects on the CNS. An unexplained reduction in cognitive function or mood should prompt consideration of changing from a more lipophilic beta-blocker (e.g., metoprolol, carvedilol) to one that is more hydrophilic (e.g., bisoprolol) [51], although the value of this intervention is unproven. Diuretics can also cause fatigue due to dehydration, electrolyte disturbances, and/or worsening renal function. Diuretic-induced hypovolemia is often subtle in older patients, and the diagnosis requires a high index of suspicion. An additional and under-recognized cause of fatigue and low energy in older HF patients is low BP due to the cumulative effects of multiple medications. Age-related alterations in the CNS autoregulatory system reduce the older patient's capacity to maintain CNS perfusion as BP declines [52]. As a result, acute reductions in BP may lead to altered mental status, even in the absence of dizziness or syncope. Chronic low BP in older HF patients, whether due to low cardiac output or medications, often manifests as fatigue and low energy. In addition, blood pressure reduction may be associated with impaired cognition in older adults [53].

Older patients who report chronic fatigue and low energy should be evaluated for depression, anemia, sleep disorders, thyroid disease, and other organic causes of these symptoms. A comprehensive review of all medications should also be conducted to identify potential pharmacological causes of fatigue. When feasible, dosages of implicated drugs should be reduced or the agents should be discontinued. In patients with relatively low BP (e.g., systolic BP<110 mmHg) with persistent limiting fatigue despite the above measures, consideration should be given to reducing the doses of one or more HF medications to allow the systolic BP to increase to perhaps 120–130 mmHg while monitoring the effects of these interventions on the patient's sense of well-being, exercise tolerance, and HF symptomatology.

Summary and Conclusions

Diverse changes in multiple organ systems in conjunction with the effects of polypharmacy predispose older patients in general and HF patients in particular to an increased risk for adverse drug events and drug interactions. In order to minimize these risks, it is essential that clinicians avoid prescribing unnecessary medications, adjust medication dosages in order to optimally balance benefits and side effects, and remain ever vigilant to the potential for medications to cause or contribute to clinically important adverse events and impaired quality of life. In treating older HF patients, the oft-cited dictum "start low, go slow" clearly applies. Despite the inherent challenges, with careful management and close follow-up, most older HF patients can be successfully treated through the judicious use of guideline-recommended HF therapies.

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9 Age-Related Changes in Vascular Biology and Implications for Heart Failure Therapy in the Aging Population

Michael Sean McMurtry

Introduction

Heart failure is a very common cardiovascular disease, affecting more than six million adults in the USA [1] and accounting for approximately one death in nine [1]. Though heart failure can affect people of any age group, it is predominantly a disease of the elderly, with incidence roughly doubling with each decade over 65 in men and women [1]. Heart failure incidence, particularly among men, has not declined with advances in medical therapy [2, 3], and the preponderance of new incident cases has affected the elderly [4]. While advances in medical therapy have improved survival of heart failure overall [2–4], more than half of heart failure patients still die within 5 years [2], and improved medical therapy has benefitted the elderly the least [3]. Scientists and policymakers from the American Heart Association predict that heart failure prevalence will increase by ~25 % by 2030, affect 3.5 % of the population of the USA, and cost more than $US 77.7 billion in 2008 currency [5]. Heart failure statistics are similar in Canada; heart failure in Canada predominantly affects the elderly, is a common cause of morbidity and mortality, and is the source of substantial costs to the Canadian healthcare system [6]. Heart failure in the elderly is an important and growing problem worldwide.

While heart failure is more common and pernicious in the elderly in part due to higher prevalence and severity of risk factors for heart failure, like hypertension and coronary artery disease [1], the aging cardiovascular system is also affected by structural and functional changes, of both blood vessels and the myocardium, that contribute to heart failure pathogenesis and can exacerbate heart failure in elderly patients [7, 8]. The elderly are also more susceptible to heart failure with preserved left ventricular ejection fraction (HFPEF) [9, 10], a distinct subtype of heart failure that may be due in part to stiffening of the arterial vasculature [11]. Advanced age may also complicate medical therapy for heart failure, due to comorbidities and increased risk of side effects from medications [12]. This review will survey the epidemiology of heart failure in the elderly, the structural and functional changes of the cardiovascular system that are associated with aging, and the biological and molecular mechanisms associated with these changes and discuss their implications for the pathophysiology and management of heart failure in the elderly.

The Contribution of Risk Factors for Heart Failure in the Elderly

Heart failure is common in the elderly, affecting 11.5 % of men and 11.8 % of women over the age of 80 in the USA (see Fig. 9.1a) [1]. By contrast,

M.S. McMurtry, MD, PhD (✉)
Division of Cardiology, Department of Medicine, University of Alberta, 2C2 WMHSC 8440 112th Street, Edmonton, AB, Canada T6G 2B7
e-mail: mcmurtry@ualberta.ca

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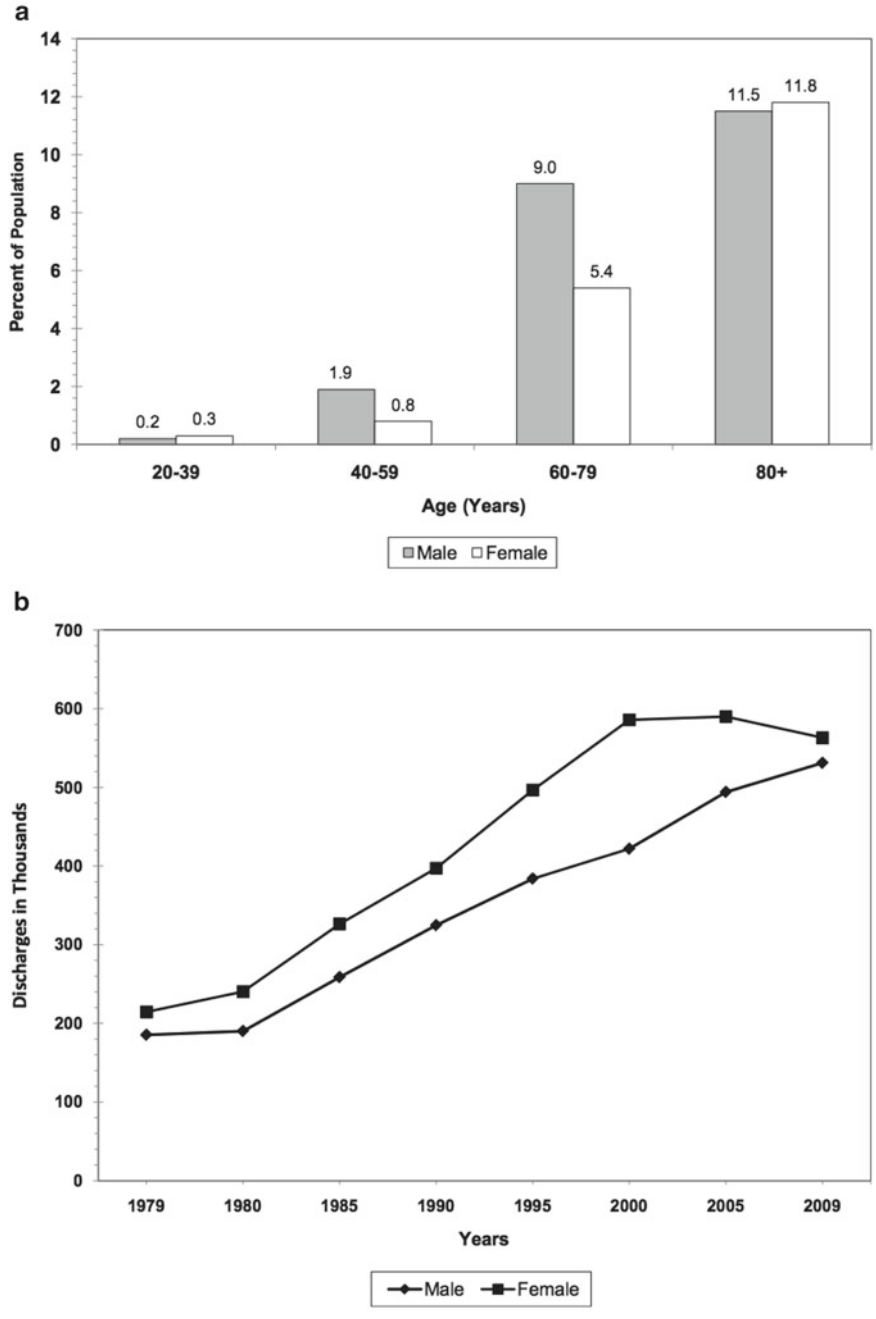

Fig. 9.1 Panel (**a**) Prevalence of heart failure by sex and age (National Health and Nutrition Examination Survey: 2005–2008). *Source*: National Center for Health Statistics and National Heart, Lung, and Blood Institute. Panel (**b**) Hospital discharges for heart failure by sex (United States: 1979–2009). Note: Hospital discharges include people discharged alive, dead, and status unknown. *Source*: National Hospital Discharge Survey/National Center for Health Statistics and National Heart, Lung, and Blood Institute (reprinted from Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics–2012 update: A report from the American heart association. Circulation. 2012;125:e2–e220. With permission from Wolters Kluwer Health)

the prevalence of heart failure before the age of 60 is an order of magnitude lower [1]. Similarly, data for the incidence of heart failure demonstrate that age is a marker of risk for incident heart failure, with the frequency of incident cases doubling with each decade over 65 (see Fig. 9.1b) [1]. A major reason for this preponderance of heart failure in the elderly is that the risk factors for heart failure disproportionately affect the elderly. In North America, the two main variables associated with incident heart failure are hypertension and myocardial infarction, though other modifiable risk factors such as tobacco smoking, physical inactivity, obesity, and chronic kidney disease are also important [13–15]. Prevalence of both coronary artery disease and hypertension increases dramatically with age, paralleling the age-associated increased prevalence of heart failure (Fig. 9.2) [1]. Since the main determinants of heart failure are more prevalent in the elderly, heart failure itself is more prevalent in the elderly. Increased exposure time to harmful variables, such as hypertension, may also explain the increase in heart failure with age [8], as pathogenic exposures like hypertension require time in order to induce heart failure. In addition, both hypertension and coronary artery disease worsen outcomes in those with established heart failure. Hypertension is associated with early mortality for those with cardiovascular disease [16], heart failure after myocardial infarction [17, 18], and worse survival for patients with established heart failure [19]. Myocardial infarction predicts incident heart failure [1], and prior myocardial infarction is associated with worse survival in heart failure, with very high mortality for those with cardiogenic shock [20]. Other comorbidities also complicate the course of patients with heart failure, and these comorbidities are more common in elderly patients with heart failure than young patients with heart failure [21]. Age-associated changes in pharmacokinetics, as well as polypharmacy for multiple medical conditions, can worsen outcomes in older patients with heart failure as well [12], and heart failure is associated with increased risk for adverse drug reactions [22]. Risk factors for heart failure, especially hypertension and myocardial infarction, and other comorbidities, play large roles in the development of heart failure with age, as well as outcomes associated with heart failure in the elderly.

Aging and the Peripheral Vasculature

In addition to increased prevalence of risk factors for heart failure associated with age, or increased exposure time to harmful influences like hypertension, aging is associated with specific structural changes in blood vessels over time in humans and in animals [8]. The circumference of the aorta in humans increases over time [23], as does the thickness of the aortic intima [24]. The aorta also increases in length over time [25]. Increases in intimal thickness occur in both rabbits [26] and nonhuman primates [27] as well (Fig. 9.3a). Noninvasive measurements of carotid intimal thickness have demonstrated age-dependent increases in multiple cohorts of human patients [28]. Though some have argued that increased intimal thickness is a form of early atherosclerosis, these changes are observed in humans at low risk of atherosclerosis [24], and carotid intimal–medial thickness on ultrasound only weakly predicts atherosclerotic events after adjustment for other cardiovascular risk factors [29, 30]. Other age-associated structural changes within the aorta have been described, including pooling of mucoid material, or cystic medial necrosis; elastin fragmentation; fibrosis, or increase in collagen at the expense of smooth muscle cells; and loss of smooth muscle cells (medionecrosis), but it is not clear if these are normal features of aging or features of disease [23, 31, 32]. Vascular wall stiffening (arteriosclerosis) induced by an increased collagen to elastin ratio occurs in rats, supporting that this is a typical feature of aging [33]. These age-associated structural changes alter the biomechanical properties of arteries and have hemodynamic consequences that are relevant for human diseases [34].

Functional changes occur within the walls of arteries with age, as well [35, 36]. Aging is associated with reduced endothelial vasodilatory function in both men and women, but this loss of

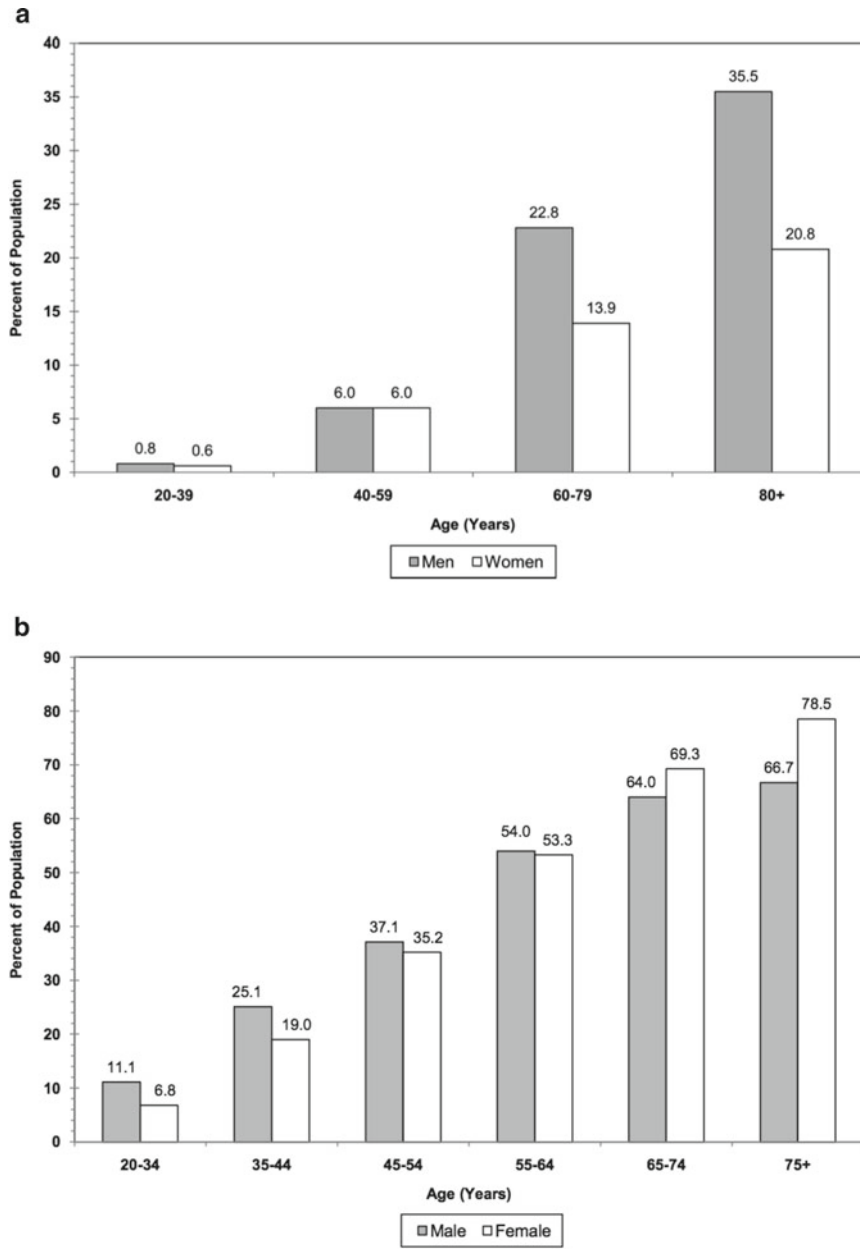

Fig. 9.2 Panel (**a**) Prevalence of coronary heart disease by age and sex (National Health and Nutrition Examination Survey: 2005–2008). *Source*: National Center for Health Statistics and National Heart, Lung, and Blood Institute. Panel (**b**) Prevalence of high blood pressure in adults ≥20 years of age by age and sex (National Health and Nutrition Examination Survey: 2005–2008). Hypertension is defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, taking antihypertensive medication, or being told twice by a physician or other professional that one has hypertension. *Source*: National Center for Health Statistics and National Heart, Lung, and Blood Institute (reprinted from Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics–2012 update: A report from the American heart association. Circulation. 2012;125:e2–e220. With permission from Wolters Kluwer Health)

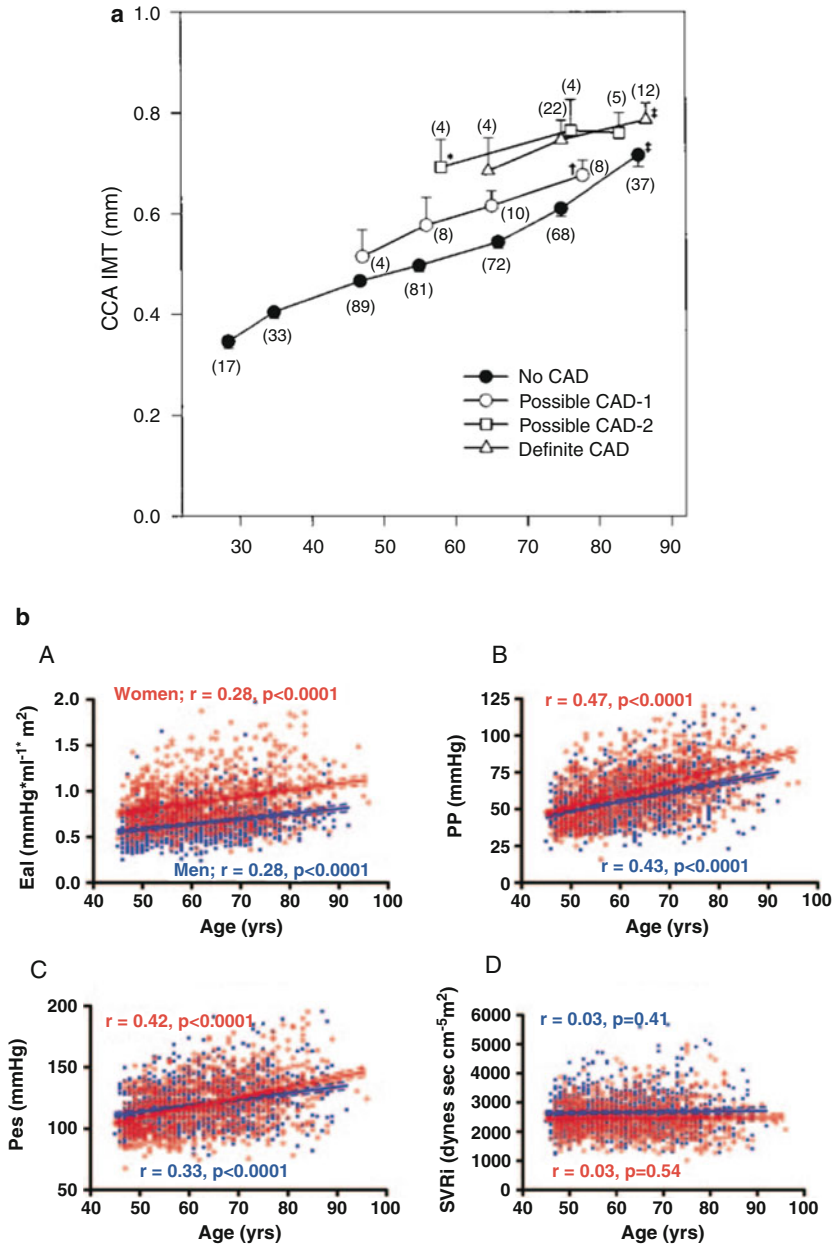

Fig. 9.3 Panel (**a**) CCA IMT by CAD status defined by exercise ECG, thallium scintigraphy, and clinical manifestations. Group definitions are as follows: possible CAD-1, subset with positive exercise ECG but negative thallium scan; possible CAD-2, subset with concordant positive exercise ECG and thallium scan; and no CAD and definite CAD. Each point represents the mean IMT of subjects in a given age decade for a specific CAD category (*asterisk*: 1950s and 1960s combined for possible CAD-2, *dagger*: 1970s and 1980s combined for possible CAD-1, and *double dagger*: 1980s and 1990s combined for no CAD and definite CAD). Error bars indicate SE; *numbers in parentheses* indicate number of subjects represented by each data point. After adjustment for age, IMT significantly increased from no CAD to possible CAD-1 to possible CAD-2 but did not differ between possible CAD-2 and definite CAD (adapted from Nagai Y, Metter EJ, Earley CJ, Kemper MK, Becker LC, Lakatta EG, Fleg JL. Increased carotid artery intimal-medial thickness in asymptomatic older subjects with exercise-induced myocardial ischemia. Circulation. 1998;98:1504–1509. With permission from Wolters Kluwer Health). Panel (**b**) Association of age with vascular function in men and women in the population. Arterial elastance indexed to BSA (EaI, **b**-A), pulse pressure (PP, **b**-B), and Pes (**b**-C) increases with age in men (*blue*) and women (*red*) in the population. SVRi (**b**-D) does not change with age. Raw data points, the linear regression line with 95 % CIs, Pearson's correlation coefficient, and probability values for the associations are shown (adapted from Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: A community-based study. Circulation. 2005;112:2254–2262. With permission from Wolters Kluwer Health)

endothelial function occurs later in women [37], corresponding the later age at which atherosclerotic cardiovascular disease afflicts women [1]. Endothelial dysfunction is observed in aged monkeys as well, independent of atherosclerosis [38], suggesting an age-dependent, as opposed to a disease-dependent, phenomenon. Reductions in vasodilation in the context of aging appear linked to loss of function located with endothelial cells, with the ability of vascular smooth muscle cells in the media to relax preserved with age [39]. Multiple endothelial-dependent relaxing mechanisms are impaired by age, including the nitric oxide pathway, the prostacyclin pathway, and the endothelium-derived hyperpolarizing factor pathway [40–43]. Excesses of reactive oxygen species within the artery wall, such as superoxide [44] and peroxynitrite [45], may also be important in age-associated endothelial dysfunction. Age-related reductions in gene expression of relevant enzymes, such as prostacyclin synthase [46] and nitric oxide [47], may explain these findings, though the specific molecular mechanism may vary across vascular beds [48]. Alterations in endogenous vasoconstrictors, like endothelin, may also contribute to impairments in vascular tone with age [43, 49]. Some of these age-associated changes in endothelial function may be reversible. For example, exercise restores the expression of endothelial nitric oxide synthase in rats [50] and is associated with improved nitric oxide availability and reduced endothelin-1 concentration in humans [51, 52].

In addition to structural changes and loss of endothelial function with age, other pathological processes can also affect blood vessels with age. Atherosclerosis is age dependent, and atherosclerosis of coronary, cerebral, and peripheral arteries, including the aorta, increases with age [1]. It has been shown that age-related alterations in arterial structure interact with atherosclerotic exposures, such as high-cholesterol diet, to yield more severe and complex atherosclerotic lesions [26]. Endothelial dysfunction in humans, measured by flow-mediated vasodilation, is associated with incident atherosclerotic events [53, 54], supporting that the two processes are linked and that accumulated atherosclerosis has functional consequences. Epidemiologic data support that concomitant coronary artery disease is associated with worse outcomes in heart failure patients [20]. In addition to atherosclerosis, calcification is an important arterial structural change associated with both age and cardiovascular disease [55]. Vascular calcification can affect the intima and media and results from a complex process in which a balance of promoting and inhibiting factors is perturbed [56]. Several cell types have been implicated in this complex process, including vascular smooth muscle cells [57], interstitial valve cells [58], circulating osteoprogenitor cells [59], and mesenchymal pluripotent cells [59]. Calcification of the arterial tree, in particular the aorta, has long been associated with both age and cardiovascular disease [59]. Coronary calcium scores, measured by CT scan, are a superior tool to predict cardiovascular events in humans [60]. Calcification of the aorta is associated with arterial calcification in other beds and predicts mortality [61, 62]. The extent and location of arterial calcification may modulate the risk for total mortality, cardiovascular mortality, and cardiovascular events [63].

Hemodynamic Changes with Age

The structural and functional changes of arteries associated with aging have functional consequences [64]. Epidemiologic studies have shown that with age, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and pulse pressure all increase over the years 30–60 [65]. After age 60, diastolic pressure declines, pulse pressure rises steeply, and mean arterial pressure and systolic pressure increase modestly, consistent with increased large artery stiffness [65]. Vascular resistance increases as well, but only large artery stiffness explains the increasing pulse pressure and falling diastolic blood pressure after the age of 60 (Fig. 9.3b) [65]. Aortic pulse wave velocity, a measure of aortic stiffness [66], is also an independent predictor of cardiovascular events in humans with hypertension [67] and is a good marker of subclinical large artery stiffening in older individuals [68]. Age and blood pressure appear to account for most

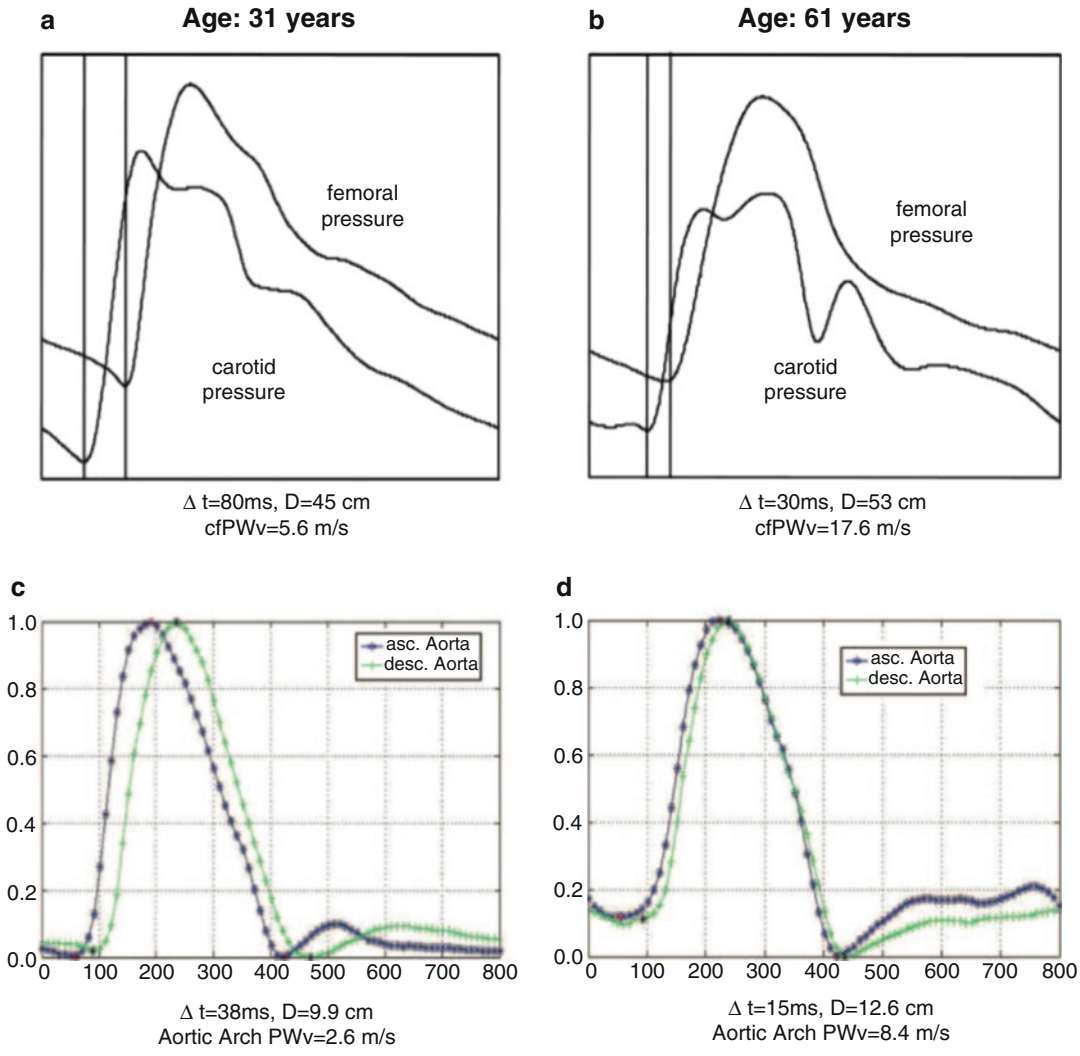

Fig. 9.4 Aortic arch PWV assessment with MRI and cfPWV measured by tonometry. cfPWV assessed with carotid–femoral tonometry in a young (**a**) and older participant (**b**). Corresponding measurements of aortic arch PWV (**c** and **d**) showing simultaneously acquired normalized flow *curves* by phase-contrast MRI in the ascending and descending aorta. The younger participant shows preserved aortic elasticity (normal pulse wave velocities), whereas the older participant presents increased pulse wave velocities in relation with a stiffer aorta. Δt indicates transit time; D, transit distance; x axis, time in milliseconds; y axis, in arbitrary units (reprinted from Redheuil A, Yu WC, Wu CO, Mousseaux E, de Cesare A, Yan R, Kachenoura N, Bluemke D, Lima JA. Reduced ascending aortic strain and distensibility: Earliest manifestations of vascular aging in humans. Hypertension. 2010;55:319–326. With permission from Wolters Kluwer Health)

of the variance in arterial stiffness in humans [69, 70], with risk factors for atherosclerosis, including dyslipidemia, smoking, and diabetes of less importance. At least one study has suggested that these other risk factors may affect smaller, as opposed to large, artery stiffness [71]. While aortic or large artery stiffness can be detected in younger individuals and is increased by exposure to cardiovascular risk factors, the aortic augmentation index, rather than aortic pulse wave velocity, is a better metric of aortic stiffening associated with aging humans less than 50 years of age [70]. Aortic pulse wave velocity is the superior metric to noninvasively detect aortic stiffness in humans >50 (Fig. 9.4) [70].

Alterations in elastin content [72], endothelial dysfunction, and calcification [73] are all linked with increased arterial stiffness, which in turn is linked with cardiovascular disease, including hypertension, myocardial infarction, stroke, and death [74]. Increased aortic pulse pressure, linked to aortic stiffness, is superior to systolic or diastolic blood pressure in predicting cardiovascular events, supporting that aortic stiffness is a key variable in the pathogenesis of cardiovascular disease [75, 76]. Increased pulse pressure also predicts incident heart failure in the elderly [77]. One mechanism by which arterial stiffness may be deleterious is that it permits higher pulsations to affect the peripheral vasculature, potentiating target organ damage [78]. While precise mechanisms by which age-associated increased aortic or large artery stiffness is deleterious are not known, it is clear that age-associated increased aortic and large artery stiffness is an important contributor to cardiovascular disease in the elderly.

Aging and the Heart

Just like the arterial tree, the myocardium is subject to structural and functional changes over time [7]. Aging is associated with loss of cardiomyocytes and ventricular myocardial mass in men, but not women [79]. As a result, there are changes in the ratio of collagen to cardiomyocytes over time in male human hearts. However, left ventricular wall thickness appears to increase with age in both men and women [7, 80]. A key hemodynamic change in left ventricular performance is reduction of the left ventricular filling rate, which is reduced with age by as much as 50 % by the age of 80 [80–82]. This reduction in diastolic function with aging does not appear to be associated with alterations in left ventricular volume at the end of diastole [83, 84]. Left ventricular systolic function appears to be preserved with normal aging [7], but impairments in sympathetic modulation of heart rate and contractility have been described [85]. The aging heart and vasculature interact, and changes in afterload, related to age-associated changes of the arterial tree, may explain changes in myocardial performance associated with age more than changes intrinsic to the ventricle [86]. A mismatch between vascular and ventricular loading, in which LV elastance does not increase in proportion to vascular elastance, has been proposed as a mechanism for reduced cardiac reserve with exercise in the elderly [7]. These vascular changes, or mismatch, may improve with exercise training [87]. Additional comorbidities associated with aging, including arrhythmias like atrial fibrillation and flutter, can also alter cardiac function in the elderly [7]. Age-associated changes intrinsic to the myocardium influence interactions with the arterial tree and alter cardiac performance with age.

Putative Molecular Mechanisms of Aging in the Cardiovascular System

The molecular mechanisms behind age-related changes in the vasculature are not completely understood, but are an active area of research [88]. Several putative molecular mechanisms of cardiovascular aging have been described, which may affect not only the aging vasculature but also the aging myocardium to contribute to heart failure in the elderly.

Endothelial Dysfunction

Loss of endothelial function, mentioned above, has been linked to deficiencies of nitric oxide, prostacyclin, and the endothelium-derived hyperpolarizing factor [40–43], as well as excess of reactive oxygen species like superoxide [44] and peroxynitrite [45]. These imbalances lead to impaired endothelium-dependent vasodilation, a potential mechanism for hypertension, vascular stiffness, and ultimately heart failure. Endothelial dysfunction has been linked with both heart failure from systolic dysfunction [89] and heart failure with preserved ejection fraction [90] in humans.

Telomere Dysfunction

Telomeres are sequences of deoxyribonucleic acid (DNA) in which a TTAGGG sequence repeats, and they are located on the ends of chromosomes. In health, these telomeres appear

to protect the ends of chromosomes from deterioration or fusion with neighboring chromosomes, and telomere shortening, an apparent obligatory by-product of the cell cycle, leads ultimately to cell senescence [91, 92]. Dysfunctional telomeres activate a DNA damage signaling pathway that converges on p53, which induces reductions in mitochondrial biogenesis and function and metabolic changes associated with senescence and tissue deterioration [93]. Cell senescence and tissue degradation either in the vasculature or myocardium could contribute to heart failure. Shorter telomere length in circulating leukocytes has been linked with adverse outcomes in human patients with heart failure [94].

Impaired Metabolism

In addition, several metabolic regulators have been linked to aging via experiments evaluating longevity associated with caloric restriction in animals, including targets of rapamycin (TOR), PPARγ coactivator-1α (PGC1α), sirtuins, and the Forkhead box "O" (FOXO) transcription factors [95–97]. TOR is a member of the phosphatidylinositol-3-kinase-related kinase protein family and acts as a sensor of cellular energy levels and redox status [98]. TOR has been implicated in longevity in model organisms, such as strains of yeast [99]. PGC1α is a transcriptional coactivator that is believed to regulate energy metabolism, including oxidative phosphorylation and mitochondrial biogenesis [100]. The proteins p16 and p19 are cyclin-dependent kinase inhibitors, function upstream of the tumor suppressor gene p53, and have been implicated in aging and senescence of the endothelium [101, 102]. The seven mammalian sirtuins (SIRT1–7) are nicotinamide adenine dinucleotide-dependent histone deacetylase proteins that are linked with extended life span that is seen in animals that receive low-calorie diets [103, 104]. The FOXO family of transcription factors is linked with increased longevity nematodes [95, 97] and appears to function as transcriptional activators and repressors that result in activation of phosphoinositol-3-kinase and protein kinase B [105]. Impaired metabolism and myocardial energetics are linked with heart failure [106], and so these metabolic derangements linked with aging may contribute to heart failure in the elderly.

Mitochondria and Free Radicals

The free-radical theory of aging suggests that intracellular production of reactive oxygen species is a major mediator of life span. Though reactive oxygen species are produced in various cellular compartments, including at the plasma membrane by NADPH oxidase, in the cytoplasm by cyclooxygenases and xanthine oxidase, and within the mitochondria during oxidative phosphorylation, the bulk of reactive oxygen species are formed within the mitochondria and have led some to propose that mitochondrial-derived superoxide and hydrogen peroxide are a major cause of age-related damage and degeneration [107]. In addition to deleterious direct effects of reactive oxygen species, mitochondria have been proposed as mediators of the renin–angiotensin–aldosterone system, adrenergic signaling, growth hormone and insulin-like growth factor 1 signaling, and vascular inflammation, all of which might be important in the aging vasculature and in heart failure [108]. Changes in mitochondrial function and oxidative stress are well described in heart failure [109].

Angiogenesis

Angiogenesis, or new capillary formation, is also impaired in the elderly, which limits vascular repair after ischemic injury and may contribute to cardiovascular disease in the aged [110]. Hypoxia-inducible factor (HIF)-1α, a key mediator of angiogenesis, appears to be downregulated in the aged due to reductions in activity [111] and translocation to the cell nucleus [112]. Sirtuins like SIRT1 may also directly interact with HIF-1α and deacetylate it, leading to inactivation [113]. The cyclin-dependent kinase inhibitors, p16 and p19, may also impair angiogenesis by downregulation of vascular endothelial growth factor (VEGF)-A, a key mediator of HIF-1α-dependent angiogenesis. While there is no unified theory that explains the molecular mechanisms of aging within the cardiovascular system, several putative mechanisms have been described and are linked with heart failure in either model organisms or humans.

Heart Failure with Preserved Left Ventricular Ejection Fraction

More than one-third of patients with heart failure do not have significant left ventricular systolic dysfunction, but instead have preserved left ventricular ejection fraction, or HFPEF [10]. HFPEF appears to be an epidemiologically distinct entity from heart failure with reduced ejection, requiring different diagnostic criteria and therapies [114, 115]. The percentage of patients hospitalized for heart failure with HFPEF, as opposed to left ventricular systolic dysfunction, is also increasing over time and may in time become the most common cause of heart failure [10, 116]. As with heart failure secondary to systolic dysfunction, rates of HFPEF are highest in the elderly [9, 117], and rates of subclinical disease are high [9]. HFPEF has risk factors in common with heart failure due to left ventricular systolic dysfunction, including hypertension and coronary artery disease [118]. Comorbidities like coronary artery disease are often present and adversely affect prognosis [119]. Morbidity and mortality rates are high, rivaling those with left ventricular systolic dysfunction [10, 117–119]. There have been only marginal improvements in mortality from HFPEF over time [10, 116], and it remains a key public health issue. Though recent data support that there remains room to improve outcomes due to HFPEF by applying evidence-based therapies for the risk factors for HFPEF, like hypertension [10], there have been no positive randomized controlled trials for therapies for HFPEF, and there are no therapies for HFPEF per se [115, 120]. An incomplete understanding of the pathogenesis of HFPEF has arguably limited development of therapies to date.

The pathogenesis of HFPEF is not entirely understood and is an active area of research. The original description of the mechanism for HFPEF gave left ventricular diastolic dysfunction a central role, and in fact HFPEF was called "diastolic heart failure" [121, 122]. While both active [123] and passive [124] components of diastolic function have been proposed as possible contributing factors to impaired diastolic function in HFPEF, the fundamental understanding of the hemodynamics of HFPEF is that the slope of the end-diastolic pressure–volume relation increases [121]. More recently, however, the premise that increases in the end-diastolic pressure–volume relation are the mechanism for HFPEF has been challenged. A small report of normal and HFPEF patients evaluated pressure–volume relations and found that, though end-diastolic pressures may be increased in HFPEF patients, the cause is not a shift in the end-diastolic pressure–volume relation but instead a shift to higher volumes at end diastole [11]. The proposed mechanism for this shift to higher volumes at end diastole was a measured increase in arterial stiffness and systolic ventricular stiffness [125], implicating changes within the systemic arterial tree in the mechanism for HFPEF [11, 121]. Community-based studies support that systolic ventricular stiffness and arterial stiffness are common in the elderly and may contribute to HFPEF [126]. Some investigators have provocatively proposed that exacerbations of HFPEF represent a syndrome of "acute vascular failure," in which increased arterial stiffness and abrupt increases in peripheral vascular resistance lead to a mismatch between afterload and ventricular systolic performance, resulting in increased left ventricular diastolic pressure and lower cardiac output [127]. In support of this concept of "acute vascular failure" are data that show that patients with exacerbations of HFPEF often have spikes in blood pressure, are hypertensive [128], and have increased systemic vascular resistance [129]. Also, patients with HFPEF appear to have both increased arterial stiffness and systolic ventricular stiffness that is higher than would be expected due to age and comorbidities, which can worsen diastolic function [11]. Arterial stiffness, over and above intrinsic myocardial function, may also limit exercise capacity in patients with HFPEF [130]. While the pathogenesis of HFPEF remains incompletely understood, it is clear that arterial stiffening associated with age, as well as age-related changes intrinsic to the myocardium, contributes to the common disorder and is relevant to future research on therapies for HFPEF in particular and heart failure in the elderly in general.

Implications for Heart Failure Therapy in the Aging Population

Age-related changes in arterial structure and function have clear implications for therapy for heart failure in the aging population. Since age is accompanied by increased prevalence and severity of risks for heart failure, including hypertension and coronary atherosclerosis, elderly patients with heart failure will require more exhaustive testing and therapies for conditions other than heart failure to optimize their care. Higher prevalence of renal and liver dysfunction may have direct implications for drug choice and appropriate dosing. The goals of therapy may also change. For example, comorbidities might provoke a premium on quality of life rather than prevention of mortality or cardiovascular events per se, and drug therapies that are known to enhance survival in younger patients may only reduce morbidity in this age group [131]. Judicious use of available therapies, and including the values and preferences of the elderly patient in the therapeutic decisions, will be essential [132].

Given the structural and functional changes in arteries with age, especially arterial stiffness in large arteries, new drug therapies will be required to treat both heart failure in the elderly related to systolic dysfunction and heart failure with preserved ejection fraction. Future studies of therapy for heart failure in the elderly should include evaluation of which therapies selectively reduce pulse pressure, or aortic stiffness, over and above the decrease they induce in mean blood pressure [66]. Therapeutic lifestyle change will likely remain a cornerstone of management of heart failure. The elderly are less active than younger patients [133], potentially decreasing endothelial function and increasing aortic stiffness [134]. Exercise appears to mitigate age-associated changes in large artery stiffness and may be a cornerstone of therapy for heart failure in the elderly until specific drug therapies are available [135, 136]. A healthy diet, low in sodium, may also help reduce aortic stiffness, over and above any influence on fluid retention [134].

Drugs that specifically reduce vascular smooth muscle tone in large arteries, rather than small arteries, may have benefit (Fig. 9.5). An alternate approach may be to directly attempt to alter the structure of the aorta and large arteries by changing the composition of the artery walls. Studies in human patients support that different classes of currently available antihypertensive therapies have differential effects on the aging vasculature. For example, in one study of 347 patients, thiazide use and renin–angiotensin blockers were associated with increased pulse wave velocity and aortic stiffness, but calcium channel blockers and beta-blocker were not [137]. Angiotensin-converting enzyme inhibitors consistently reduce aortic stiffness independent of changes on blood pressure [138] and have perhaps the most evidence to support their use to reduce arterial stiffness specifically [139]. Angiotensin-converting enzyme inhibitors are already an important component of medical therapy for heart failure with preserved ejection fraction [140]. Other potential agents to directly lower arterial stiffness proposed in the literature include blockers of the angiotensin II AT1 receptor [141], aminoguanidine [142], and vasopeptidase inhibitors [143]. Finding drugs that well reduce arterial stiffness to treat hypertension and heart failure in the elderly, especially heart failure with preserved ejection fraction, will likely remain an important area of research.

Conclusion

Heart failure is a common and serious disorder that is highly prevalent in the elderly. In addition to increasing the prevalence of risk factors for heart failure, or prolonging exposure to risk factors that cause heart failure, aging induces structural and functional changes on both the arterial tree and myocardium that directly contribute to the heart failure pathogenesis. In particular, HFPEF, an increasingly prevalent form of heart failure afflicting the elderly, may in large measure be a consequence of age-related stiffening of the arterial tree and the interactions between the stiff arterial tree and aging ventricle. While opportunities

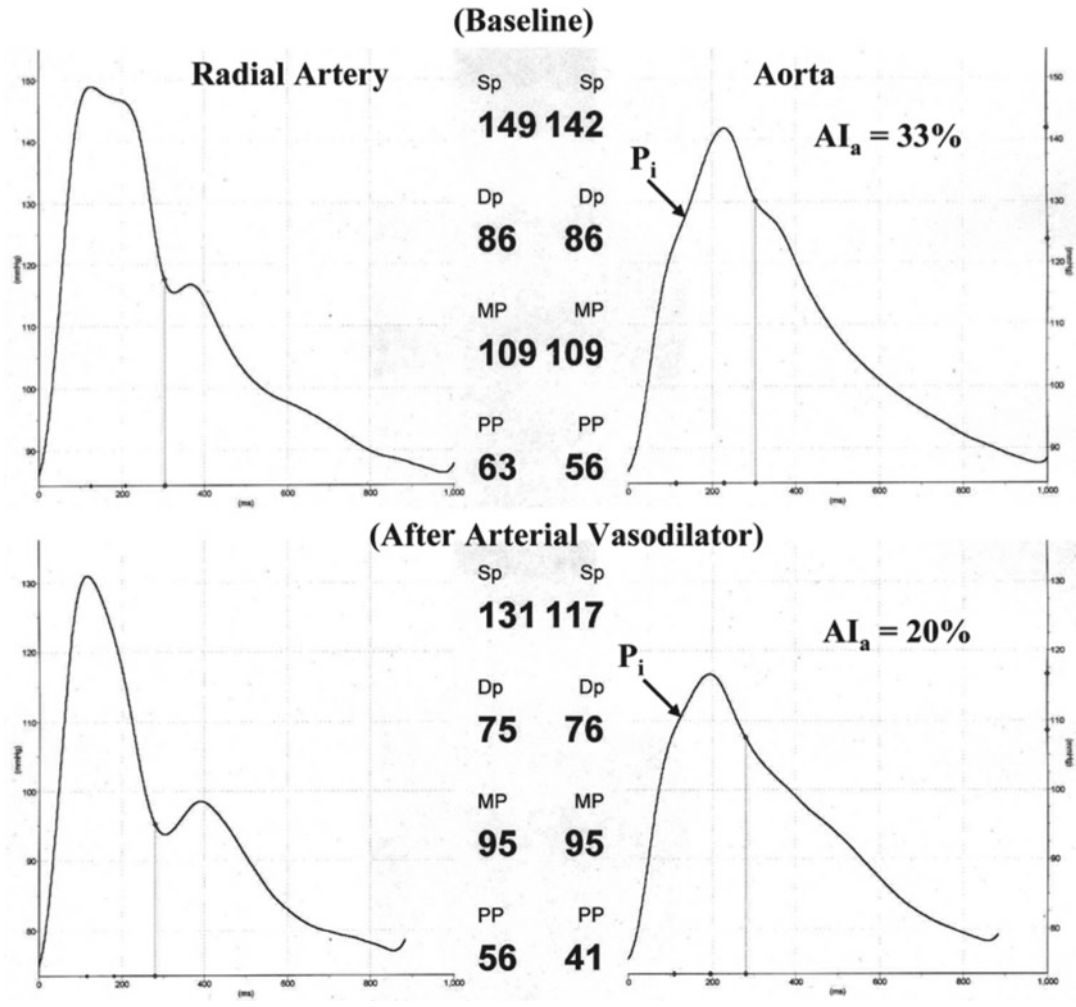

Fig. 9.5 Measured radial artery (*left*) and synthesized aortic pressure (*right*) waves recorded in a hypertensive patient at baseline (*top*) and after treatment with the angiotensin-converting enzyme inhibitor lisinopril (*bottom*). The vasodilator caused a delay in transmission velocity of the reflected wave from the periphery to the heart that resulted in a decline of augmented pressure (from 18 mmHg to 8.0 mmHg), augmentation index (AI_a) (from 33 % to 20 %), and AI_a@75 (from 25 % to 16 %). Reflected wave systolic duration decreased from 158 ms to 139 ms. Aortic systolic blood pressure decreased 25 mmHg, while brachial systolic blood pressure was less sensitive, decreasing 18 mmHg (reprinted from Nichols WW, Denardo SJ, Wilkinson IB, McEniery CM, Cockcroft J, O'Rourke MF. Effects of arterial stiffness, pulse wave velocity, and wave reflections on the central aortic pressure waveform. Journal of clinical hypertension. 2008;10:295–303. With permission from John Wiley & Sons, Inc.)

to prevent and treat heart failure in the elderly can be found in treating or preventing the risk factors for heart failure, like hypertension and coronary artery disease, new treatments are needed that address the component of pathophysiology of heart failure that depends on the stiff arterial tree. Such therapies are a departure from previous therapies for systolic dysfunction, and, given the burden of heart failure in our aging populations, this field is ripe for further research.

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Biomarkers and Optimal Management of Heart Failure in the Aging Population

10

Hanna K. Gaggin and James L. Januzzi Jr.

Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
ADHERE	Acute Decompensated Heart Failure National Registry
AHA	American Heart Association
ANP	Atrial natriuretic peptide
ARB	Angiotensin II receptor blockers
BACH	Biomarkers in Acute Heart Failure
BATTLESCARRED	The NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death
BNP	B-type natriuretic peptide
CHS	Cardiovascular Health Study
GDF	Growth differentiation factor
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
hsTnT	Highly sensitive troponin T
LVSD	Left ventricular systolic dysfunction
MR-proADM	Mid-regional pro adrenomedullin
MR-proANP	Mid-regional pro atrial natriuretic peptide
NP	Natriuretic peptide(s)
NT-proBNP	Amino-terminal B-type natriuretic peptide
PCWP	Pulmonary capillary wedge pressure
PRIDE	ProBNP Investigation of Dyspnea in the Emergency Department
PROTECT	ProBNP Outpatient Tailored Chronic Heart Failure Therapy
REDHOT	Rapid Emergency Department Heart Failure Outpatient Trial
sST2	Soluble ST2

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H.K. Gaggin, MD, MPH (✉)
Cardiology Division, Department of Medicine,
Massachusetts General Hospital,
55 Fruit St. Yawkey 5B, Boston, MA 02114, USA
e-mail: hgaggin@mgh.harvard.edu

J.L. Januzzi Jr., MD
Cardiology Division, Department of Medicine,
Boston, MA USA

B.I. Jugdutt (ed.), *Aging and Heart Failure: Mechanisms and Management*,
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TIME-CHF	Trial of Intensified versus Standard Medical therapy in Elderly Patients with Congestive HF
Val-HeFT	Valsartan Heart Failure

Heart Failure and Age

The diagnosis of heart failure (HF) and age is intricately linked both in terms of incidence and relative to its impact. First, the prevalence of HF increases dramatically with age, 0.9 % for 55–64 years to 17.4 % for >85 years [1]; thus, the lifetime risk for HF development is estimated to be 20 % [2]. This population burden of HF is expected to amplify as baby boomers grow older and more people are surviving into advanced age with better treatment for once-fatal disorders such as coronary artery disease and cancer. Second, given the diagnosis of HF is associated with soaring cost and poor prognosis, this burden is disproportionately large in the elderly; in the USA, HF-related costs are estimated at $30 billion with 80 % of HF hospitalizations and 90 % of HF-related deaths occurring in the elderly and 75 % of HF resources being consumed by the elderly [3].

Heart Failure and Physiological Changes in the Elderly

There are various physiological changes, even with normal aging, that affect the cardiovascular system: alterations in the vasculature, myocardium, and neurohormonal activation. These changes render the elderly patient at risk for HF as well as diminish the body's reserve for compensation when HF exists.

The ratio of non-distensible (collagen and basement membrane) to distensible (smooth muscle and elastin) components in vessels increases with age and results in less compliant vasculature over time [4]. This can result in increased afterload for the heart with or without hypertension, a major risk factor for developing HF. In addition, there is diffuse vascular calcium and lipid deposition over time, increasing the risk of ulceration or thrombosis and resulting in myocardial infarction, another major risk factor for HF [5]. Aging is also associated with reduced vasoregulatory peptide synthesis such as endothelial nitric oxide, ultimately resulting in reduced capacity to vasodilate in response to stress, increased oxidative stress, and increased subintimal thickening and luminal widening [6].

With advancing age and increased afterload, cardiomyocytes have tendency to hypertrophy over time [7]. Myocardial hypertrophy is then associated with increased impetus for fibrosis and apoptosis which further increases stress on the remaining cells [8]. Additionally, there is alteration of calcium intake into myocardial sarcoplasmic reticulum, a crucial component in ventricular diastolic relaxation and contraction [9]. The cumulative effect of these age-related changes is less compliant myocardium and reduced diastolic reserve. Furthermore, impairment of neurohormonal activation can impact the aging heart's function and its ability to respond to stress; blunted beta 1 adrenergic response to exertion can result in chronotropic and inotropic incompetence and reduced beta 2 adrenergic response can result in further impairment in the ability to vasodilate and increased afterload [10].

Challenges in Caring for the Elderly Heart Failure Patients

Diagnosis

An early and accurate diagnosis of HF is important in reducing mortality and morbidity. However, in the elderly, there are several challenges to HF diagnosis and can result in a delay in therapy. Such delays are linked with poor prognosis [11].

The diagnostic evaluation for HF traditionally includes history, physical examination, and chest radiography. However, studies have shown that traditional assessment, by individual finding or by a combination of findings in validated diagnostic criteria (such as the Framingham criteria for HF), has limited sensitivity and specificity

[12]. In the elderly, this diagnostic dilemma is even more exaggerated as their clinical presentation can be quite uncharacteristic; the elderly tend to present with subtle and nonspecific complaints such as confusion, fatigue, failure to thrive, and changes in appetite. Memory impairment further worsens the diagnostic performance for HF. Similarly, physical examination findings tend to be nondiagnostic as elderly patients may already have chronic changes on examination such as heart murmurs, atelectasis, or lower extremity edema due to increased comorbidities associated with aging. Comorbidities often broaden differential diagnosis and can easily lead to inappropriate diagnostic procedures and misdiagnosis [13, 14].

Several noninvasive imaging studies such as echocardiogram can provide important data such as left ventricular ejection fraction; the presence of left ventricular systolic dysfunction (LVSD), while important, does not necessarily mean that a patient has the clinical syndrome of symptomatic (or American Heart Association [AHA]/American College of Cardiology [ACC] Stage C or D) HF nor does it rule out HF with preserved ejection fraction (HFpEF). Making diagnosis even more challenging for the elderly is the fact that this prevalence of asymptomatic LVSD and HFpEF increases with increasing age [15, 16].

Invasive procedures such as right heart catheterization can determine HF status by measuring cardiac output and pulmonary capillary wedge pressure (PCWP), but there is small but real risk of serious complications such as damage to the vessels and heart, arrhythmia, pulmonary infarction, thromboembolic events, and even death. Advanced age is one of the major risk factors for complications for these invasive procedures, and often invasive procedures are foregone in the elderly, leaving them without clear diagnosis and treatment [17].

Lastly, there are various nonphysiological barriers to HF diagnosis. Many elderly patients delay seeking medical help as HF signs and symptoms are often mistaken for signs of getting older. Access to transportation, mobility issues, and financial constraints can often hinder follow-up visits and completing diagnostic tests, further adding to the challenge.

Management

In general, HF prognosis worsen with increasing age [18] and there are a number of challenges that come with managing elderly patients affected with HF.

In acutely decompensated HF, the most important step in treating patients is to identify and to reverse the precipitating cause. However, in the elderly, challenges associated with diagnosis impair our ability to identify reversible causes in a timely fashion. As noted, advancing age is associated with decreasing hemodynamic reserve and older patients can thus rapidly decompensate into symptomatic HF after a relatively small destabilizing event.

In chronic HF, therapeutic options differ for HF with LVSD versus HFpEF, as there are a number of proven, lifesaving medications for the former diagnosis, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), beta blockers, and mineralocorticoid receptor antagonists [19]; HFpEF continues to lack a defined treatment strategy. While higher doses of medications for LVSD have been proven to be of benefit, they may be less well tolerated in the elderly, with greater degrees of symptomatic intolerance as well as a greater propensity towards adverse hemodynamic or metabolic responses. Besides, most of the studies that have established the doses for the guidelines have often excluded elderly patients; thus the benefit of the drugs as well as the optimum dose of HF medications in the elderly is uncertain. Some studies even suggest that ACE inhibitors and beta blockers may not be as effective in the elderly [20]. Worse yet, advanced age is a common reason for failing to utilize HF medications in the elderly [19]. In HFpEF, specific therapies are aimed at treating underlying causes and can consist of many medications, each specifically intended for each underlying cause. In either case, when elderly patients are already taking a large number of

medications for other chronic conditions, adding a slew of HF medications can easily result in polypharmacy, which itself is associated with increased drug–drug interactions and decreased medication compliance. In addition, altered pharmacokinetics and preexisting dysfunctions in renal and autonomic functions further increase the risk of adverse drug reactions [21].

Monitoring and guiding HF management present a special challenge in this growing population. Innovative approaches are needed to improve the care of the elderly patients with HF. In the recent decades, the emergence of HF biomarkers, natriuretic peptides (NP) in particular, has dramatically impacted the diagnosis and management of HF patients, and this high-risk group may have the most to benefit from such novel management strategy.

The Role of Biomarkers in Heart Failure Patients

At every step of HF development and progression, there exists a myriad of biomarkers that reveal important biological information regarding the pathophysiology of HF. Objective, quantifiable, and convenient, the inclusion of biomarkers in HF assessment has considerably altered the way the diagnosis is managed. Some, such as B-type natriuretic peptide (BNP) and amino-terminal B-type natriuretic peptide (NT-proBNP), have been established as the gold standard biomarkers in the diagnosis and prognosis of HF. Together with appropriate clinical assessment, all major cardiology societies recommend these NP measurements [22].

In recent years, new data and interest in other HF biomarkers have exploded and some, such as mid-regional pro-atrial natriuretic peptide (MR-proANP), soluble ST2 (sST2), cardiac troponin, mid-regional pro-adrenomedullin (MR-proADM), growth differentiation factor (GDF)-15, and galectin-3, show promise. However, their use in HF is not yet as established.

As with general data on HF in the elderly, there is a shortage of HF biomarker studies in this population and this remains a fertile ground for future research. The largest amount of data exists on NP and will be the focus of the next section. Regardless, given the challenges our older patients face, they may have the most to benefit from the information these biomarkers can provide.

Natriuretic Peptides in the Diagnosis of Heart Failure in Elderly Patients

Natriuretic Peptides

The NPs are a group of peptide hormones that share a common ring structure required for biological activity. Of the NPs, atrial natriuretic peptide (ANP) and BNP play a crucial role in HF as a part of a dual NP system; they have biological activities of natriuresis, diuresis, vasodilation, sympatho-inhibition, and anti-fibrogenic and anti-hypertrophic properties, all properties intricately tied to the development and progression of HF. When atrial and ventricular walls are biomechanically stretched, as happens in HF, both ANP and BNP are induced [23]. However, from this point on, ANP and BNP appear to have discrete physiological and pathophysiological roles. Normally, circulating BNP levels are much lower than that of ANP (16 % of ANP), but in advanced HF, BNP levels can easily exceed ANP levels and thus BNP is generally used in clinical practice [24].

Induction of the BNP gene results in two products: biologically active BNP and biologically inert NT-proBNP. Typically, the circulating NT-proBNP concentration is higher than BNP as it is cleared from the circulation more slowly by various organs including the skeletal tissue, liver, and kidneys [25]. BNP, on the other hand, is actively cleared by NP receptors or neutral endopeptidases and has a half-life that is shorter than NT-proBNP (about 20 versus 120 min). Both are equally affected by renal function for clearance [26]. Once drawn into tubes after phlebotomy, NT-proBNP is considerably more biochemically stable than BNP.

Concentrations of BNP and NT-proBNP are elevated in patients with asymptomatic or symptomatic LVSD and HF and correlate closely with other objective measures of ventricular dysfunction

such as left ventricular ejection fraction, left ventricular end-diastolic pressures, and PCWP [27].

When compared with individual history, physical examination, or chest radiography findings that are traditionally used for diagnosis of acute HF, an elevated BNP or NT-proBNP is often the single, strongest predictor of diagnosis of acute HF. Of course, clinical evaluation is a mixture of objective and subjective findings, and data suggest the best strategy for diagnosis of HF is the addition of NP testing to clinical assessment [28, 29]. In the elderly population where patients often present with atypical symptoms and traditional examination findings are nonspecific, NP measurement can be extremely useful. In chronic compensated HF patients, concentrations of BNP or NT-proBNP can be elevated, but usually to a lesser extent than those in acute decompensated HF [29]. In addition, BNP and NT-proBNP are also elevated in HFpEF (though to a lesser extent than in systolic HF) and can be used to diagnose HF [30]. Again, in the elderly population where the prevalence of HFpEF is high, such a biomarker measurement can greatly assist in the diagnostic process.

There are several important caveats to the use of NP in clinical practice—NP can be elevated in non-HF situations. In many of the cases, elevated NPs are thought to be more of a reflection of increased left or right ventricular wall tension due to a variety of causes, as happens in acute coronary syndrome, significant valvular disease, atrial fibrillation, and severe pulmonary disease, especially those involving pulmonary hypertension such as pulmonary embolism with right ventricular strain. Nonetheless, with good clinical judgment, NP measurement can still be used with reasonable accuracy to diagnose acute HF [23].

The relationship between NP concentration and renal dysfunction is more complicated. NP concentrations tend to be elevated in renal dysfunction starting with a threshold estimated glomerular filtration rate of about 60 mL/min/1.7 m^2 [31], but this is far more than simply due to reduced clearance. Of course, as a portion of NP is cleared by kidneys, circulating levels tend to increase as renal function gets worse. Complicating this picture is the fact that patients with chronic renal dysfunction tend to have higher blood volume and higher blood pressures as well as relevant cardiac comorbidities such as left ventricular hypertrophy; all are associated with increased ventricular wall tension and NP. Again, diagnosing acute HF in a patient with renal dysfunction is possible with mindfulness of the patient's baseline NP values and clinical presentation [32, 33]. As renal dysfunction is modestly correlated with advancing age, correction of the upper reference limit of NT-proBNP for age mitigates the need to further adjust for renal function [34].

Natriuretic Peptides and Age

Concentrations of BNP and NT-proBNP tend to increase with increasing age (Fig. 10.1). In the Framingham cohort [35], the 95th percentile of BNP for healthy men increases from 21 pg/mL for those aged 20–59 years old to 48 pg/mL for those aged 70 years and older. For women, the 95th percentile BNP values are about 10–20 points higher. Similarly, in another study, 95th percentile NT-proBNP value for healthy men ages 45–54 years was 87 pg/mL and increased to 140 pg/mL in those 65–74 years old. For women, NT-proBNP values are typically slightly higher in healthy subjects [36], but in the context of HF, the sex-related differences are no longer seen.

There are many potential reasons why NP levels may increase with age; concomitant renal dysfunction, coronary artery disease, hypertension, LVSD, diastolic dysfunction, valve disease, as well as heart rhythm abnormalities are all more common with age. Some of the increase in the NP concentrations can be explained by each of these components; however, even when adjusting for all of these factors, age remains an independent predictor [37]. As noted above, age-based cutoff values for diagnosis of HF have been advocated for NT-proBNP; in the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study [28], age-stratified NT-proBNP cutoff points outperformed age-independent cutoff point. In patients <50 years old, a single cutoff point of 900 pg/mL was only 73 % sensitive while still with a great specificity (96 %). But in the elderly patients, the same cutoff point was much

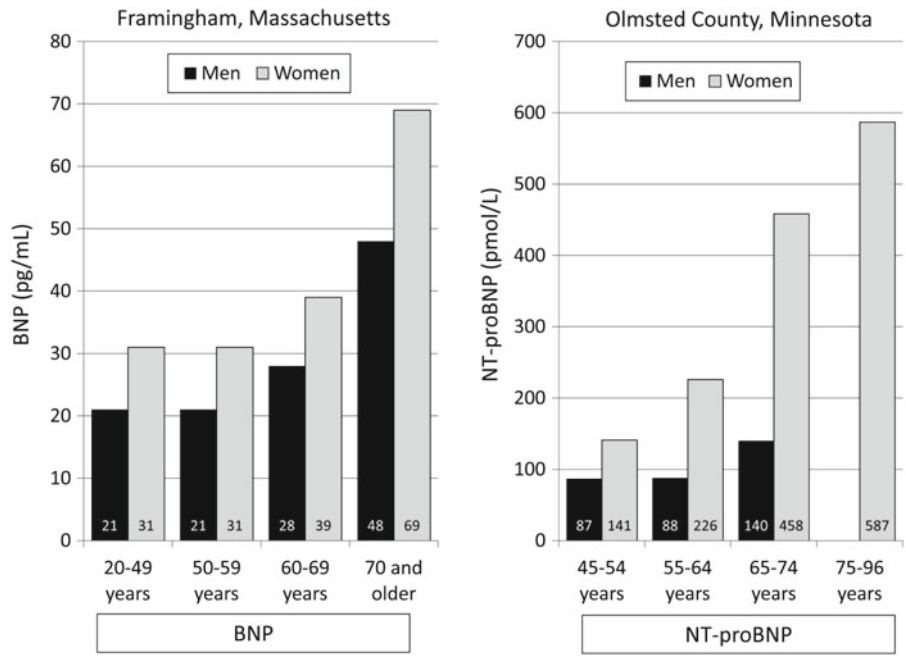

Fig. 10.1 95th percentile BNP and NT-proBNP values in healthy normal cohorts (adapted from Refs. [35, 36])

more sensitive but less specific (91 % sensitive 80 % specific). The optimal cutoff point was 450 pg/mL for <50 years and 900 pg/mL for ≥50 years and likely reflects the need for higher specificity in the older age group with a high prevalence of comorbidities. In a larger analysis [34], a third category of >75 years of age was added with a cutoff point of 1,800 pg/mL. At present age-stratified cutoffs are unknown for BNP. Table 10.1 shows the recommended optimum cutoff points for both BNP and NT-proBNP [38].

Natriuretic Peptides in the Prognosis and Management of Heart Failure in Elderly Patients

Elevated NP values are closely associated with poor prognosis in a variety of settings including healthy asymptomatic subjects and acute and chronic HF patients.

In a community-based sample of 3,346 persons without HF, each incremental elevation of standard deviation in log BNP or NT-proBNP resulted in 30 % increase in the risk of death even after adjusting for baseline clinical characteristics, including age [39]. In another study, elevated NP levels were predictive of increased mortality even after adjusting for echocardiographic parameters such as systolic or diastolic dysfunction [40].

Specific to the elderly population, the Cardiovascular Health Study (CHS) examined the role of serial measurement of NT-proBNP in a community-based patient population with a mean age of 65 years [41]. In this analysis of 2,975 subjects with risk factors but no established HF (thus, ACC/AHA Stage A), a baseline value of NT-proBNP predicted future onset of Stage C or D HF over a 12-year follow-up. Additionally, and importantly, a second value for NT-proBNP obtained at a 2- or 3-year follow-up period reclassified risk such that a rising value from a previously normal concentration was highly associated with risk for new HF (hazard ratio 2.13), and a decreasing concentration was associated with an attenuated risk (hazard ratio 0.58). Curiously, the same investigators found that exercise was

Table 10.1 Optimum cutoff points for BNP and NT-proBNP in acute heart failure

	Cutoff value	Sensitivity	Sensitivity	PPV	NPV	Ref.
Rule out						
BNP	<30–50 pg/mL	97 %	62 %	71 %	96 %	[29]
NT-proBNP	<300 pg/mL	99 %	68 %	62 %	99 %	[28]
Single cutoff point rule in						
BNP	<100 pg/mL	90 %	76 %	79 %	89 %	[29]
NT-proBNP	<900 pg/mL	90 %	85 %	76 %	94 %	[28]
Age-stratified cutoff point rule in						
NT-proBNP	<450 pg/mL for age <50 years <900 pg/mL for age 50–75 years < 1,800 pg/mL for age > 75 years	90 %	84 %	88 %	66 %	[34]

BNP brain natriuretic peptide; *NPV* negative predictive value; *NT-proBNP* N-terminal B-type natriuretic peptide; *PPV* positive predictive value; *Ref* reference

associated with a potentially protective effect on NT-proBNP values.

In patients with acutely decompensated HF, elevated NP concentrations are associated with both increased in- and out-of-hospital mortality rates. In 48,629 patients in the Acute Decompensated Heart Failure National Registry (ADHERE), there was a linear relationship between BNP and in-hospital mortality [42]. The Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT) study showed that the 90-day combined event rate (HF visits or admissions and mortality) for patients admitted with BNP >200 pg/mL was almost three times as much as the event rate for patients with BNP ≤200 pg/mL [43]. As for NT-proBNP, a level >986 pg/mL was found to predict long-term outcomes [44]. These values appear to be age independent.

The prognostic value of NPs is similar in chronic HF patients. In the Valsartan Heart Failure (Val-HeFT) study [45], both BNP and NT-proBNP were strongly predictive of prognosis, ranking as the strongest independent predictor of outcomes after adjustment for major clinical risk factors including age; a baseline median NT-proBNP value of 895 pg/mL was used as a cutoff point. NT-proBNP appeared to be superior compared with BNP in predicting clinical outcomes. Interestingly, serial NT-proBNP measurements and classification into categories of change according to a threshold value of 1,078 pg/mL were more accurate in determining prognosis than a single measurement [46]. In a similar fashion to acutely decompensated HF, the prognostic value of NPs in chronic HF again appeared to be age independent.

From a therapeutic perspective, as many of the same therapies that have been shown to improve mortality and morbidity in HF have also been shown to decrease NP levels over time [47], there is great interest in the use of BNP or NT-proBNP to "guide" HF management, using a strategy of NP lowering plus clinical judgment for the application of therapies [47]. While substantial heterogeneity exists in the design of these studies and all are generally underpowered, a clear consensus is developing that the strategy is of value, and two meta-analyses actually suggest that there is a 20–30 % mortality benefit to guided therapy beyond standard management [48, 49].

It is noteworthy that, as with many studies in cardiology, the average age of patients in many biomarker-guided HF studies were younger than the typical community-based HF patient, thus the merits of biomarker-guided HF in the elderly remain in debate. This is partially due to the fact that two of the larger studies, the Trial of Intensified versus Standard Medical therapy in Elderly Patients with Congestive HF (TIME-CHF) [50] and The NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death (BATTLESCARRED) trials [51], specifically looked into the effect of age in guided therapy. The investigators found that NP-guided therapy was beneficial only in patients <75 years

and not in the older patient group ages >75 years and suggested that guided therapy may be ineffective in the elderly.

Although this is a valid initial supposition, there are some important reasons why these results may be misleading. In both of these studies, there were no significant reductions in NP despite guided therapy in the elderly patients, and it remains unclear whether the interventions in the elderly population were adequate to lower the risk in HF. In contrast, in a post hoc analysis of the ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study [52], both elderly and non-elderly patients benefited from guided therapy. A more detailed look revealed that there was a significant reduction in NT-proBNP in both the younger and the older group with guided therapy; upon further examination, compared to TIME CHF or BATTLESCARRED, in the PROTECT study, substantial reduction in NT-proBNP was achieved in the elderly, and outcomes closely followed the reduction in NP. To achieve lower NT-proBNP values in the elderly, these patients were seen more frequently than younger subjects, but with gradual up-titration, their medication regimen yet optimized. Thus, the question is far from answered, and a larger randomized trial with effective NP reduction from guided therapy is needed to definitively know for sure whether the approach is effective in elders.

Other Heart Failure Biomarkers in Elderly Patients

Few data exist on the role of other novel biomarkers in elderly HF patients, but studies suggest that several biomarkers can add substantial physiological and prognostic information beyond BNP or NT-proBNP.

As mentioned earlier, ANP production is increased in HF; due to biological instability, ANP is challenging to reliably measure. MR-proANP is a stable form of ANP that can be detected in HF. The Biomarkers in Acute Heart Failure (BACH) trial [53] showed that the use of MR-proANP with a cutoff point ≥120 pmol/L improved the diagnostic accuracy of acute HF in certain groups of patients with a high degree of uncertainty including those in the BNP "gray zone" (BNP levels 100–500 pg/mL). As older age is a common cause of a "gray zone" result, the performance of MR-proANP in those with advanced age (age ≥ 70 years) was no better than younger subjects. In another study, in a prespecified subgroup of older subjects, age-adjusted cutoff points for MR-proANP (≥104 pmol/L [for age <65 years] and ≥214 pmol/L for age ≥ 65 years) had similar diagnostic performance as the overall cohort. Elevated MR-proANP remained an independent predictor of acute HF diagnosis in a model that included age-adjusted NT-proBNP and age as well as other traditional clinical characteristics and MR-proANP reclassified false negatives and false positives when used in combination with NT-proBNP [54]. Thus, as with NT-proBNP (and probably for BNP as well), adjustment for age is a necessary exercise when using NPs in the elderly. In chronic HF, MR-proANP concentrations were higher in the elderly patients (≥70 versus <70 years) and were found to be the best predictor of prognosis even when compared with other established and novel biomarkers including NT-proBNP [55]. A change in MR-proANP values over 3 months was also shown to be predictive of future mortality.

MR-proADM is a stable prohormone of adrenomedullin, a potent vasodilatory hormone whose production is increased in HF and appears to improve cardiac output and reduce PCWP. Its potential role in HF is in determining acute and chronic HF prognosis beyond BNP or NT-proBNP and this effect was found to be independent of age [53, 56]. As with many novel and potent predictors of risk, the main question about MR-proADM is whether the risk it predicts is sufficiently finite enough to address it therapeutically. Presently, this remains unknown.

Cardiac troponins are usually used in the diagnosis of acute myocardial infarction and can help with prognosis, but their elevation is common in patients with acutely decompensated as well as chronic HF [57]. With the development of extremely high-sensitivity troponin methods, detection of even a small circulating concentrations

of troponin is possible, which informs even more prognostic information in HF [58, 59] and may even be useful to stratify risk in normal subjects; for example, in a group of community-dwelling elderly patients without HF [60], those with elevated highly sensitive cardiac troponin T values (hsTnT > 12.94 pg/mL) were almost two and a half times more likely to develop HF in the future and almost three times more likely to die from cardiovascular death. A change in hsTnT >50 % over time appeared to add further prognostic information.

Unlike most of the established and novel biomarkers, sST2, a marker of cardiac remodeling and fibrosis in HF, is unique in that it does not appear to be affected by age, renal function, or body mass index [61]. sST2 is one of the rare biomarkers that can potentially surpass NT-proBNP in its ability to determine prognosis in acute and chronic HF patients, but as both biomarkers provide independent information, combining both may be the best option [62, 63].

GDF-15 is thought to be intimately involved in cardiac remodeling and apoptosis. In chronic HF patients, it is associated with increased long-term risk of death even after adjusting for traditional clinical characteristics and NT-proBNP, and a change in GDF-15 concentration over time appears to add further prognostic information [64]. Age potently affects GDF-15, however, so its specific application in the elderly remains unclear.

A similar story can be told of another biomarker that is closely linked with cardiac remodeling and fibrosis, galectin-3. In chronic HF patients, elevated galectin-3 level was found to be prognostic of clinical outcomes. However, galectin-3 may be especially useful in HFpEF in predicting prognosis [65] which thus gives it potential promise in the elderly where the prevalence of HFpEF is dramatically increased.

Future Role of Biomarkers in HF Management for the Elderly

In the elderly population, where there are special challenges in the diagnosis and management of HF, the use of objective, quantifiable, and convenient biomarker(s) has the potential to greatly aid and improve their care. It is tempting to speculate that the age-related rise in risk for HF may be informed through the measurement of biomarkers predicting its onset, such that specific interventions to reduce its risk may be applied. Given the increase in the number of novel biomarkers that add independent information to those already provided by the established NP, there is a potential for a multi-marker approach to the care of the elderly and tailoring therapy for each patient. Much more data are needed in this regard.

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Benefits of Exercise in the Elderly

11

Ezra A. Amsterdam and C. Tissa Kappagoda

Introduction

Margaret Hill used the occasion of the F.E. Williams Lecture given at the Royal College of Physicians of London in 1952 to draw attention to the dangers of physical inactivity in the elderly. She stated that, "Between 1871 and 1950 the number of old men and women had increased from 1.25 million to 5.5 million (in the United Kingdom (UK)). It is estimated that in another 20 years there will be nearly ten million people of pensionable age…. Actually the number (of the elderly) in hospitals and institutions is only between 3 % and 5 % of the total number of the old. Many others are desperately in need of care of some sort though not necessarily in institutions. There is a great deal of untreated disease in old people, and it must always be remembered that the process of growing old, apart from disease, produces biological changes, none of which are to the good…" [1].

E.A. Amsterdam, MD
Department of Internal Medicine, University of California Davis, Sacramento, CA, USA

C.T. Kappagoda, MBBS, PhD (✉)
Department of Internal Medicine, TB 172, University of California Davis, One Shields Avenue, Sacramento, CA 95616, USA
e-mail: ctkappagoda@ucdavis.edu

Is There a Problem Today?

Despite the fact that the number of people over the age of 65 years reached ten million in the UK only in 2011, much of the contents of that lecture would be relevant to contemporary society with the caveat that this was a problem that has acquired global dimensions. Although it has been recognized that habitual physical activity is associated with longevity and multiple health benefits, the available data show that 31 % of the world's population does not meet the minimum recommendations for physical activity [2]. In addition, there is evidence suggesting that 6–10 % of all *deaths* from non-communicable diseases worldwide can be attributed to physical inactivity and that this percentage is even higher for specific diseases such as ischemic heart disease (30 %) [3]. Physical inactivity is linked to 6 % of the *burden of disease* from coronary heart disease (CHD), 7 % from type 2 diabetes, 10 % from breast cancer, and 10 % from colon cancer [3].

In 2008, inactivity was estimated to account for 9 % of premature mortality, i.e., >5.3 million of the 57 million deaths that occurred worldwide. If inactivity was decreased instead by 10 %, more than 533,000 deaths could be averted every year. A decrease of 25 % would avert more than 1.3 million deaths. It was also estimated that elimination of physical *inactivity* would increase the life expectancy of the world's population by a median value 0.68 (range 0.41–0.95) years [3]. The direct and indirect healthcare costs in the USA associated with physical inactivity have been estimated

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DOI 10.1007/978-1-4939-0268-2_11,

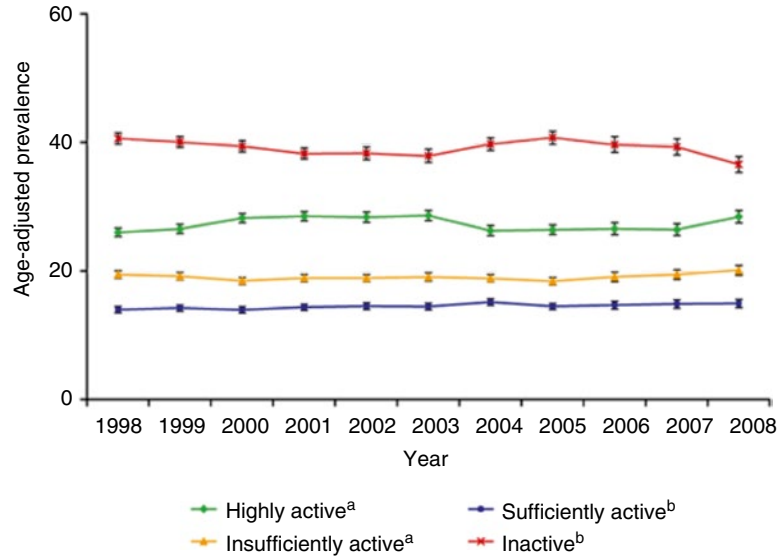

Fig. 11.1 Estimated prevalence of four levels of aerobic activity among US adults as defined in the *2008 Guidelines*, National Health Interview Survey 1998–2008. *Note:* Error bars represent the upper and lower bounds of the 95 % CI. [a]Significant quadratic effect ($p<0.05$), [b]Significant linear effect ($p<0.05$) [5]

to be approximately $420 per head [2]. According to the *2008 Physical Activity Guidelines for Americans*, adults need to engage in at least 150 min/week of moderate-intensity activity or its equivalent (defined as "aerobically active") to obtain substantial health benefits and more than 300 min/week (defined as "highly active") to obtain more extensive health benefits. In addition to aerobic activity, the *2008 Guidelines* recommend that adults participate in muscle-strengthening activities on 2 or more days/week [4]. Carlson et al. [5] assessed the degree of adherence to these guidelines by both men and women >18 years from the 1998–2008 National Health Interview Survey (analyzed in 2010). In 2008, 43.5 % of US adults were aerobically active, 28.4 % were highly active, 21.9 % met the muscle-strengthening guideline, and 18.2 % both met the muscle-strengthening guideline and were aerobically active (Fig. 11.1). The likelihoods of meeting each of these four activity criteria were similar and were associated with being male, being younger, being non-Hispanic white, having higher levels of education, and having a lower BMI. Trends over time were also similar for each part of the *2008 Guidelines*, with the prevalence of participation exhibiting a small but significant increase when comparing 1998–2008 (difference ranging from 2.4 to 4.2 % points). The overall conclusion was that 56.5 % of all US adults were not aerobically active during their leisure time, 71.6 % were not highly aerobically active, and 81.8 % did not participate in minimum recommended levels of *both* aerobic and muscle-strengthening activities.

Physical Activity and the Death Rate in Elderly People

Paffenbarger et al. [6] examined the physical activity and other lifestyle characteristics of approximately 17,000 alumni of Harvard University aged 35–74 years and found that the death rates declined steadily as energy expended increased from less than 500 to 3,500 kcal/week, beyond which rates increased slightly. Rates were one-quarter to one-third lower among alumni expending 2,000 or more kcal (based on a Physical Activity Index) during exercise per week than among less active men. These differences were preserved even after adjustments for *hypertension, cigarette smoking, extremes or gains in body weight, or early parental death*. These and similar observations

[7–9] formed the basis of a series of recommendations from several national agencies that addressed the need for healthy older adults to increase their level of physical activity [10, 11]. It is of interest to note that even in both men and women aged 60–70 years, increasing physical activity is associated with a gain in life expectancy [12] and a life free of disability before death in people in their eighties [13].

Recommendations for Physical Activity for the Elderly

Both the American Heart Association and the American College of Sports Medicine have provided recommendation for physical activity directed at the elderly [10]. These recommendations recognize the fact that in elderly populations there are likely to be multiple comorbidities that would necessitate modifications to a conventional exercise program. The recommendations and precautions for elderly populations are summarized in Tables 11.1 and 11.2.

Physiological Response to Exercise in the Elderly

The ability of the heart to deliver an adequate blood supply to meet the demand dictated by activity [i.e., the cardiac output (CO)] is based on two fundamental physiological variables: heart rate (HR) and stroke volume (SV) operating against a background of an adequate venous return. Thus,

$$\mathrm{CO}\left(\mathrm{L/min}\right)=\left\{\mathrm{SV}\left(\mathrm{mL/beat}\right)\times\mathrm{HR}\left(\mathrm{beats/min}\right)\right\}/1{,}000 \tag{11.1}$$

Based on the Fick equation,

$$\mathrm{CO}\left(\mathrm{L/min}\right)=\left[\mathrm{VO}_2\left(\mathrm{mL/min}\right)/\mathrm{a\text{-}v\,oxygen\,difference}\left(\mathrm{mL/100\,mL}\right)\right]/10 \tag{11.2}$$

where VO_2 is the oxygen consumption.

Combining Eqs. (11.1) and (11.2),

$$\left[\mathrm{SV}\times\mathrm{HR}\right]/1{,}000=\left[\mathrm{VO}_2/\mathrm{a\text{-}v\,oxygen\,difference}\right]/10$$

By rearranging the terms,

$$\mathrm{VO}_2\,\alpha\,\mathrm{SV}\times\mathrm{HR}\times\mathrm{a\text{-}v\,difference}$$

At maximum exercise, VO_{2max} is determined by the maximum SV, HR, and the $a-v$ difference. In any given individual in the sedentary state, the two latter terms are constants. Thus,

$$\mathrm{VO}_{2\,\max}\,\alpha\,\mathrm{SV}\times\mathrm{K}_1\times\mathrm{K}_2 \tag{11.3}$$

Since the maximum HR declines with ageing, the extent to which the maximum CO is maintained in the elderly is determined primarily by SV. The latter is influenced to a significant extent by whether the exercise is undertaken in the upright or supine posture.

Functional Capacity and Ageing

It is known that VO_{2max} (which is a proxy for the CO) declines with age [14]. Although the rate of this decline is estimated to be ~10 % per decade in sedentary subjects, there is no consensus on the magnitude of the associated changes. Based on Eq. (11.3) above, it is apparent that a reduction in VO_{2max} associated with ageing has to be accompanied by changes in the maximum heart rate, stroke volume, and oxygen extraction represented by the a-v oxygen difference.

The SV increases with exercise and exhibits a plateau as the workload increases above ~40 % of the maximum. In certain circumstances, it may either continue to increase or even decline

Table 11.1 Summary of physical activity recommendations for older adults—2007. They should perform the following activities

Activity	Frequency
(1) *Moderate-intensity aerobic (endurance) physical activity* This involves a moderate level of effort relative to an individual's aerobic fitness. On a 10-point scale, where sitting is 0 and all-out effort is 10, moderate-intensity activity is a 5 or 6 and produces noticeable increases in heart rate and breathing. On the same scale, vigorous-intensity activity is a 7 or 8 and produces large increases in heart rate and breathing. For example, given the heterogeneity of fitness levels in older adults, for some older adults a moderate-intensity walk is a slow walk, and for others, it is a brisk walk	Minimum of 30 min on 5 days/week or vigorous-intensity aerobic activity for a minimum of 20 min on 3 days/week
(2) *Muscle-strengthening activities using the major muscles of the body that maintain or increase muscular strength and endurance* In order to maximize strength development, a resistance (weight) should be used that allows 10–15 repetitions for each exercise. The level of effort for muscle-strengthening activities should be moderate to high	It is recommended that 8–10 exercises be performed on at least two nonconsecutive days per week using the major muscle groups
Combinations of moderate- and vigorous-intensity activity can be performed to meet these recommendations. These activities are in addition to the light-intensity activities frequently performed during daily life (e.g., self-care, washing dishes) or moderate-intensity activities lasting 10 min or less (e.g., taking out trash, walking to parking lot at store or office)	

Adapted from Nelson ME, Rejeski WJ, Blair SN, et al. Physical Activity and Public Health in Older Adults. Circulation 2007;116:1094–105. With permission from Wolter Kluwers Health

Table 11.2 Precautions for elderly people undertaking exercise programs

To maintain the flexibility necessary for regular physical activity and daily life, older adults should perform activities that maintain or increase flexibility on at least 2 days each week for at least 10 min each day
To reduce risk of injury from falls, community-dwelling older adults with substantial risk of falls should perform exercises that maintain or improve balance
Older adults with one or more medical conditions for which physical activity is therapeutic should perform physical activity in a manner that effectively and safely treats the condition(s)
Older adults should have a plan for obtaining sufficient physical activity that addresses each recommended type of activity
Those with chronic conditions for which activity is therapeutic should have a single plan that integrates prevention and treatment
For older adults who are not active at recommended levels, plans should include a gradual (or stepwise) approach to increase physical activity over time. Many months of activity at less than recommended levels are appropriate for some older adults (e.g., those with low fitness) as they increase activity in a stepwise manner. Older adults should also be encouraged to self-monitor their physical activity on a regular basis and to reevaluate plans as their abilities improve or as their health status changes
Since there is a dose–response relationship between physical activity and health, older persons who wish to further improve their personal fitness, reduce their risk for chronic diseases and disabilities, or prevent unhealthy weight gain are likely to derive a greater benefit by exceeding the minimum recommended amount of physical activity

Adapted from Nelson ME, Rejeski WJ, Blair SN, et al. Physical Activity and Public Health in Older Adults. Circulation 2007;116:1094–105. With permission from Wolter Kluwers Health

depending upon age, gender, prior level of physical activity, body weight and composition of the subjects, and subclinical coronary artery disease [15].

These relationships were examined by Ogawa et al. [14] in sedentary and endurance-trained younger and older men and women by measuring oxygen uptake, CO, HR, and other cardiovascular responses to submaximal and maximal treadmill exercise. All subjects were healthy nonsmokers and had a resting blood pressure

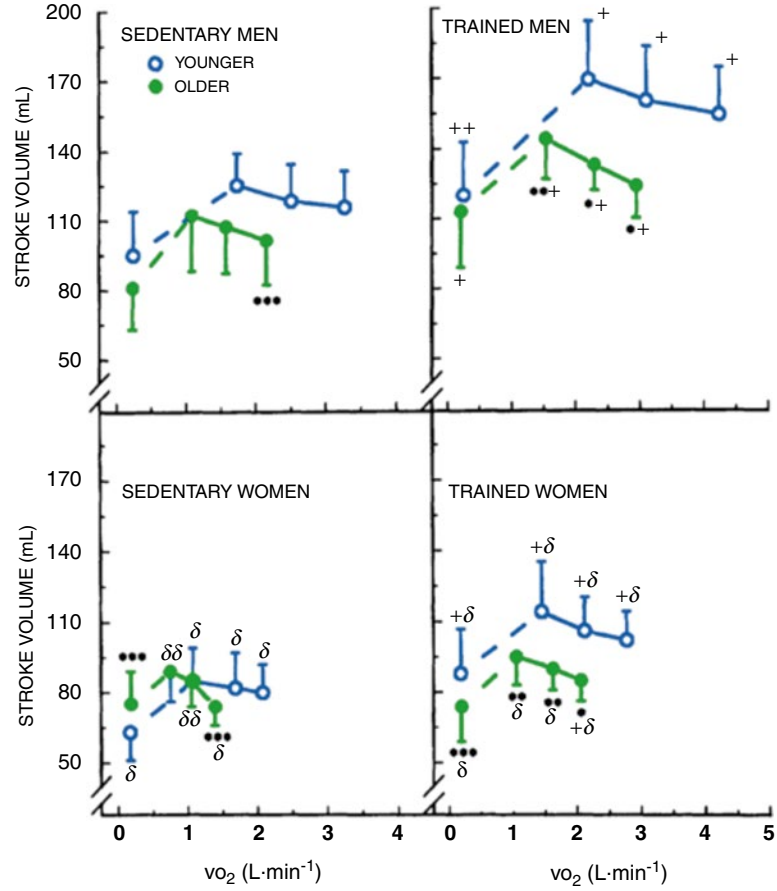

Fig. 11.2 Effect of age on sedentary and trained men and women. The figure shows a reduction in SV associated with age. There is also a corresponding reduction VO_{2max} [14]. Graphs showing SV at rest and during submaximal and maximal treadmill exercise in younger and older sedentary men, trained men, sedentary women, and trained women. Statistically significant differences are designated for corresponding values at rest and at each level of submaximal or maximal exercise. $*p<0.001$, $**p<0.01$, and $***p<0.05$ vs. younger subjects of the same sex and training status. $+p<0.001$ vs. sedentary subjects of similar age and the same sex. $\delta p<0.001$ and $\delta\delta p<0.01$ vs. men of similar age and training status

<140/90 mm Hg. The physical examination and resting electrocardiogram were within normal limits, and a maximal treadmill exercise electrocardiogram (ECG) showed no evidence of cardiovascular disease by conventional criteria. The exercise tests were performed on a treadmill using the Bruce protocol, and the CO was measured using the acetylene (C_2H_2) re-breathing technique. The SV was calculated from the CO and the HR. It was found that in both men and women the passage of 3–4 decades was associated with a ~40 % reduction in VO_{2max} in sedentary subjects and a 25–32 % reduction in VO_{2max} in trained individuals. A smaller SV accounted for nearly 50 % of these *age-related* differences, and the remainder was explained by a lower maximal HR and reduced oxygen extraction (Fig. 11.2).

In trained subjects, these age-related changes maximal HR and oxygen extraction were significantly smaller. Training per se was also associated with an increase in the a-v O_2 difference in

previously sedentary men and women which probably contributed to the overall beneficial effect of training in the elderly. However, the acetylene re-breathing technique used for measuring hemodynamic changes did not permit estimation of ventricular dimensions.

The changes in ventricular dimensions associated with exercise were studied by Rodeheffer et al. [16]. The functional capacity in elderly people without overt or occult coronary artery disease was measured using serial blood pool scans during progressive *upright* exercise to exhaustion. The subjects were 61 healthy community-dwelling participants in the Baltimore Longitudinal Study of Ageing (aged 25–79 years) who were free of cardiac disease based on their histories, physical examination, resting and stress electrocardiograms, and stress thallium scintigraphic examinations. They observed no age-related changes in CO, end-diastolic or end-systolic volumes, or ejection fraction (EF) *at rest*.

During vigorous exercise (125 W), there was an age-related increase in end-diastolic volume and SV and an age-related decrease in HR. The maximal CO achieved did not appear to change with age. The age-related increase in stroke volume at this high workload appeared to be dependent on diastolic filling leading to a higher end-systolic volume which, in turn, led to a lower EF with increasing age. The authors concluded that, although ageing did not limit cardiac output per se in the elderly, the hemodynamic profile accompanying exercise is altered by age and can be explained by an age-related diminution in the cardiovascular response to beta-adrenergic stimulation (Fig. 11.3).

The SV responses to graded *supine exercise* stress were investigated by Stratton et al. [17] using radionuclide ventriculography in 13 older (aged 60–82 years) and 11 young (aged 24–32 years). The subjects were rigorously screened healthy men who were tested (beginning at 200 kpm and increasing by 200 kpm every 3 min till exhaustion) before and after 6 months of endurance training. They concluded that there was an age-associated decline in HR, EF, and CO responses to supine exercise in healthy men (i.e., similar to that observed during upright exercise). Although the SV responses of the young and old were similar, the elderly subjects tended to increase SV during (supine) exercise through cardiac dilatation, with an increase in end-diastolic volume (+8 %) but without a significant change in EF. The young increased their EF with no cardiac dilatation.

However, it is necessary to sound a note of caution in accepting these findings derived from nuclear imaging. The first relates to the timing of the injection of the isotope with respect to exhaustion which is not always predictable, and second is the precise time at which the data is acquired with respect to the end of the exercise [18]. Further, these findings based on nuclear imaging are potentially at variance with those reported using echocardiography. For instance, Chen et al. [19] reviewed the echocardiographic data from the Framingham Study and observed a specific pattern of left ventricular remodeling associated with ageing with respect to the structure and function of the LV. These changes, observed in the resting state, included LV wall thickening, shrinking cavity dimensions, and increased fractional shortening with corresponding changes in ventricular systolic and diastolic diameters [19]. This ventricular remodeling is the anatomical basis of a reduction in ventricular compliance associated with ageing, and there is evidence that they could be reversed by exercise training in the elderly [20, 21].

During upright bicycle exercise, changes in LV volumes have been evaluated using contrast echocardiography. In healthy male endurance athletes ($n=24$), the maximal oxygen uptake and oxygen pulse were measured separately using cardiopulmonary exercise testing. The end-diastolic volume increased by 18 % ($p<0.001$) and end-systolic volume decreased by 21 % ($p<0.002$) when the subjects exercised to reach a heart rate of 160 beats/min starting from rest. The SV showed an almost linear increase during exercise (45 % increase, $p<0.001$). The increase in end-diastolic volume contributed to 73 % of the increase in SV. No significant differences were observed between stroke volume calculated from LV volumes with contrast echocardiography and

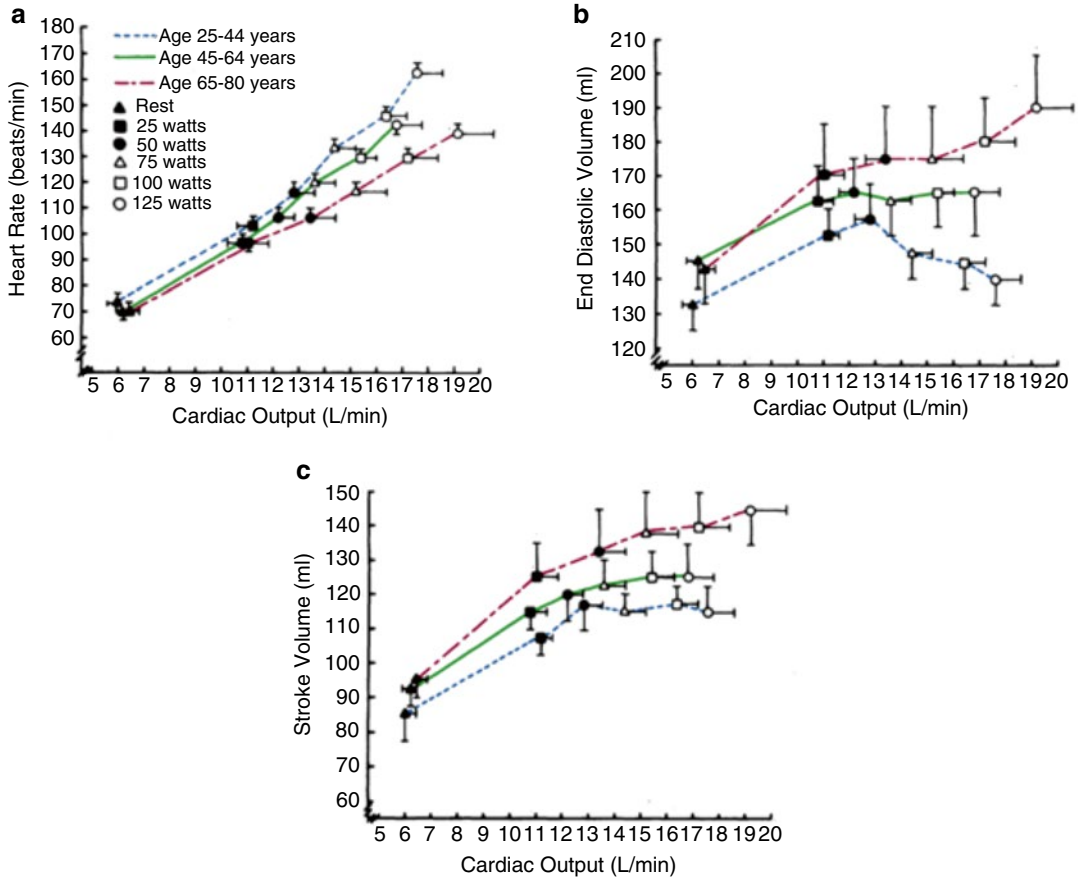

Fig. 11.3 Relationship between HR (**a**), end-diastolic volume (**b**), and SV (**c**) and CO across the stipulated range of workloads. The subjects are divided a priori into the three following age groups: 25–44 years old ($n=22$), 45–64 years old ($n=23$), and 65–79 years old ($n=16$). In the older age group, the same higher CO during exercise is attained with a lower HR, higher EDV, and higher SV. The effect of age was significant, by analysis of covariance, for HR ($p=0.001$), EDV ($p=0.04$), and for SV ($p=0.002$). The number of subjects able to complete the exercises period decreased with increasing workload, at a workload of 125 W $n=16$ in group 1, $n=15$ in group 2, and $n=11$ in group 3. When the data were analyzed including only those who were able to achieve 125 W, a similar pattern was observed in all three parameters, and the significance of the age effect was unchanged [16]. Data was obtained during continuous upright graded exercise on a bicycle ergometer starting at 25 W and increasing in increments of 25 W for each successive period using gated ventriculography. Each exercise period was 3 min in length, and images were acquired during the last half minute of each period

stroke volume calculated from oxygen pulse at heart rates of 130 and 160 beats/min [22]. The changes in LV dimensions associated with ageing were studied in 66 subjects without cardiovascular diseases (32 with a mean aged 71 ± 4 years and 34 with a mean aged 33 ± 6 years) using echocardiography by Fioranelli et al. [23]. The changes observed at rest were similar to those observed by Chen et al. During exercise at 100 W, there was an age-related increase in end-diastolic volume (142 ± 10.6 vs. 127 ± 4.3; $p=0.01$) and an age-related decrease in heart rate (HR 100 W: 148 ± 10.7 vs. 169 ± 10.9; $p=0.05$). Similar findings were reported by Donal et al. [24] (see Table 11.3). The delay between the termination of exercise and acquisition of the echocardiographic images remains a contentious issue in interpreting the findings of these studies.

Table 11.3 Left ventricular size and systolic function at rest and during exercise

Variable	Athletes		Sedentary	
	Seniors	Youths	Senior	Youths
End-diastolic volume (mL)				
Rest	120.5 ± 20.6	157.3 ± 23.6¶	117.5 ± 23.2	116.8 ± 21.2
Exercise	128.2 ± 18.3§	159.2 ± 20.8¶	109.2 ± 26.8	122.8 ± 17.0
End-systolic volume (mL)				
Rest	46.6 ± 11.4	57.0 ± 12.5*	43.7 ± 12.0	43.3 ± 13.1
Exercise	39.7 ± 9.0§	45.1 ± 7.7 ‡	31.3 ± 12.8†	35.3 ± 10.0
Stroke volume (mL)				
Rest	74.0 ± 14.5	97.4 ± 20.3§	76.2 ± 14.3	81.5 ± 17.3
Exercise	88.8 ± 15.9	115.9 ± 21.4¶	79.8 ± 16.4	81.8 ± 15.3
Ejection fraction (%)				
Rest	61.4 ± 6.0	63.6 ± 7.2	62.8 ± 6.8	63.3 ± 6.0
Exercise	68.9 ± 5.9	71.4 ± 5.1	72.1 ± 6.9	71.5 ± 6.1
Cardiac output (L/min)				
Rest	4.9 ± 1.2	5.4 ± 0.8	5.1 ± 0.9	5.6 ± 1.6
Exercise	9.7 ± 1.8	13.0 ± 2.2¶	8.8 ± 1.8	9.5 ± 1.7

Echocardiograms recorded at rest and during submaximal exercise were analyzed in 59 athletic seniors and 16 sedentary seniors (aged ≥50 years) and in 18 athletic youth and 27 sedentary youth (aged <35 years). All subjects were healthy. Data are expressed as mean ± SD

Adapted from Donal E, Rozoy T, Kervio G, Schnell F, Mabo P, Carre F. Comparison of the Heart Function Adaptation in Trained and Sedentary Men After 50 and Before 35 Years of Age. The American Journal of Cardiology 2011;108:1029–37

*$p < 0.001$, athletes vs. sedentary; †$p < 0.01$, senior athletes vs. senior sedentary; ‡$p < 0.01$, sedentary youth vs. others; §$p < 0.05$, senior athletes vs. senior sedentary; ¶$p < 0.05$, sedentary youth vs. others

Exercise and Fitness in the Elderly

Studies in elderly individuals (>65 years) suggest that in *untrained* sedentary individuals, LV compliance (reflecting diastolic function) is lower than in those who are well trained. One year of vigorous exercise failed to improve LV compliance in the former. Fujimoto et al. [20] studied sedentary seniors and master athletes (12 of each) who were without comorbidities. They underwent invasive hemodynamic measurements with pulmonary artery catheterization to define Starling and LV pressure–volume curves. Doppler echocardiography, magnetic resonance imaging assessment of cardiac morphology, arterial stiffness index (total aortic compliance and arterial elastance), and maximal exercise testing were also undertaken to obtain secondary functional outcomes. Nine of 12 sedentary seniors (70.6 ± 3 years; 6 male, 3 female) completed 1 year of endurance training after which the measurements were repeated. Before training, VO_{2max}, LV mass, end-diastolic volume, and SV were significantly smaller, and the ventricle was less compliant in sedentary seniors than in master athletes. After training, the sedentary group showed improvements in maximal workload and increases in EF, SV index, and cardiac index at peak exercise. These responses were not different in the two groups.

Role of Catecholamines in the Exercise Response in the Elderly

The above findings suggest that although ageing per se does not limit CO in healthy elderly subjects, the hemodynamic profile accompanying exercise is altered by age and can be explained by an age-related diminution in the cardiovascular response to beta-adrenergic stimulation. With advancing age, there is a shift from a catecholamine-mediated increase

in HR and reduction in end-systolic volume to a greater reliance on the Frank-Starling mechanism [16]. These authors contended that there was substantial evidence to support the hypothesis that the effectiveness of beta-adrenergic modulation of myocardial contractility, HR, and vascular tone declines with advancing adult age. Taken together, the results of these studies present a cogent argument that the responses of target organs in the cardiovascular system to catecholamine stimulation diminish with age and this mechanism alone is sufficient to explain all of the age-related changes in the hemodynamic response to exercise observed in these subjects. Thus, reduced HR and contractile responses to beta-agonist stimulation appear to characterize normal cardiac ageing [25, 26].

Stratton et al. also showed that the diastolic responses declined with ageing. Ventricular diastolic filling responses to isoproterenol were determined in 13 older (60–82 years) and 11 young (24–32 years) healthy men who were extensively screened for coronary artery disease (those >40 years had a thallium scan) before and after endurance training [26]. Filling rates (gated blood pool scans) were expressed in three ways: (1) normalized to end-diastolic volume per second, (2) normalized to SV per second, and (3) as absolute milliliters of blood (mL/s). Peak early filling rates by all methods were reduced significantly at rest and during all isoproterenol doses with ageing. During isoproterenol, both peak early and peak atrial filling rates increased significantly in both groups (all $p<0.01$), but the increases were not different with ageing. Endurance training did not augment diastolic filling responses to isoproterenol. Thus, the age-associated declines in HR, EF, and CO responses to beta-adrenergic stimulation with isoproterenol do not extend to diastolic filling responses [26]. In addition, this study showed that there were no significant changes in the responses to isoproterenol associated with training in older individuals.

Consistent with these findings are the changes observed in resting metabolic rate (ventilated hood, indirect calorimetry) during the infusion of either a nonselective beta-adrenergic receptor antagonist (propranolol) or saline (control) [27]. This study was conducted on 55 healthy sedentary or endurance exercise-trained adults, aged 18–35 or 60–75 years (29 men and 26 women), before and during beta-adrenergic receptor antagonism. The resting metabolic rate during beta-blockade, adjusted for fat-free mass, was reduced to a lesser extent in (1) older compared with young adults, (2) sedentary compared with endurance exercise-trained adults, and (3) women (-105 ± 33 kJ/day) compared with men (-318 ± 50 kJ/day; all $p<0.01$). Reductions in resting metabolic rate during beta-adrenergic receptor antagonism were positively related to higher baseline resting metabolic rate and plasma catecholamine concentrations and negatively related to adiposity (all $p<0.05$). Resting metabolic rate was unchanged in response to saline control in all groups. These findings provided experimental support for the hypothesis that ageing, sedentary living, and female gender are associated with attenuated sympathetic nervous system support of resting metabolic rate in healthy adult humans [27].

Despite the age-related decline in functional capacity, it is possible to reverse some of these tends by exercise training (see [28] for review). Similar beneficial effects are evident in older men [29] and women [30]. It is emphasized that both aerobic exercise training and strength training also result in an increase in VO_{2max} [31, 32].

Exercise and Cardiovascular Disease

Coronary Artery Disease (Primary and Secondary Prevention)

CHD is recognized as one of the leading causes of death among men and women in the USA. The benefits derived from exercise are multiple (see Table 11.4) and can be viewed as occurring in two categories of people:

1. Those with no previous history of CHD (i.e., associated with primary prevention programs)

Table 11.4 Benefits of cardiac rehabilitation programs

Exercise capacity	
Estimated METS	+35 %
Peak VO_2	+15 %
Peak anaerobic threshold	+11 %
Reduction in obesity indices	
Body mass index	−1.5 %
Percent fat	−5 %
Metabolic syndrome	−37 % (prevalence)
Improvements in lipids	
Total cholesterol	−5 %
Triglycerides	−15 %
HDL-C	+6 % (13–16 % increase in subgroups with low HDL-C levels)
LDL-C	−2 %
LDL-C/HDL-C	5 %
Inflammatory markers	
hs-CRP	−40 %
Changes in autonomic regulation of the circulation reflected in improved baroceptor function and increased heart rate variability. Both the heart rate and blood pressure at submaximal workloads decrease, thereby reducing myocardial oxygen demand	
Improvements in behavioral characteristics such as depression, anxiety, somatization, and hostility	
Improvements in overall quality of life and its components	
Improvement in blood rheology and viscosity	
Improvements in endothelial function	
Reduction in homocysteine levels	
Reduction in overall morbidity and mortality (especially associated with depression and psychological distress)	
Reduction in hospitalization costs	

hs-CRP high-sensitivity CRP
Adapted from Lavie CJ, Milani RV. Cardiac Rehabilitation and Exercise Training in Secondary Coronary Heart Disease Prevention. Progress in cardiovascular diseases 2011;53:397–403. With permission from Elsevier

2. Those who have recovered from a major cardiac event (i.e., associated with secondary prevention)

The benefits enjoyed by these two categories of patients are reflected in a reduced rate of major cardiac events and enhanced survival. It should be recognized that the studies relating to the first group are observational in nature while the latter are supported by multiple randomized clinical trials.

Exercise and Primary Prevention

The Health Professionals Follow-up Study tracked a cohort of 44,452 US men at 2-year intervals from 1986 through January 31, 1998, to assess potential CHD risk factors and identify newly diagnosed cases of CHD (incidence of nonfatal myocardial infarction or fatal CHD) and their relationship to leisure-time physical activity [33]. The relative risk corresponding to moderate (4–6 METs) and high (6–12 METs) activity intensities were 0.94 and 0.83 compared with low activity intensity (<4 METs) ($p = 0.02$ for trend). A half hour per day or more of brisk walking was associated with an 18 % risk reduction (RR 0.82; 95 % CI, 0.67–1.00). Walking pace was associated with reduced CHD risk independent of the number of walking hours. Total physical activity, running, weight training, and walking were each associated with reduced CHD risk. Average exercise intensity was associated with reduced risk independent of the number of MET-hours spent in physical activity.

Similar conclusions were drawn from the findings of the Women's Health Study which examined the relationship between physical activity and CHD among women, focusing on walking (a light-to-moderate activity depending on pace). The study cohort consisted of 39,372 healthy female health professionals aged 45 years or older, enrolled throughout the USA between September 1992 and May 1995, with follow-up to March 1999. Recreational activities, including walking and stair climbing, were reported at study entry. A total of 244 cases of CHD occurred during the follow-up. Adjusting for potential confounders, the relative risks (RRs) of CHD for <200, 200–599, 600–1,499, and ≥1,500 kcal/week expended on all activities were 1.00 (referent), 0.79, 0.55, and 0.75, respectively (p for linear trend = 0.03). Vigorous activities were associated with lower risk (RR 0.63) comparing highest and lowest categories. The inverse association between physical activity and CHD risk did not differ by weight or cholesterol levels (p for interaction = 0.95 and 0.71, respectively), but there were significant interactions with smoking and hypertension status. Physical activity was inversely related to risk in current

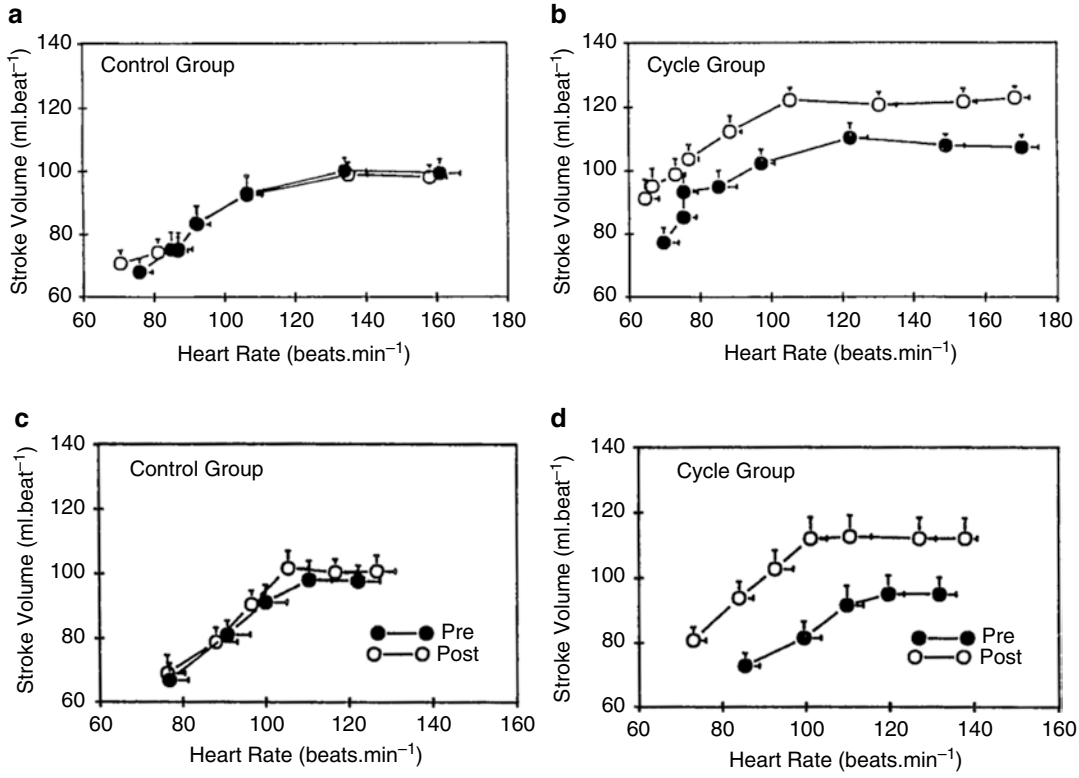

Fig. 11.4 Effect of training on the stroke volume/heart rate relationship. *Upper panel*—normal subjects [38]. (**a**) Control subjects and (**b**) experimental subjects who underwent exercise training on a bicycle ergometer. *Lower panel*—subjects who had recovered from coronary artery bypass surgery [39]. (**c**) control subjects and (**d**) experimental subjects who underwent exercise training on a bicycle ergometer

smokers but not in hypertensive women (p for interaction = 0.01 and 0.001, respectively) [34].

Several studies have also addressed the beneficial effects of exercise training on the lipid profiles of elderly men and women [35–37]. The general consensus to emerge from these studies is that exercise training increases the serum concentration of high-density lipoproteins and generates a more favorable lipid profile with respect to cardiovascular risk.

Exercise in Secondary Prevention of CHD

These benefits refer to patients with established CHD who participate in secondary prevention programs designed to prevent new cardiac events and cover a range factors that have a bearing on the outcome of these patients. The major benefit that accrues from regular exercise is an increase in functional capacity which is reflected best in the relationship between the heart rate and stroke volume during exercise (Fig. 11.4). Exercise training in both normal subjects and those with CHD has the capacity to increase the stroke volume at comparable heart rates, resulting eventually in an increase in work capacity. However, much of the activity in life is undertaken at submaximal levels of exercise, and they would be carried out at a lower heart rate and blood pressure in trained individuals compared to those who are untrained. As discussed previously, it is clear that the myocardial oxygen demand during submaximal activity would be lower in trained subjects. It is likely that the reduction in perceived exertion observed in them during submaximal exercise tests is a reflection of this physiological adaptation.

A recent systematic review of 47 randomized clinical trials has addressed the issue of all-cause and cardiac mortality in patients who enroll in cardiac rehabilitation programs. The analysis was based on 10,794 patients who were randomized to exercise-based cardiac rehabilitation or usual care. In medium to longer term (i.e., 12 or more months follow-up), exercise-based cardiac rehabilitation reduced overall and cardiovascular mortality [RR 0.87 (95 % CI 0.75, 0.99) and 0.74 (95 % CI 0.63, 0.87), respectively], and hospital admissions [RR 0.69 (95 % CI 0.51, 0.93)] in the shorter term (<12 months follow-up) with no evidence of heterogeneity of effect across trials. Neither intervention had any effect on the occurrence of nonfatal myocardial infarction or the need for revascularization [40]. The mortality benefits (both overall and cardiovascular) were evident in trials that extended for periods longer than 12 months. As in elderly healthy individuals, both resistance and aerobic training were found to be effective, and a program that combined both modalities was deemed most effective [41]. See Table 11.4 for summary of exercise training on secondary prevention.

Diabetes Mellitus

It has been recognized for many years that physical exercise is an integral part of the management of type 2 diabetes. The Diabetes Prevention Program (DPP) clinical trial provided clear evidence that intensive lifestyle changes that included physical exercise were successful in reducing the incidence of diabetes [42]. The goals for the intensive lifestyle intervention were to achieve and maintain a weight reduction of at least 7 % of initial body weight through healthy eating and physical activity and to achieve and maintain a level of physical activity of at least 150 min/week (equivalent to 700 kcal/week) through moderate-intensity activity (such as walking or bicycling).

The study was undertaken on nondiabetic individuals with a high risk of progression to type 2 diabetes. It is very likely that the majority of these subjects met the criteria for the metabolic syndrome. Those individuals with conditions that might increase the risk of adverse effects from the interventions or severely reduce life expectancy were excluded. The subjects were assigned at random to one of three intervention groups: an intensive lifestyle intervention focusing on a healthy diet and exercise and two masked medication treatment groups (metformin or placebo) each combined with standard diet and exercise recommendations. Participants were recruited during a 32-month period and were followed for an additional 39–60 months after the close of recruitment. At the end of the follow-up (average 2.8 years), the incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and intensive lifestyle groups, respectively. The lifestyle intervention reduced the incidence by 58 % and metformin by 31 % as compared with placebo, the lifestyle intervention being significantly more effective than metformin [43].

Subsequently, all active DPP participants were eligible for continued follow-up. Approximately 900 people from each of the three original groups (88 % of the total) enrolled for a median additional follow-up of 5.7 years. All three groups were offered group-implemented lifestyle intervention. Metformin treatment was continued in the original metformin group (850 mg twice daily as tolerated), with participants unmasked to assignment, and the original lifestyle intervention group was offered additional lifestyle support. During the 10.0-year (interquartile range: 9.0–10.5) follow-up since randomization to DPP, it was found that the incidence of diabetes remained lowest in the intensive lifestyle group [44].

A systematic review of trials examined the effects of aerobic or resistance exercise training on clinical markers of CHD risk, including glycemic control, dyslipidemia, blood pressure, and body composition in patients with type 2 diabetes [45]. Aerobic exercise training alone or combined with resistance training (RT) significantly reduced HbA1c by 0.6 and by 0.67 % (95 % CI: −0.93 to −0.40), respectively. In addition, there were significant reductions in systolic blood pressure by 6.08 and 3.59 mm Hg and triglycerides by 0.3 mmol/L (for both forms of exercise), respectively. Waist circumference was significantly reduced by 3.1 cm

(95 % CI −10.3 to −1.2) with combined aerobic and resistance exercise, although fewer studies and more heterogeneity of the responses were observed in the latter two markers.

Hypertension

Several studies have addressed the issue of blood pressure and peripheral vascular resistance on blood pressure and autonomic function following exercise training. Cornelissen et al. [46] studied the effect of exercise training in middle-aged sedentary men and women at two levels of training intensity. They found that both levels of training intensity reduced the systolic blood pressure to a similar degree. These changes were also accompanied by a reduction in heart rate at submaximal workloads. The findings on the effect of exercise on blood pressure were essentially similar to those reported by Ogawa [14] and Bonnano and Lies [47]. A meta-analysis of clinical trials which included exercise as a component also concluded that physical activity contributed to better control of blood pressure [48].

It has been suggested that in patients with coronary heart disease these changes in blood pressure following exercise training are associated with changes in the concentrations of biomarkers of inflammation in peripheral blood [49]. The concentrations of C-reactive protein, interleukin 6, fibrinogen, and vascular cell adhesion molecule 1 were lower after exercise training. There was also a concurrent increased in high-density lipoprotein cholesterol. One of the possible mechanisms responsible for the improvement in blood pressure is that exercise attenuates endothelial dysfunction and inflammation and improves the nitric oxide bioavailability. It also increases the number of endothelial progenitor cells and a concurrent reduction in the level of pro-inflammatory cytokines and C-reactive protein.

Obesity

The *body mass index* (BMI) is a common means of estimating overweight and obesity in both adults and children. It is a calculated number based on height and weight and used to compare and analyze the health effects in all people. The conventional formula for its calculation is the weight in kilograms divided by height in meters squared.

Table 11.5 Interpretation of BMI values

<18.5	Underweight
18.5–24.9	Normal
25.0–29.9	Overweight
≥30.0	Obese

For instance, if the weight is 68 kg and the height is 165 cm (1.65 m), the BMI is $68 \div (1.65)^2 = 24$ (Table 11.5).

The BMI number and body fat are fairly closely related, but there is some variation associated with gender, race, and age. For instance, at the same BMI:

- Women tend to have more body fat than men.
- Older people, on average, tend to have more body fat than younger adults.
- Highly trained athletes may have a high BMI because of increased muscularity rather than increased body fatness.

The BMI is only one factor related to risk for disease. For assessing someone's likelihood of developing overweight- or obesity-related diseases, the National Heart, Lung, and Blood Institute guidelines recommend reviewing other predictors:

- The individual's waist circumference (because abdominal fat is a predictor of risk for obesity-related diseases).
- Other risk factors the individual has for diseases and conditions associated with obesity (e.g., high blood pressure or serum cholesterol).
- Ethnicity or race is also a factor. The World Health Organization has recommended that the normal/overweight threshold for Southeast Asian body types be lowered to a BMI of 23. The new cutoff BMI index for obesity in Asians is 27.5 compared with the traditional WHO figure of 30. An Asian adult with a BMI of 23 or greater is now considered overweight, and the ideal normal range is 18.5–22.9.

Although weight management is beyond the scope of this chapter, it should be recognized that an effective exercise program should be an essential ancillary tool in any regimen designed to control weight. The recommendations of the CDC with respect to exercise are addressed later in this chapter.

How Much Exercise?

In the statement addressing the recommendation for adults, the American College of Sports Medicine and the American Heart Association drew attention to the fact that US adults were still not sufficiently active [11]. In 2005, less than 50 % of US adults met the Centers for Disease Control and Prevention and the American College of Sports Medicine physical activity recommendation. Men were marginally more active than women, and younger people were more likely to be active than older people. The prevalence of those meeting these recommendations declined from 59.6 % among those 18–24 years of age to 39.0 % among those 65 years. For those >65 years, with no limiting conditions, a summary of the current recommendations are given in Table 11.1. Precautions to be followed by elderly people in undertaking an exercise program are shown in Table 11.2.

Other Benefits of Exercise

Risk of Falls

One of the benefits attributed to a regular exercise program in elderly people is an improvement in their sense of balance and a potential for reducing falls. Most of the controlled clinical trials in this field have shown that exercise training results in an improved sense of balance. In some studies, this effect was not accompanied by a reduction in falls [50], while in others such an effect has been noted [51, 52] together with a reduction in the number of hip fractures [53].

Exercise protects against loss in bone mass. Better bone density will reduce the risk of osteoporosis and lowers risk of falling and broken bones. Postmenopausal women can lose as much as 2 % bone mass each year, and men also lose bone mass as they age. Seventy-one older women were randomly assigned to resistance exercise, aerobic exercise, or a control group. Both interventions were conducted three times per week for 8 months. Outcome measures included proximal femur bone mineral density, muscle strength, balance, body composition, serum osteoprotegerin, and receptor activator of nuclear factor kappa B ligand (RANKL) levels. After 8 months, only the resistance group improved their bone mineral densities [at the trochanter (2.9 %) and total hip (1.5 %)] and body composition. Both forms of exercise improved balance [54]. Similar benefits have been demonstrated in older women taking bone-enhancing medications [55].

Immune Function

It has been suggested that moderate exercise training enhanced immune function in the elderly by modulating the function of T-helper cells. This effect is believed to reduce the risk of infections and autoimmune disease in the elderly [56]. Aerobic exercise training has also been shown to exert a modest additional benefit to the effects of vaccination for influenza [57]. These findings, though suggestive of benefit, have not been supported by the findings of controlled clinical trials. Campbell et al. studied the effect of exercise on in vitro immune function in a 12-month randomized clinical trial in postmenopausal women. The subjects were overweight, or obese sedentary women ($n = 115$), aged 50–75 years who were randomized to either an experimental group who exercised up to 45 min/day, 5 days/week or a control group who participated in stretching classes 1 day/week. After 12 months, the exercise group had participated in 87 % of the prescribed physical activity minutes per week and increased maximal O_2 uptake by 13.8 %, while the control group experienced no change in fitness. The main outcomes, natural killer cell cytotoxicity and T-lymphocyte proliferation, did not change [58].

Gastrointestinal Function

Regular exercise promotes the efficient elimination of waste and encourages digestive health. Physically active patients with irritable bowel syndrome face less symptom deterioration compared with physically inactive patients, and physical activity has been recommended as a primary treatment modality in this condition [59]. A large prospective observational study undertaken in Denmark has provided some insights into the role of exercise on the incidence of colorectal cancer. 55,487 men and women aged 50–64 years, not previously diagnosed with cancer were followed for a median period of 9.9 years. The aim was to evaluate the association between a simple lifestyle index based on the recommendations for five lifestyle factors and the incidence of colorectal cancer and to estimate the proportion of colorectal cancer cases attributable to lack of adherence to the recommendations. The lifestyle index was based on physical activity, waist circumference, smoking, alcohol intake, and diet (dietary fiber, energy percentage from fat, red and processed meat, and fruits and vegetables) modeled through Cox regression.

During the follow-up period, 678 men and women were diagnosed with colorectal cancer. After adjustment for potential confounders, each additional point achieved on the lifestyle index was associated with a lower risk of colorectal cancer (incidence rate ratio 0.89 (95 % CI 0.82–0.96)). In this population, an estimated total of 13 % (95 % CI 4–22 %) of the colorectal cancer cases were attributable to lack of adherence to merely one additional recommendation among all participants except the healthiest. If all participants had followed the five recommendations, 23 % (9–37 %) of the colorectal cancer cases might have been prevented. Results were similar for colon and rectal cancer, but only statistically significant for colon cancer [60].

Systemic Failures

Evidence summarized in this review has shown that engaging in regular physical activity reduces medication dependence, helps maintain functional independence, and improves the quality of life for older adults. Despite the weight of this evidence, the proportion of US adults receiving advice regarding physical exercise is somewhat limited (Fig. 11.5). Physicians and other health professionals can be influential sources of health information, and exercise counseling by primary care physicians has been shown to increase patients' participation in physical activity.

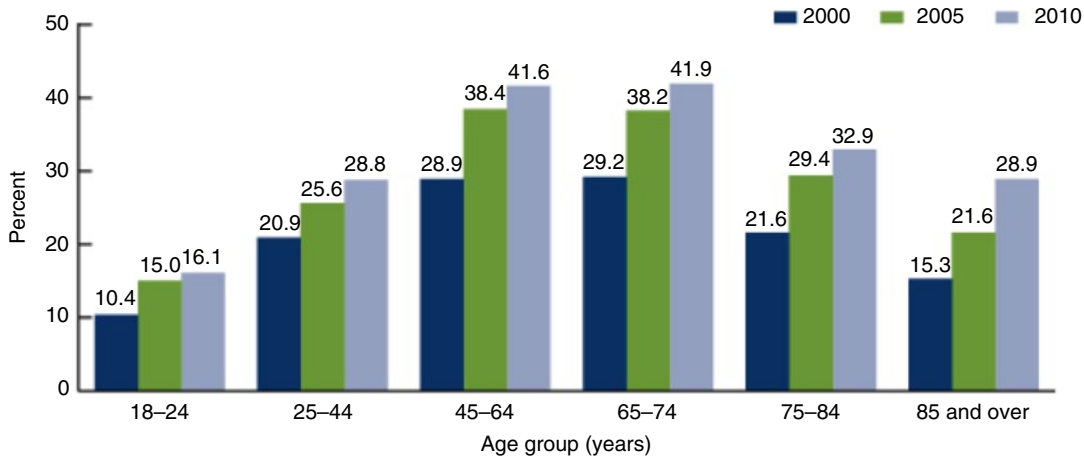

Fig. 11.5 Percentage of adults aged 18 and over whose physician or other health professional recommended exercise or physical activity, by age group and year: United States, 2000, 2005, and 2010 [61]

National Health Interview Survey, 2000, 2005, and 2010 shows that:

- In 2010, about one in three adults (32.4 %) who had seen a physician or other health professional in the past 12 months had been advised to begin or continue to do exercise or physical activity.
- Between 2000 and 2010, the percentage of adults receiving advice to exercise increased by about 10 % points.
- Among adults aged 85 and over, the percentage receiving advice to exercise nearly doubled between 2000 (15.3 %) and 2010 (28.9 %).
- Receiving advice to exercise increased for adults with hypertension, cardiovascular disease, cancer, and diabetes.
- Adults who were overweight or obese had the largest percentage point increases over the decade 2000–2010 in being advised to exercise.

Conclusions

Many Western societies have come to realize that physical inactivity plays a significant role in the total economic burden associated with ill-health. In fact, it is the fourth leading cause of death worldwide. The evidence summarized in this chapter points to the advantages associated with regular physical activity ranging from enhancing life expectancy to the management of non-communicable diseases such as diabetes, hypertension, coronary artery disease, and diabetes. What is also clear is that there is no specific age above which physical activity could be deemed to be harmful. Despite these considerations, physicians, nurses, and other caregivers appear to be reluctant not only to accept the results of well-designed studies that have addressed these issues but also to translate them into specific recommendations relating to physical activity.

> "If exercise could be purchased in a pill, it would be the single most widely prescribed and beneficial medicine in the nation."
>
> Robert H. Butler (Pioneer in Geriatric Medicine)

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The RAAS in Heart Failure: An Update on Clinical Trials and Opportunities for Therapy

12

C. Tissa Kappagoda and Ezra A. Amsterdam

Introduction

The most recent estimate (2010) of the prevalence of heart failure (HF) among Americans >20 years of age is 2.8 % (6.6 million). It is projected that by 2030, an additional 3 million people will have HF. The annual *rates of new cases (per 1,000 population)* of HF-related events for white and African-American men and women are shown below (Table 12.1). Even though the estimates for the oldest men and women are questionable, these figures highlight a growing problem for the health-care system [1].

In *Medicare beneficiaries* (<85 years of age), the trend in the HF hospitalization rate showed a decline from 31.7 % in 1999 to 29.6 % in 2008 ($P < 0.001$), a relative reduction of 6.6 % [2]. The long-term survival after the diagnosis of HF in the *population at large* was evaluated in the Rochester Epidemiology Project in which 4,537 Olmsted County residents (57 % women; mean age, 74 ± 14 SD years) with a diagnosis of HF who were followed up between 1979 and 2000 to determine the incidence of new episodes of HF and survival after the initial diagnosis. The incidence of new episodes of HF was higher among men than women (378/100,000 men vs. 289/100,000 women). After a mean follow-up of 4.2 years, it was found that 3,347 deaths had occurred (1,930 among women and 1,417 among men). Survival after the diagnosis of HF was worse among men than women (relative risk, 1.33; 95 % CI, 1.24–1.43), but overall, it improved over time (5-year age-adjusted survival, 43 % in 1979–1984 vs. 52 % in 1996–2000, $P < 0.001$). However, men and younger persons experienced larger survival gains, contrasting with less or no improvement for women and elderly persons. The authors concluded that the incidence of HF had not declined during two decades, and the improvement in survival after onset of HF was associated with the inclusion of greater numbers of younger people [3]. Even this modest improvement in overall survival has been based upon therapeutic regimens derived from the renin-angiotensin-aldosterone system (RAAS). These therapeutic advances will be reviewed in this chapter.

Nature of HF

Despite the development of improved methods of detection of changes in ventricular function during both systole and diastole, it is evident that HF itself is a clinical syndrome made up of signs and symptoms and that there is no single test or number that defines it, regardless of whether the

C.T. Kappagoda, MBBS, PhD (✉)
Department of Internal Medicine,
TB 172, University of California, Davis,
One Shields Avenue, Sacramento, CA 95616, USA
e-mail: ctkappagoda@ucdavis.edu

E.A. Amsterdam, MD
Department of Internal Medicine,
University of California, Davis, Sacramento, CA USA

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Table 12.1 Rates of new HF-related events/1,000

Age (years)	White		African-American	
	Men	Women	Men	Women
65–74	15.2	8.2	16.9	14.2
75–84	31.7	19.8	25.5	25.5
>85	65.2	45.6	50.6[a]	44.0[a]

[a]Unreliable data

dysfunction is systolic or diastolic. This situation is further complicated by the lack of a clinically practical method or parameter for measuring diastolic function, similar to the role that stroke volume (SV) plays in systolic HF.

HF is traditionally divided into two categories, one where the left ventricular ejection fraction (EF) is reduced (systolic HF) and the other where it is preserved (diastolic HF). Both groups have reduced exercise tolerance and associated dyspnea, neurohumoral activation, abnormal left ventricular filling dynamics, and impaired ventricular relaxation. Regardless of EF, the severity of HF and its prognosis and degree of exercise intolerance are closely related to the degree of diastolic filling abnormalities. Patients with HF and a reduced EF have ventricular dilatation and elongated myocytes, whereas patients with HF and a normal EF do not. Although a normal EF indicates that pump performance is adequately compensated, some of them have reduced longitudinal systolic velocity indicating cardiac muscular contractile dysfunction. Thus, patients with HF have diastolic abnormalities regardless of EF and many patients with HF and a normal EF have contractile abnormalities despite preserved systolic pump performance [4].

Thus, the diagnosis of diastolic HF can present a challenge, often requiring accurate definition of diastolic dysfunction (DD). Doppler echocardiography is the standard technique for assessing DD, but multiple physiological factors (heart rate, age, loading conditions), atrial fibrillation, and technical factors influence its evaluation and interpretation. For these reasons a diagnosis of diastolic heart failure needs to be supported by additional biochemical measurements such as B-type natriuretic peptide [5] and its biologically inactive fragment N-terminal proBNP [6]. More recently Martos et al. [7] have suggested that serological markers of collagen turnover could be a better supportive predictor of diastolic dysfunction. They found that markers of collagen turnover, particularly matrix metalloproteinase-2, identified patients with heart failure, with preserved EF, and with diastolic dysfunction.

It should be recognized that patients with diastolic HF have significant exercise intolerance related to failure of the Frank-Starling mechanism with reduced peak cardiac output, heart rate, and SV and increased LV filling pressure. They also appear to have increased vascular stiffness, accelerated systolic blood pressure response to exercise, neuroendocrine activation, and reduced quality of life. Pulmonary edema is a frequent occurrence and is associated with severe hypertension, sodium indiscretion, and medication noncompliance [8].

The Cardiovascular Health Study which was undertaken in 4,842 independent living, community-dwelling subjects aged 66–103 years old [9] yielded information regarding the prevalence of congestive HF (CHF). The presence of CHF was determined from both the diagnosis of CHF by a physician and treatment of CHF (i.e., a current prescription for a diuretic agent and either digitalis or a vasodilator). In addition, symptoms, signs, and chest X-ray findings of CHF were reviewed by the CHS Events Committee, which classified all cardiovascular events. Overall, the prevalence of CHF was 8.8 % and was associated with increasing age, particularly in women, in whom it increased more than twofold from age 65–69 (6.6 %) to age 85 years (14 %). Notably, 55 % of subjects with CHF had normal LV systolic function and *80 % had either normal or only mildly reduced systolic function*. Among those with CHF, women had normal systolic function more frequently than did men (67 % vs.42 %; $P<0.001$). *Thus, CHF is common among community-dwelling elderly individuals, increases with age, and is usually associated with normal systolic LV function, particularly among women*. Similar findings were seen in slightly younger subjects in the Framingham Heart Study [10]. It is now clear that diastolic HF is an important, perhaps even dominant form of HF in older female Americans (see [8] for review).

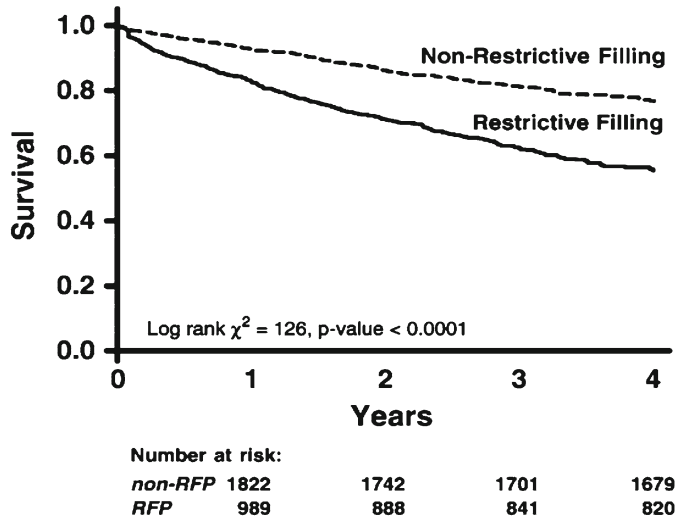

Fig. 12.1 Kaplan–Meier survival curves for patients with heart failure with restrictive filling pattern vs. nonrestrictive filling pattern (reprinted from Meta-analysis Research Group in Echocardiography Heart Failure C. Independence of restrictive filling pattern and LV ejection fraction with mortality in heart failure: An individual patient meta-analysis. European Journal of Heart Failure 2008;10:786–92. With permission from Oxford University Press)

Among stable outpatients mortality rates are about 50 % lower in diastolic failure than in systolic HF [11, 12] (Fig. 12.1). However, in hospitalized and very elderly patients, the mortality rate appears similar in both forms of failure [13]. Furthermore, the total mortality attributable to diastolic failure in the older population exceeds that of systolic HF due to its higher prevalence in this group.

Dyspnea as a Symptom of HF

Regardless of the contribution of ventricular function to the syndrome of heart failure, the condition is accompanied by a change in distribution of extracellular fluid in the body predicated by alternations in the Starling forces which regulate the transfer of fluid across capillaries, particularly in the lung. In the case of left ventricular failure (both systolic and diastolic), there is a net transfer of fluid, first into the airway mucosa and later into the alveoli when the pulmonary venous pressure increases leading to symptoms such as bronchospasm and dyspnea on exertion. (The corresponding situation in the case of the right ventricle results congestion of organs in the abdominal and lower extremities eventually resulting in peripheral edema.)

The clinical manifestations associated with *left ventricular* failure include tachypnea, dyspnea (accompanied by an associated sense of distress), bronchospasm, and cough [14]. These features are preceded by an increase in the volume of fluid in the extravascular space of the lung. Paroxysmal nocturnal dyspnea is a particular manifestation of left ventricular failure when the extravascular fluid accumulates in the lung at night after the subject assumes a horizontal position during sleep. The most consistent associated feature of left ventricular failure, regardless of its etiology, is an increase in left atrial pressure which in turn leads to a disturbance of the Starling forces in a manner which favors an increase in extravascular fluid in the airways and lung.

In *right ventricular failure*, the hydrostatic pressure increases in the right atrium and the vena cavae. The hydrostatic pressures in the microcirculation of the lung are not affected to the same extent as in left ventricular failure. However, as discussed below, homeostasis of the extravascular fluid volume of the airways and lung also depends on effective lymph drainage from the lung. The pumping pressure in the

lymphatic vessels close to the external jugular vein is approximately 17 cm H_2O [15]. Thus, when this pressure is exceeded in the jugular veins, it is likely that pulmonary lymphatic drainage will be compromised leading to an increase in the extravascular fluid volume.

Symptomatology of Heart Failure

The fundamental principle governing the exchange of fluid between microvessels and the extravascular space was proposed by Starling [16]. He postulated that "at any given time, there must be a balance between hydrostatic pressure and the osmotic pressure alteration of the blood…" thereby linking the three main factors which determine the extravascular fluid volume (space) in any tissue, i.e., hydrostatic pressure, oncotic pressure exerted by proteins, and the flow of lymph.

Three decades later, these ideas were consolidated further by the experiments of Landis [17] who summarized his findings in the form of the following equation:

$$J_v / A = L_p \left[\left(P_c - P_i \right) - \sigma \left(\Pi_c - \Pi_i \right) \right]$$

where J_v/A is the rate of fluid filtration or resorption (mL/min) per unit area of vessel wall; L_p is the hydraulic permeability of the vessel wall (mL/min/mmHg); P_i and Π_i are the hydrostatic and plasma oncotic pressures of the interstitial fluid, respectively (mmHg); P_c and Π_c are the hydrostatic and oncotic pressures of plasma, respectively (mmHg); and σ is the reflection coefficient of the wall to plasma protein (factor varying from 0 to 1).

The hydrostatic pressure in the pulmonary microcirculation can be readily increased by raising the left atrial pressure and the oncotic pressure decreased by plasmapheresis [18]. Pulmonary microvascular permeability can also be increased by chemicals such as histamine [19] and by compounds such as alloxan [20] and bradykinin which result from the blockage of kininases by ACE inhibitors (see [21] for review). In HF, these hemodynamic adjustments occur against a background of a series of regulatory mechanisms involving the handling of salt (NaCl) and water by the kidney which results in significant changes in the fluid volume in the body as a whole.

Recent studies in this field have suggested that capillary permeability could be altered by other factors such as nitric oxide released in endothelial cells. It has been argued that capillary permeability is enhanced in the absence or reduction in the production of NO from endothelial cells in the lung secondary to the effect of angiotensin II (see below) [22, 23].

Overview of the Neurohumoral Interactions in the Kidney in HF

The RAAS directly regulates the blood volume, systemic vascular resistance, and indirectly regulates the cardiac output and arterial pressure. There are three important components to this system: (1) renin, (2) angiotensin, and (3) aldosterone.

Renin, which is primarily released by the kidneys, initiates the formation of angiotensin in blood and tissues, which in turn stimulates the release of aldosterone from the adrenal cortex. It is a proteolytic enzyme that is released into the circulation primarily by the kidneys. Its release is stimulated by (a) sympathetic nerve activation (acting via β_1-adrenoceptors), (b) renal artery hypotension (caused by systemic hypotension or renal artery stenosis), and (c) decreased sodium delivery to the distal tubules of the kidney. In HF, (a) and (b) above could be viewed as the primary stimuli for the release of renin, while (c) could be viewed as a feature that consolidates the changes in sodium hemostasis associated with heart failure.

Juxtaglomerular (JG) cells associated with the afferent arteriole entering the renal glomerulus are the primary site of renin storage and release in the body. A reduction in afferent arteriole pressure causes the release of renin from the JG cells, whereas increased pressure inhibits renin release [24, 25]. Renin is also released by two other stimuli besides a low pressure in the afferent glomerular artery: (1) activation of

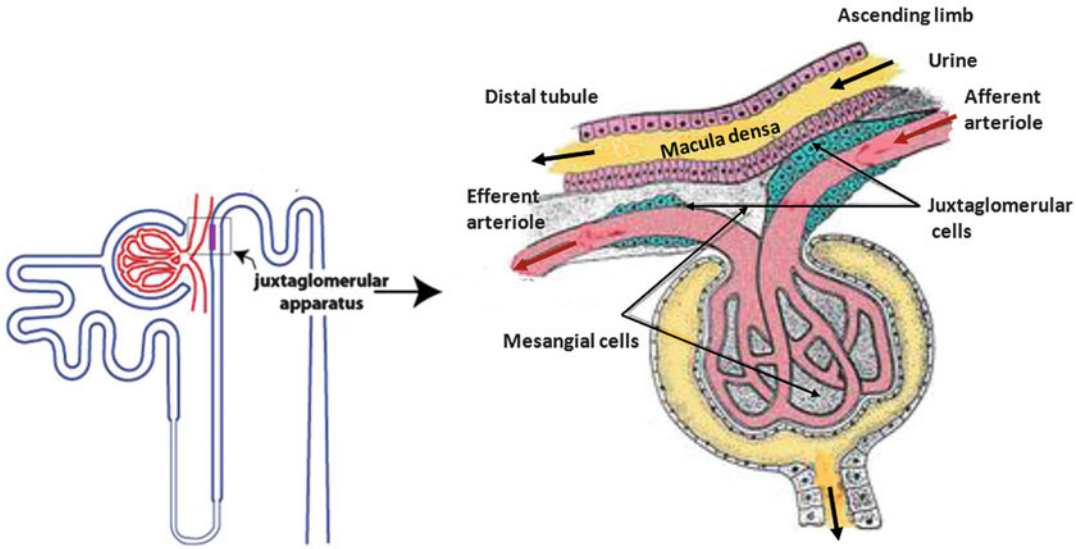

Fig. 12.2 Schematic view of the juxtaglomerular apparatus. When afferent arteriole pressure is reduced, glomerular filtration decreases thereby reducing NaCl in the distal tubule. This effect is an important mechanism contributing to the release of renin when there is afferent arteriole hypotension

sympathetic nerves leading to stimulation of β_1-adrenoceptors located on the JG cells and (2) specialized cells (macula densa) of distal tubules lying adjacent to the JG cells of the afferent arteriole sensing the amount of sodium and chloride ion in the tubular fluid. When these ions are elevated in the tubular fluid, renin release is inhibited. In contrast, a reduction in tubular NaCl stimulates renin release by the JG cells. A reduction in arteriole pressure decreases glomerular filtration thereby reducing NaCl in the distal tubule thus facilitating the release of renin (Fig. 12.2). The latter mechanism serves as an important mechanism contributing to the release of renin when there is afferent arteriolar hypotension as in HF. While the idea of sympathetic activation in HF is still accepted the precise mechanism by which this activation is achieved has been questioned in recent years (see [26, 27] for reviews).

Specialized cells of distal tubules (macula densa) lie adjacent to the JG cells of the afferent arteriole. The macula densa senses the amount of sodium and chloride ion in the tubular fluid. When NaCl is elevated in the tubular fluid, renin release is inhibited. In contrast, a reduction in tubular NaCl stimulates renin release by the JG cells. There is evidence that prostaglandins (PGE_2 and PGI_2) stimulate renin release in response to reduced NaCl transport across the macula densa.

When renin is released into the blood, it acts upon a circulating substrate, angiotensinogen, which undergoes proteolytic cleavage to form the decapeptide angiotensin I. The vascular endothelium, particularly in the lungs, has an enzyme, angiotensin-converting enzyme (ACE), which cleaves off two amino acids to form the octapeptide, angiotensin II (AII). However, many other tissues in the body (heart, brain, vascular) also can form AII.

AII has several functions:

- Activates AII [AT_1] receptors and constricts resistance vessels thereby increasing systemic vascular resistance and arterial pressure
- Stimulates the adrenal cortex to release aldosterone which acts on the kidneys to increase sodium and fluid retention
- Stimulates the release of vasopressin (antidiuretic hormone, ADH) from the posterior pituitary, which increases fluid retention by the kidneys

- Stimulates thirst centers within the brain
- Facilitates norepinephrine release from sympathetic nerve endings and inhibits norepinephrine reuptake by nerve endings, thereby enhancing sympathetic adrenergic function
- Stimulates cardiac and vascular hypertrophy

The RAAS pathway is regulated not only by the mechanisms that stimulate renin release, but it is also modulated by natriuretic peptides (ANP and BNP) released by the heart which act as an important counter-regulatory system. Therapeutic manipulation of the RAAS has become the cornerstone in the management of hypertension and heart failure (see below). With progressive ventricular dysfunction, clinically evident HF develops and neurohormonal systems that affect sodium excretion are activated through the effect of angiotensin II through several mechanisms:

- Increases the resistance of the afferent arterioles, decreases the glomerular filtration rate through reduction of renal perfusion, and increases Na and water reabsorption in the proximal tubule.
- Concurrent activation of the sympathetic nervous system leads to increased peripheral resistance and heart rate that increase afterload, reduce cardiac output, decrease renal and tissue perfusion, enhance proximal tubular Na reabsorption further, and decrease water and Na delivery to the distal diluting segments eventually leading to hyponatremia [28, 29].

Circulating levels of arginine vasopressin (AVP) are 2–3 times greater among hyponatremic HF patients compared with normal subjects. The trigger for non-osmotic release of AVP in HF remains unclear, but arterial underfilling from reduced cardiac output is the leading hypothesis. Both low cardiac output and high angiotensin II levels are also potent thirst stimuli; patients with severe HF may develop hyponatremia with an intake of only 1–2 L of water per day [28].

Other Effects of RAAS

Although it was once considered to be an endocrine system, the RAAS is now widely recognized as at least a dual (circulating and local/tissue) or probably a multiple hormonal systems (endocrine, paracrine, and intracrine) (see [30–32] for recent reviews). In addition to the classical renin/angiotensin I/angiotensin II pathway described above, several other systems and pathways have also been described (e.g., the prorenin/(pro)renin receptor (PRR)/MAP kinase axis, the ACE2/Ang (1–7)/Mas receptor axis, and the Ang IV/AT_4/insulin-regulated aminopeptidase axis), resulting in extension of the role of RAAS beyond blood pressure control, aldosterone synthesis, and body fluid and electrolyte homeostasis.

Prorenin, the precursor of renin, had long been considered to be an inactive form. However, a (pro)renin receptor that binds to both renin and prorenin has been identified recently. Both prorenin and renin bind to (pro)renin receptors resulting in angiotensinogen cleavage into angiotensin (Ang) I and trigger activation of (pro)renin receptor-stimulated signal transduction pathways, independent of generating Ang II. Intracellular signaling pathways activated by prorenin have been demonstrated in cardiomyocytes, mesangial cells, podocytes, distal tubular cells, vascular endothelial cells, and vascular smooth muscle cells, indicating that prorenin mediates intracellular effects in various cardiovascular and kidney cells (see [33]).

Angiotensin

Angiotensin II (Ang II) acts through two receptor subtypes, the AT1 and AT2 receptors. The physiological effects of Ang II, such as vasoconstriction, aldosterone and vasopressin release, sodium and water retention, and sympathetic facilitation, are mediated by the AT1 receptor. Ang II, via its AT1 receptor, is also involved in cell proliferation, left ventricular hypertrophy, nephrosclerosis, vascular media hypertrophy, endothelial dysfunction, and neointima formation and processes leading to atherothrombosis. Recent investigations have established a role for the AT2 receptor in cardiovascular, brain, and renal function as well as in the modulation of various biological processes involved in development, cell differentiation, tissue repair, and apoptosis [34].

Besides these two angiotensin receptors, two other subtypes (AT3 and AT4) have been described, but their precise biological effects remain unresolved at this time [35].

Against this background it is not surprising that the management of chronic HF has focused on the use of drugs that block the production of Ang II. However, there is evidence that chronic use of ACE inhibitors leads to a condition described as "ACE escape" in which Ang II levels return to normal values suggesting that the blockade of the RAAS by ACE inhibitors is incomplete. It is unclear how complete the blockade by ACE inhibitors is and if there is continuing angiotensin II (Ang II) formation during chronic treatment with ACE inhibitors [36].

For instance, human heart tissue contains chymase, a serine protease, which is able to form angiotensin II from Ang I and cannot be blocked by ACE inhibitors. Wolney et al. [37] showed incomplete ACE inhibition in human heart tissue after chronic ACE inhibitor therapy. They also showed that a serine protease was responsible for the majority of Ang II production in both the membrane preparation and Ang I-induced contractions of isolated coronary arteries. They suggested that in humans, the serine protease pathway is likely to play an important role in cardiac Ang II formation. Thus, drugs such as renin inhibitors and Ang II receptor blockers might be able to induce a more complete blockade of the renin-angiotensin system, providing a more efficacious therapy [38].

Azizi et al. [38] have suggested that the "escape" observed when a single site within the RAS is blocked is due to the interaction between clearance from the body of the drug at the end of the dosing interval and the counter-regulatory "reactive" rise in plasma active renin. This discrepancy increases the ACE substrate Ang I or the AT1R agonist Ang II (based on the negative feedback on renin release). This recurring discrepancy between Ang II and the blocking of AT2 receptors has led to the concept of combined RAS blockade [with an ACE and angiotensin receptor blocker (ARB)] as a means of combating the variable blood pressure-lowering response seen with ACE inhibitors alone. In many patients with HF, incomplete RAS blockade may also contribute to deterioration of LV function and to a poor cardiac prognosis despite maximally recommended doses of ACE inhibitors.

The combination of two pharmacological agents that inhibit two consecutive RAS steps, ACE and AT1R, can minimize or even overcome the escape observed with single-site RAS blockade. At the time when the ACE inhibitor dissociates from ACE active sites and Ang II reappears in the presence of an increased level of plasma and interstitial Ang I, the concurrent administration of an AT1R antagonist will protect the AT1R from the newly produced agonist. Reciprocally, when less AT1R antagonist is bound to the AT1Rs, an ACE inhibitor will reduce the production of Ang II available to compete with the antagonist. The alternative proposed to this physiological explanation is that an AT1R antagonist in combination with an ACE inhibitor blocks the effects of Ang II generated by pathways other than renin and ACE, such as the chymase referred to above.

Aldosterone

Luetscher and Johnson [39] first observed that adults and children with HF secreted a steroid hormone in the urine with sodium-retaining properties. This hormone was later identified as aldosterone and was found to be produced in excess in the adrenal gland in edematous states [40]. Aldosterone levels are elevated in patients with HF due to both increased adrenal production and decreased hepatic clearance. It is found to play several crucial roles in the pathogenesis of the syndrome. Even more significant is the fact that the concentrations of aldosterone correlate with disease severity and predict mortality. Overall, patients whose neurohormonal systems are highly activated have the highest mortality, independent of other clinical variables such as symptoms and left ventricular ejection fraction [41].

Aldosterone exerts its effects by binding to the mineral corticoid receptor. Spironolactone is a nonselective mineral corticoid receptor antagonist (MRA) that is structurally similar to progesterone. In addition to its aldosterone-blocking effects, spironolactone inhibits the effects of dihydrotestosterone at the receptor site and increases the peripheral conversion of testosterone into estradiol. As a result, it is associated with antiandrogenic and progestogenic adverse effects including gynecomastia, impotence, and menstrual irregularities.

In patients with HF, stimulants for aldosterone release include angiotensin II (especially when intravascular volume is reduced with diuretic therapy), serum potassium concentration, and corticotrophin [42]. Additional stimuli that play a minor role in normal adults but are upregulated in HF include circulating arginine vasopressin, catecholamines, and endothelin. In the myocardium, aldosterone exerts growth-promoting and profibrotic effects on myocytes and the interstitium, respectively. Besides the adrenal cortex, aldosterone is produced by vascular endothelial cells where it promotes inflammation and fibrosis leading to endothelial dysfunction. Transgenic mouse models demonstrate that cardiac-specific overexpression of 11β-hydroxysteroid dehydrogenase type 2 with activation of MRAs leads to concentric ventricular remodeling, myocardial fibrosis, and premature death [43]. This phenotype can be attenuated and survival enhanced with aldosterone receptor blockade. Reduction in dietary salt intake may also play a key role in limiting aldosterone-mediated cardiovascular damage [44].

In the kidney, aldosterone has long been understood to promote reabsorption of sodium and water from tubular fluid, an effect that is regulated by the α-subunit of the epithelial sodium channel. More recent data suggest that stimulation of mineral corticoid receptors in the renal cortex can also contribute to ischemic injury, mesangial cell proliferation, and nephrosclerosis [45], and these effects can be reversed with spironolactone or eplerenone indicating that aldosterone antagonists may have protective effects on both the heart and kidney.

HF Therapy Based on RAAS

Anti-renin Therapy

The most recent approach to inhibiting the RAS in patients with HF is renin inhibition. Aliskiren binds to the S3bp binding pocket of renin, essential for its activity. Binding to this pocket prevents the conversion of angiotensinogen to angiotensin I. The rationale for developing this drug was the concern that many drugs that control blood pressure by interfering with angiotensin or aldosterone when used chronically, the body increases renin production, which drives blood pressure up again. These fears have been unfounded in studies in which aliskiren has been used in the management of high blood pressure either alone [46] or in combination [47].

The efficacy and safety of the renin inhibitor aliskiren is being tested in two clinical trials in HF, the Aliskiren Trial of Minimizing OutcomeS for Patients with HEart failuRE (ATMOSPHERE) [48] and the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) [49]. A third study, the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Disease Endpoints (ALTITUDE), which compared placebo or aliskiren 300 mg once daily, added to background ACE inhibitor or ARB therapy in patients with diabetes and either (1) increased urinary albumin excretion or (2) both a reduced estimated glomerular filtration rate (eGFR 30–60 mL/min/1.73 m^2) and established cardiovascular disease, was stopped on the recommendation of its Data Monitoring Committee. The primary outcome in ALTITUDE is a composite of cardiovascular death, resuscitated sudden death, nonfatal myocardial infarction, nonfatal stroke, unplanned hospitalization for heart failure, end-stage renal disease, renal death, or doubling of baseline serum creatinine concentration, sustained for at least a month. The basis of the DMC recommendation was futility as well as safety concerns such as renal dysfunction, hyperkalemia, hypotension, and an excess of strokes. The findings of the ATMOSPHERE and ASTRONAUT trials are awaited with interest at the present time [50].

ACE Inhibitors

For almost two decades, ACE inhibitors have been used in the management of patients with heart failure and have been proposed as first-line treatments for HF by several national and international bodies [51–53]. The basis for these recommendations has been the findings of multiple clinical trials in patients with heart failure [54, 55], reported in the 1990s and later supported by either meta-analyses or systematic reviews [56, 57] demonstrating benefit in terms of mortality, morbidity, reinfarction, and hospitalizations. For instance, the SOLVD (Studies of Left Ventricular Dysfunction) trial [55] was designed to determine whether an ACE inhibitor, enalapril, would reduce mortality in patients with low ejection fractions (≤0.35). Patients (<80 years) with congestive heart failure and ejection fractions of 0.35 or less (measured by radio nucleotide or LV angiography) who were already taking drugs other than an ACE inhibitor as part of conventional therapy for congestive heart failure were eligible for the study. Those excluded were those with hemodynamic ally serious valvular disease requiring surgery, unstable angina pectoris, angina thought to be severe enough to require revascularization procedures, myocardial infarction during the previous month, severe pulmonary disease, serum creatinine level higher than 177 mol/L (2 mg/dL), or any other disease that might substantially shorten survival or impede participation in a long-term trial.

All the patients eligible for either trial entered a run-in and stabilization phase. The subjects were initially given 2.5 mg of enalapril twice daily in a single-blind fashion for 2–7 days to identify patients who could not tolerate even a small dose of the drug for a short period and those who were unable to comply with the regimen. Treatment was begun in the hospital for only 1.2 % of patients. A total of 310 of 7,402 patients were excluded from the study during this phase for worsening renal function, symptomatic hypotension, and noncompliance.

There were 510 deaths in the placebo group (39.7 %), as compared with 452 in the enalapril group (35.2 %) (reduction in risk, 16 %; 95 % confidence interval, 5–26 %; $P=0.0036$). Although reductions in mortality were observed in several categories of cardiac deaths, the largest reduction occurred among the deaths attributed to progressive heart failure (251 in the placebo group vs. 209 in the enalapril group; reduction in risk, 22 %; 95 % confidence interval, 6–35 %). There was little apparent effect of treatment on deaths classified as due to arrhythmia without pump failure. Fewer patients died or were hospitalized for worsening heart failure (736 in the placebo group and 613 in the enalapril group; risk reduction, 26 %; 95 % confidence interval, 18–34 %; $P<0.0001$) [55]. Essentially similar findings were obtained in the CONSENSUS Trial undertaken in Scandinavian countries [54].

Angiotensin Receptor Blockers

Several trials have addressed the use of ARBs in the management of heart failure either in placebo controlled trials or as an add-on drug in patients already under treatment with an ACE. Heran et al. [58] performed a meta-analysis of 24 trials that have been published up to 2012. These trials collectively enrolled a total of 25,051 patients with symptomatic HF. Twenty-two studies randomized 17,900 patients with LVEF ≤ 40 % and two studies randomized 7,151 patients with LVEF > 40 %. All clinical events or other outcome measures reported post-randomization were included in this review. No maximum limit was imposed on the length of follow-up.

Primary end points: (1) total mortality, (2) cardiovascular mortality, (3) non-cardiovascular mortality, (4) cardiovascular morbidity, (5) myocardial infarction (MI), (6) stroke, (7) total heart failure-related hospitalizations, and (8) hospitalizations

Secondary end points: (1) withdrawals due to adverse effects

The findings of the meta-analysis by Heran et al. are summarized in Table 12.2 [58]. Based on this meta-analysis the authors concluded that:

1. ARBs do not reduce total mortality or all-cause mortality compared to a placebo regardless of EF.

Table 12.2 Summary of heart failure trials with ARBs

End point	EF < 40 %	EF > 40 % (i.e., preserved EF)
ARBs vs. placebo		
Mortality	No benefit in total mortality (7 trials)[a] No benefit in CV and non-CV mortality	No effect on total, CV, or non-CV mortality (2 trials/7,151 subjects)
	No difference (2 trials/2,298 subjects)	No data
	Higher with ARB	No data
Hospitalizations	Three trials and one trial contributed >90 % of data Increase in all-cause hospitalizations Heart failure admissions was reduced	No benefit (2 trials, 7,151 subjects)
Withdrawal due to adverse effects[b]	More withdrawals in the ARB groups but not statistically significant (6 trials, 3,766 subjects)	Greater in ARB groups (2 trials with 7,151 subjects)
ARB vs. ACEI		
Mortality	No differences in total (4 trials), CV (4 trials), and non-CV mortalities (4 trials)	
Stroke	No difference (1 study)	
MI	No difference (2 studies)	
Hospitalization	Four (n = 4,310) of the included studies reported total hospitalizations, hospitalizations for HF, and hospitalizations for other causes. There were no differences	
Withdrawals	Less with ARBs (6 trials)	
ARB + ACEI vs. ACEI alone		
Mortality	With respect to total mortality (7 trials), cardiovascular mortality (2 trials), or non-cardiovascular mortality (2 trials), there were no differences between combination therapy and ACEI monotherapy groups	
Stroke	No difference (1 trial)	
MI	Benefit with combination therapy	
Hospitalization	Combination therapy reduced heart failure admissions, but this potential benefit was offset by admissions for other causes	
Withdrawals	More withdrawals with combination therapy	

[a]Two unpublished trials sponsored by the manufacturer were excluded to avoid bias
[b]Combining all trials regardless of EF showed that there were more withdrawals due to ARBs

2. ARBs do not reduce total or all-cause mortality compared with an ACE in symptomatic patients with an EF < 40 %.
3. Adding ARB to an ACE does not reduce total mortality or all-cause hospitalizations in HF patients with an EF < 40 %. Also, adding an ARB to ACE increases the risk for withdrawal of treatment.

A recent meta-analysis of 33 randomized controlled trials with 68,405 patients (mean age 61 years, 71 % men) and mean duration of 52 weeks extended these observation to include direct renin inhibition [59]. Dual blockade of the renin-angiotensin system was not associated with any significant benefit for all-cause mortality and cardiovascular mortality compared with monotherapy. Compared with monotherapy, dual therapy was associated with an 18 % reduction in admissions to hospital for heart failure (0.82, 0.74, and 0.92). However, compared with monotherapy, dual therapy was associated with a 55 % increase in the risk of hyperkalemia ($P < 0.001$), a 66 % increase in the risk of hypotension ($P < 0.001$), a 41 % increase in the risk of renal failure ($P = 0.01$), and a 27 % increase in the risk of withdrawal owing to adverse events ($P < 0.001$).

Aldosterone Receptor Antagonists

These compounds, also referred to as mineralocorticoid receptor antagonists (MRA), are currently guideline-recommended evidence-based therapy for select patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF) [60, 61]. The contribution of aldosterone

to the development and progression of HF is well established. Spironolactone was introduced in 1959 but has been mostly superseded in the management of HF and hypertension, by newer agents such as eplerenone which is structurally related to it, more selective, and which lacks many of the actions and side effects of spironolactone. Eplerenone has a 100- to 1,000-fold lower affinity for androgen, glucocorticoid, and progesterone receptors than spironolactone and as such is not associated with the antiandrogenic side effects observed with spironolactone therapy. Spironolactone has been shown to raise serum cortisol levels and hemoglobin A_{1c} in patients with mild HF, while eplerenone did not increase from baseline in patients treated with spironolactone and did not change in those treated with [62]. The clinical relevance of the latter findings is not known at present, and both drugs have been shown to improve the outcome in patients with HF.

Eplerenone is extensively metabolized to inactive metabolites, whereas spironolactone is metabolized to the active metabolite canrenone. In the distal tubule, aldosterone promotes sodium reabsorption and potassium excretion. Aldosterone antagonists block potassium excretion in the renal distal tubule and collecting ducts, leading to the risk of hyperkalemia.

MRAs and HF

Several randomized controlled trials of aldosterone antagonists in patients with HF and reduced LVEF have been conducted to date. A systematic review of these and other studies with aldosterone receptor antagonists included 10 trials that have specifically enrolled New York Heart Association (NYHA) class II patients with reduced LVEF [63]. The three main placebo controlled trials which have addressed the outcomes in patients with reduced EFs (~35–40 %) were RALES [64], EMPHASIS-HF [65], and EPHESUS [66]. The first involved spironolactone and the other two involved eplerenone (Table 12.3).

The findings of the three trials summarized in Table 12.3 demonstrate that MRAs have a beneficial effect in patients with a reduced EF in the short terms (1–2 years). These findings were largely confirmed in a meta-analysis (19 randomized controlled trials, 4 in acute MI and 15 in heart failure, $n = 10{,}807$ patients) reported by [63]. The analysis showed that aldosterone blockade reduced all-cause mortality by 20 %. This benefit was evident in both heart failure and post-MI patients. There was a significant reduction in rehospitalizations and the EF improved in the seven heart failure trials, which assessed this outcome (weighted mean difference 3.1 %, 95 % CI 1.6–4.5).

The anti-remodeling effect of canrenone (which is an active metabolite of spironolactone) in patients with mild chronic heart failure (AREA IN-CHF) trial was studied in a randomized, double-blind, placebo-controlled trial of 467 patients with NYHA class II HF symptoms and LVEF ≤ 45 % on optimal background therapy [67]. Patients enrolled had a mean age of 62 ± 9.5 years, 84 % were male, 51 % had an ischemic cardiomyopathy, and mean LVEF was 40 ± 8.6 %. Ninety-six percent were on an ACE inhibitor or ARB and 81 % were on a β-blocker. The mean dose of canrenone tolerated was 44 mg/day. The primary end point of reduction in left ventricular end diastolic volume at 12 months was not significantly different between the two groups. However, LVEF improvement was higher in the canrenone arm as compared with placebo (canrenone 39.9 ± 8.6 to 45.1 ± 9.6 vs. placebo 39.7 ± 8.6 to 42.9 ± 9.7; $P = 0.04$). After 12 months, the canrenone group had a nonsignificant reduction in all-cause mortality compared with placebo (2.8 % vs. 5.4 %, $P = 0.17$). Additionally, the composite of cardiac death or hospitalization was significantly lowered with canrenone (7.9 % vs. 15.1 %, $P = 0.02$).

On the basis of the findings of the trials described above, spironolactone and its analogues appear to exert a beneficial effect in patients which chronic HF or with evidence of a reduce EF following a myocardial infarction. Most of the trials were undertaken over a comparatively short period of time (<2 years) which may be a function of the prognosis of heart failure per se.

Table 12.3 Summary of three trials involving MRA

	RALES [63]	EMPHASIS-HF [64]	EPHESUS [65]
Study description	Placebo controlled, double-blind trial of spironolactone	Randomized, double-blind, placebo controlled trial of eplerenone	Placebo controlled trial of eplerenone
Primary outcome	All-cause mortality	Cardiovascular death or HF hospitalization	Co-primary outcome: all-cause mortality and cardiovascular death or cardiovascular hospitalization
Patient type	NYHA classes III and IV	NYHA class II HF and LVEF	3–14 days post-MI and HF signs
Age (mean; SD)	65 ± 12 years	68.7 ± 7.7 years	64 ± 11years
Gender	73 % male	78 % were male	70 % were men
Etiology	Ischemic cardiomyopathy (55 %)	Ischemic cardio-myopathy (69 %)	Post-MI
RAAS-related therapy	95 %—ACE inhibitor	94 %—ACE inhibitor or ARB	86 % ACE inhibitor or ARB
β blocker	11 %	87 %	75 %
Follow-up	24 months	21 months	16 months
Outcome	Spironolactone reduced: 1. the primary end point of all-cause mortality by 31 % 2. 30 % reduction in hospitalizations 3. 32 % reduction in cardiac mortality Significant improvement in NYHA class	Eplerenone significantly reduced the risk of the primary end point of cardiovascular death or HF hospitalization and all-cause mortality	Eplerenone reduced the co-primary end points of all-cause mortality and cardiovascular death or cardiovascular hospitalization. All-cause death or all-cause hospitalization and cardiovascular death were also reduced
The number needed to treat (NNT)	NNT with spironolactone for 2 years to save one life was nine patients	NNT with eplerenone to postpone one death per year of follow-up was 51 patients	NNT to save one life per year was 50 NNT was 33 to prevent one cardiovascular death or one cardiovascular hospitalization

Other Neurohumoral Influences on Sodium Hemostasis

Hyponatremia which is generally defined as serum sodium concentration of <135 mEq/L is associated with an increase in hospital and post-discharge mortality, prolonged hospital length of stay, and frequent rehospitalization. These effects are disproportionate to the degree of ventricular dysfunction. The importance of sodium lies elsewhere in the fact that it is the main extracellular cation that determines the serum osmolality which under physiological conditions is dependent on three factors: arginine vasopressin (AVP), renal responsiveness to AVP, and thirst. Besides these "physiological" perturbations, release of AVP is also influenced by non-osmotic mechanisms that originate in the baroreceptors which are capable of overriding the physiological osmotic stimuli [68]. In both preclinical systolic and diastolic dysfunction, renal cyclic guanosine monophosphate (cGMP) activation is impaired, which contributes to a reduction in natriuresis in response to volume expansion. These factors may contribute to volume overload and the progression of HF from a preclinical status to overt failure.

This impaired renal excretory response to volume expansion could be restored by exogenous B-type natriuretic peptide in these clinical

situations [69]. Nesiritide (Natrecor) is the recombinant form of the 32 amino acid human B-type natriuretic peptide, which is normally produced by the ventricular myocardium. Nesiritide facilitates cardiovascular fluid homeostasis through counter-regulation of the RAAS system, stimulating cGMP, leading to smooth muscle cell relaxation.

These considerations raise questions about our current management strategy for early stages of HF which have been focused primarily on systemic neurohormonal blockade [69]. They imply that potentiating the natriuretic peptide system might serve as an important therapeutic target to improve the failing cardio-renal interactions in HF during the early stages of the disease [70]. However, the effects of nesiritide on mortality have not been very convincing. Abraham et al. [71] undertook a systematic review of trials of nesiritide and concluded that the individual trials were neither designed nor powered to evaluate mortality over 30–180 days. Their systematic review appeared to suggest that the drug had no effect on mortality during this period.

In order to resolve the issue of the potential benefit of nesiritide on patients with chronic HF, O'Connor et al. randomly assigned 7,141 patients who were hospitalized with acute heart failure to receive either nesiritide or placebo for 24–168 h in addition to standard care [72]. Co-primary end points were the change in dyspnea at 6 and 24 h, as measured on a 7-point Likert scale, and the composite end point of rehospitalization for heart failure or death within 30 days. Those randomly assigned to nesiritide, as compared with those assigned to placebo, more frequently reported markedly or moderately improved dyspnea at 6 h (44.5 % vs. 42.1 %, $P=0.03$) and 24 h (68.2 % vs. 66.1 %, $P=0.007$), but these differences were not statistically significant when assessed against prespecified levels of significance. The rates of rehospitalization for HF or death from any cause within 30 days were also not significantly different in the two groups. The rates of worsening renal function, defined by more than a 25 % decrease in the estimated glomerular filtration rate, were also similar. The authors concluded that nesiritide was not associated with a significant change in the rate of death and rehospitalization (within 30 days) but had a small, nonsignificant effect on dyspnea when used in combination with other therapies. It was not associated with a worsening of renal function, but it was associated with an increase in rates of hypotension. On the basis of these results, nesiritide is not recommended for routine use in the broad population of patients with acute HF [72]. Thus, nesiritide is approved in the USA for early relief of dyspnea in patients with acute heart failure.

Diuretic-Induced Hyponatremia

HF patients are at increased risk for diuretic-induced hyponatremia because diuretics activate water-retention pathways similar to those operative in HF. Thiazides are more potent inducers of hyponatremia compared with loop diuretics. They block NaCl cotransport at the distal convoluted duct and increase distal Na delivery and preserve the medullary interstitial gradient, which then effectively prevents the excretion of maximally dilute urine and promotes reabsorption of solute-free water via the action of AVP on the collecting duct. In the largest retrospective review on this subject, thiazide and thiazide-type diuretics alone or in combination with potassium-sparing agents were responsible for hyponatremia in 94 % of 129 cases. Of note, 97 % of the doses were within the limits of pharmacological recommendations [73]. Other proposed mechanisms for diuretic-induced hyponatremia that both classes of diuretics share are the following: (1) urinary potassium loss, causing the extracellular Na to shift intracellularly; (2) non-osmotic activation of AVP; and (3) excess thirst, causing increased water intake.

Patients with advanced HF who are hyponatremic often have lower systemic blood pressures that limit the adherence to current HF treatment guidelines, because evidence-based drug therapies for HF that show survival benefits also lower systemic blood pressure. Hypotension is a potent stimulus for the neurohormonal changes seen in HF that cause hyponatremia and cardiac dysfunction [74]. Whether hypotension related to

progression of cardiac dysfunction and hypotension caused by medical therapy have different consequences is unknown.

Treatment of Diastolic HF

The conventional therapies available for patients with reduced EF do not appear to have the same benefits in patients with diastolic HF and a relatively preserved EF. The benefits that stem from the uses of ACE inhibitors (e.g., [75] and ARBs, e.g., [76]) are at best modest. This absence of benefit has provided the impetus for alternative approaches to the management of diastolic HF. Ito et al. [77] have examined that the effect of changing from an ACEi or ARB to losartan/HCTZ is associated with a reduction in BP, improvement in LV relaxation, improvement in HF, and attenuation of systemic inflammation after 24 weeks with few adverse effects in patients with hypertension and diastolic dysfunction.

As already mentioned diastolic HF is associated with myocardial fibrosis and increases in plasma levels of collagen turnover [7]. Deswal et al. [78] examined the effects of the aldosterone antagonist eplerenone, in a randomized, double-blind, placebo-controlled trial of 44 patients with diastolic HF on changes in 6-min walk distance, diastolic function, and biomarkers of collagen turnover. All patients had a history of hypertension. After 6 months of treatment, similar improvements in 6-min walk distance were noted in both groups ($P=0.91$). However, compared with placebo, eplerenone was associated with a significant reduction in serum markers of collagen turnover (procollagen type I amino-terminal peptide, $P=0.009$, and carboxy-terminal telopeptide of collagen type I, $P=0.026$) and improvement in echocardiographic measures of diastolic function (E/E′, $P=0.01$). These findings clearly merit further investigation to establish whether the changes in collagen turnover are translated into improvements in morbidity. However, it should be noted that increased peripheral collagen turnover markers were not independently associated with increased mortality and cardiovascular hospitalization in a similar population on multivariable analysis, but were associated on single-variable analysis [79].

Another therapy that has been examined is the use of phosphodiesterase-5 inhibitors in diastolic heart failure on the basis that the condition eventually results in pulmonary hypertension. Guazzi et al. [80] conducted a study on 44 patients with heart failure with preserved ejection fraction (heart failure signs and symptoms, diastolic dysfunction, ejection fraction ≥50 %, and pulmonary artery systolic pressure >40 mmHg) who were randomly assigned to placebo or sildenafil (50 mg thrice per day). At 6 months, there was no improvement with placebo, but sildenafil mediated significant improvements in mean pulmonary artery pressure and RV function. There were also concurrent improvements in wedge pulmonary pressure, lung water, and cardiac index. These benefits were maintained till the end of the trial at 12 months. These findings were attributed to the multiple effects of phosphodiesterase-5 inhibition which include improvement in pulmonary pressure and vasomotility, RV function and dimension, left ventricular relaxation and distensibility, and transfer of fluid across the pulmonary capillaries.

Endothelial Dysfunction in HF

Endothelial dysfunction is usually associated with systemic vasoconstriction in advanced HF. However, recent investigations suggest that it may have a more central role in the development of the syndrome of HF which is a condition characterized by an altered redox state with overproduction of reactive oxygen species, one consequence of which is a reduction in the bioavailability of nitric oxide (NO) [81]. Endothelium-derived NO is a paracrine factor that controls vascular tone, inhibits platelet function, prevents adhesion of leukocytes, and reduces proliferation of the intima. Endothelial dysfunction associated with loss of NO production can promote vasospasm, thrombosis, vascular inflammation, and proliferation of vascular smooth muscle cells.

Oxidative stress is mainly caused by an imbalance between the activity of endogenous pro-oxidative enzymes (such as NADPH oxidase, xanthine oxidase, or the mitochondrial respiratory chain) and anti-oxidative enzymes (such as superoxide dismutase, glutathione peroxidase, heme oxygenase, thioredoxin peroxidase/peroxiredoxin, catalase, and paraoxonase) in favor of the former. Also, small molecular weight antioxidants may play a role in the defense against oxidative stress. Increased ROS concentrations reduce the amount of bioactive NO by chemical inactivation to form toxic peroxynitrite. Peroxynitrite can "uncouple" endothelial NO synthase to become a dysfunctional superoxide-generating enzyme that contributes to vascular oxidative stress. Oxidative stress and endothelial dysfunction can promote atherogenesis. Therapeutically, drugs in clinical use such as ACE inhibitors, AT_1 receptor blockers, and statins have pleiotropic actions that can improve endothelial function, whereas clinical trials with antioxidant vitamins C and E failed to show an improved cardiovascular outcome [82].

Studies in animal models of HF have shown that the condition is accompanied by loss of endothelial function. Endothelium-dependent relaxation elicited by acetylcholine was attenuated in rats that developed heart failure after ligation of a coronary artery [83]. Studies undertaken in human subjects with HF have also shown impairment of endothelium-dependent relaxation [84]. However, it is of interest to note that loss of this property is evident even in patients with mild degrees of HF [85]. HF is traditionally associated with systemic vasoconstriction that is characterized by an altered redox state with overproduction of reactive oxygen species which in turn interferes with the bioavailability of nitric oxide. Recent studies indicate that there are interactions between NO production and the activity of intracellular RAAS which in turn would contribute to the overall loss of endothelial function [86]. These considerations open new areas for research which would impact upon the long-term treatment of HF [81].

Conclusions

At the present time treatment of heart failure is centered on the idea that its clinical manifestations are associated with a derangement of the renin-angiotensin-aldosterone system (RAAS) leading eventually to retention of salt and water. However, the RAAS can no longer be viewed as a single "conventional" endocrine system operating through blood-borne humoral agents, but as a more complex system involving a variety of cell types which influence the functions of specific components of the cardiovascular system in health and disease. The latter effects, particularly those involving endothelial cell function, nitric oxide, and the possible influence of antioxidants on this system, could open therapeutic options for the future in HF with both reduced and preserved EF.

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13 Aging and Diastolic Dysfunction: The Interplay of Inflammation and Extracellular Matrix Regulation

Peter Moritz Becher, Dirk Westermann, and Carsten Tschöpe

Abbreviations

CVF	Collagen volume fraction
ECM	Extracellular matrix
HFNEF	Heart failure with normal ejection fraction
HFPEF	Heart failure with preserved ejection fraction
HFREF	Heart failure with reduced ejection fraction
HHD	Hypertensive heart disease
LOX	Lysyl oxidase
LV	Left ventricular
LVMI	Left ventricular mass index
MMP	Matrix metalloproteinase
RV	Right ventricular
TIMP	Tissue inhibitor of metalloproteinases

Introduction

Heart failure has classically been considered to be a clinical syndrome associated with cardiac dilation and impaired cardiac contractility [1]. However, studies have found that increasing numbers of patients presenting with clinical heart failure have preserved ejection fraction (EF) [1–3]. This clinical syndrome, found predominantly in the elderly with hypertension and hypertensive heart disease (HHD), is called heart failure with preserved ejection fraction (HFPEF). The patients with HFPEF have increased mortality [4–7], and morbidity has also been found to be higher compared with patients with heart failure and reduced EF [8].

The underlying pathophysiological mechanisms in HFPEF are only partially understood. One of these mechanisms is diastolic function abnormality with an increased diastolic stiffness, but non-diastolic function abnormalities with exercise-induced changes in systolic velocity, chronotropic incompetence, and impairment in left atrial and right ventricle function [9–20]. Furthermore, left ventricular (LV) remodeling, such as changes in LV mass, volume, and geometry, is an important predictor of functional and clinical outcomes in those patients. The increased accumulation of cardiac collagen within the myocardial interstitium was found in this disease and contributes to the aggravation of diastolic dysfunction [21–23]. Otherwise, changes in cardiac fibroblasts as decreasing the degradation system (matrix metalloproteinase [MMP]-1 and their tissue inhibitor [TIMP]) also were known to be a potent contributor of pathological remodeling in diseased cardiac tissues.

Advancing age, independent of any concurrent cardiovascular disease, can itself be associated

P.M. Becher, MD (✉) • D. Westermann, MD
Department of General and Interventional Cardiology, University Heart Center Hamburg Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany
e-mail: moritzbecher@web.de

C. Tschöpe, MD
Department of Cardiology and Angiology, Charité-Universitätsmedizin Berlin, Berlin, Germany

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with significant LV structural remodeling. These age-dependent changes in LV structure may play an important role in the functional limitations that occur in advancing age. Previous studies have shown that with increasing age, the LV develops concentric remodeling (characterized by an increased LV mass-to-volume ratio), increased extracellular matrix (ECM) fibrillar collagen content, and significant abnormalities in diastolic function. Further, post-synthetic procollagen processing and subsequent collagen assembly are dependent on and influenced by soluble factors including matricellular proteins. Previous studies of secreted protein acidic and rich in cysteine (SPARC) have suggested that SPARC participates in the coordination of procollagen processing and facilitates the formation and assembly of mature cross-linked insoluble structural collagen fibrils [24]. The induction of these mechanisms is unclear and may include age-dependent and comorbidity-dependent mechanisms.

In this book chapter, we will illustrate the interplay of post-synthetic procollagen processing, ECM regulation, and cardiac inflammation as significant factors in the older HFPEF population.

Interaction Between the Inflammatory Induction and the ECM Regulation

Although the age-dependent changes in LV structure and function do not result in clinical cardiovascular disease per se, they do compromise cardiovascular reserve capacity, decrease exercise tolerance, and increase vulnerability to the effects of comorbid diseases [25]. The age-dependent mechanisms that limit exercise include changes in myocardial structure, diastolic function, responses to catecholamine stimulation, and chronotropic reserve [26]. During maximum exercise in younger subjects, end-systolic volume is decreased and end-diastolic volume, EF, heart rate, and cardiac output are all increased. In older subjects, however, the exercise-induced increases in end-diastolic volume, EF, heart rate, and cardiac output are markedly blunted [24].

Increased diastolic stiffness is the major mechanism in the pathophysiology of patients with HFPEF and significantly modulates their clinical symptoms and outcome. However, the molecular changes leading to diastolic dysfunction are still under investigation, and different pathways can influence the pathology of HFPEF. Altered isoform expression of the giant muscle protein titin can determine the elastic properties of the heart [27]. Moreover, increased myocyte tension, which can be prevented by experimental phosphorylation of titin, contributes to diastolic dysfunction [14, 27]. Additional modulatory effects on titin stiffness may arise from disulfide bonding under oxidant stress also affecting LV compliance [28]. Nevertheless, the steep part of the diastolic pressure–volume relation is mainly modified by the ECM, as can be observed when comparing stretch lengths between whole-muscle stripes and single myocytes, suggesting that excess collagen might further aggravate diastolic dysfunction [29].

Cardiac collagen is a stable protein with a low turnover (80–120 days), but its balance can be disrupted in pathological conditions [30]. Next to ischemia, which may lead to reparative cardiac fibrosis, for example, increased wall stress, angiotensin II, and TGF-β may induce profibrotic processes leading to pathological tissue fibrosis [31]. Because myocardial fibrosis is uniform for all sites in the heart in HHD, the changes in ECM and collagen accumulation can be observed by biopsy of the right ventricle (RV) interventricular septum. An increased total amount of cardiac collagen could be found in patients with HFPEF, which is in agreement with findings from patients with HHD [32, 33], including preclinical data [34–36]. But not only collagen type I can be observed to be increased, a change in the collagen type I to III ratio as well as collagen cross-linking is documented, similar to that in patients with systolic heart failure [37] (Figs. 13.1, 13.3, and 13.4). In addition to increased protein levels of collagen types I and III, also mRNA abundance was shown to be increased in endomyocardial biopsy (Figs. 13.2, 13.3, and 13.4). Another marker of excessive collagen production is type I carboxy-terminal telopeptide, a degradation

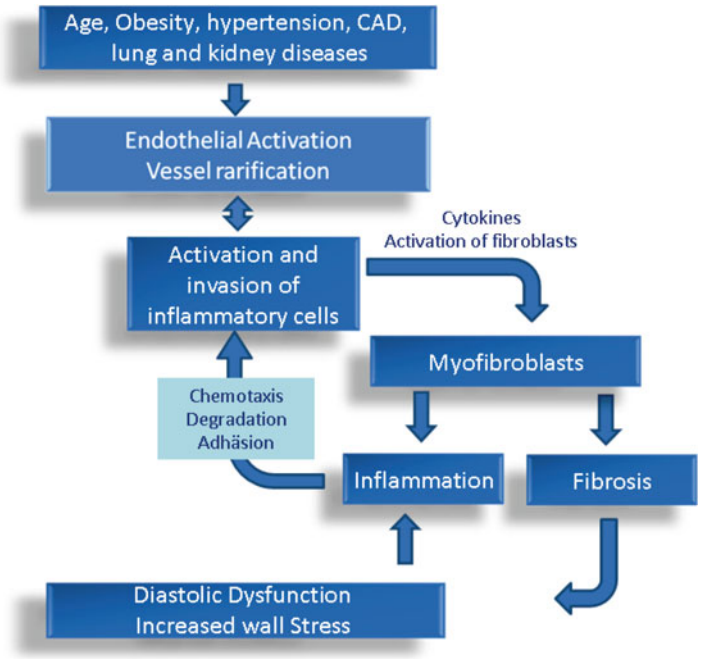

Fig. 13.1 Proposed mechanisms for the induction of fibrosis in patients with HFPEF (heart failure with preserved ejection fraction). Comorbidity-induced stress responses can stimulate myofibroblasts driving a cytokine cascade that participates in a vicious cycle of inflammatory supporter cells, triggering further fibrosis and inflammation and affecting endothelial and diastolic dysfunction

product of collagen with increased collagen turnover together with propeptide of procollagen type I, a serum marker of collagen production, both of which are increased in HFPEF patients. DHE staining reveals that oxidative stress is increased which might be the result of increased LV stiffness.

Multiple previous studies have demonstrated that one of the best-known inducers of collagen production is the profibrotic growth factor TGF-β. It also has profound effects on ECM homeostasis, in part through its ability to alter the balance between MMPs and their TIMP inhibitors. The endogenous collagen degradation system is regulated by increased activity of MMPs overcoming their tissue inhibitors [38]. MMP-1 (interstitial collagenase) is known to degrade collagen fibers, and therefore it likely favors collagen degradation. Through the activity of the activator protein-1 transcription factor, TGF-β can, on the one hand, repress MMP-1 gene expression and, on the other hand, increase TIMP-1 expression [39]. Congruent with these ex vivo data, studies could show an upregulation of TIMP-1 protein and a downregulation of MMP-1 protein levels in the biopsy samples from HFPEF patients, which leads to a significant decrease in the MMP-1–TIMP-1 ratio [40]. This inhibition of the collagen degradation system could be a mechanism contributing to the accumulation of ECM in HFPEF patients and the initiation of diastolic dysfunction over a longer time period [41]. Furthermore, and in contrast to the activator protein-1-mediated downregulation of MMP-1, increased levels of MMP-2 (controlled by activator protein-2) were found, which is a known gelatinase and has substrate affinity for denatured fibrillar collagen as well as for the basement membrane (Fig. 13.5) [42]. Recently, increased levels of MMP-2 were shown to predict heart failure in patients with diastolic dysfunction and hypertension. In that study, MMP-2 was a better prognostic marker than the well-known heart failure biomarker brain natriuretic peptide [43]. Several experimental studies in MMP-2 knockout animals have helped to advance understanding of the molecular function of MMP-2. Matsumura and colleagues showed in MMP-2 knockout mice a decrease in invading inflammatory cells and a decrease in LV rupture after myocardial infarction [44]. Those authors demonstrated that destruction of basement membrane proteins

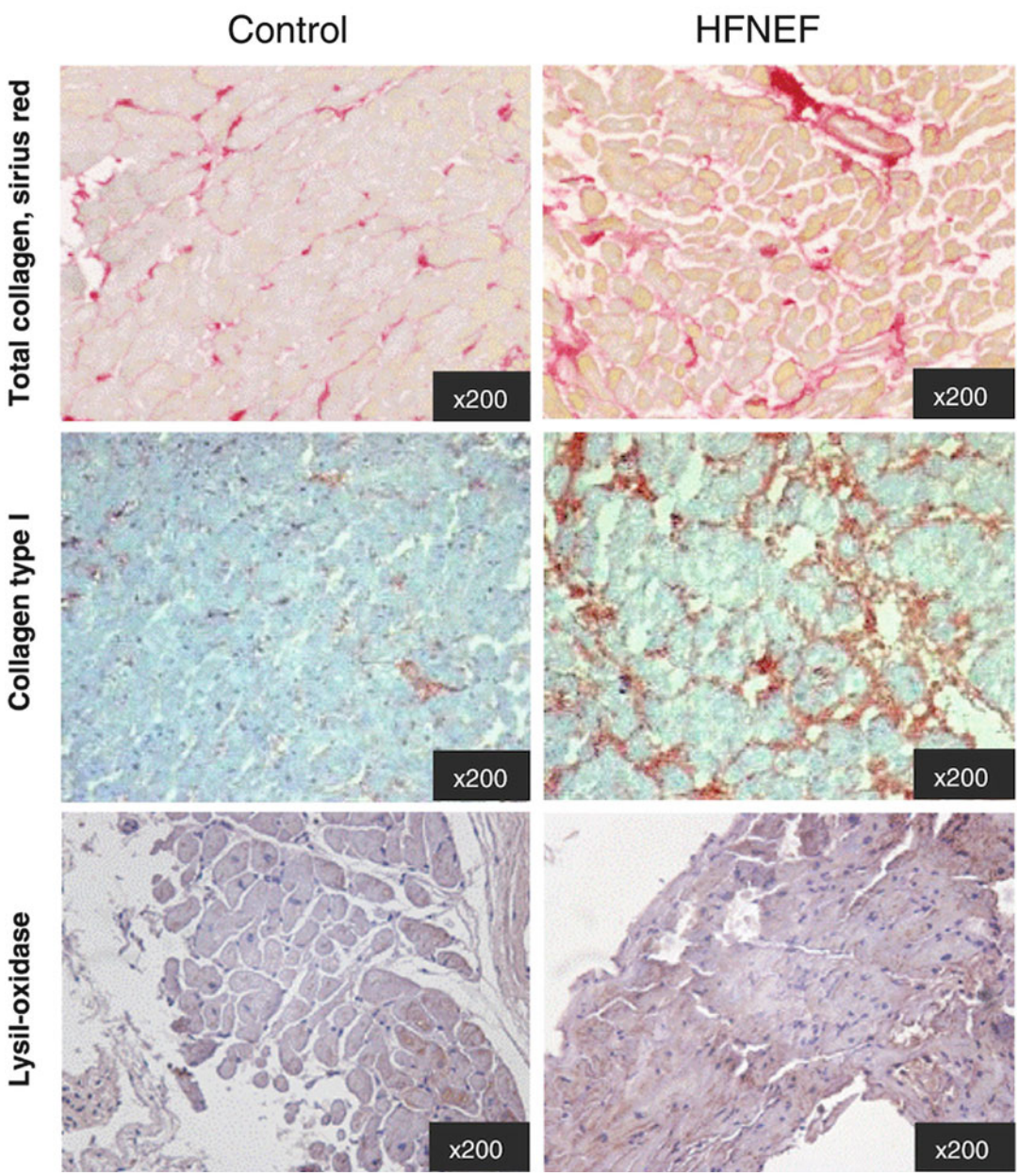

Fig. 13.2 Representative histological staining from endomyocardial biopsies in patients with HFNEF. Patients with heart failure with normal ejection fraction (HFNEF) show an increased collagen amount, as stained by Sirius red, and increased expression of collagen type I and lysyl oxidase compared with control (magnification ×)

facilitates the transendothelial migration of immunocompetent cells, thereby triggering cardiac inflammation. In light of such findings, we investigated the number of inflammatory cells in our patients and showed that HFPEF is associated with increased cardiac inflammation, with high numbers of $CD3^+$, $CD11a^+$, and $CD45^+$cells (Fig. 13.6). Moreover, the vascular cell adhesion molecule (VCAM)-1, which attracts immunocompetent cells to the endothelium and initiates transendothelial migration, was also increased in the HFPEF patients (Fig. 13.6). This result is

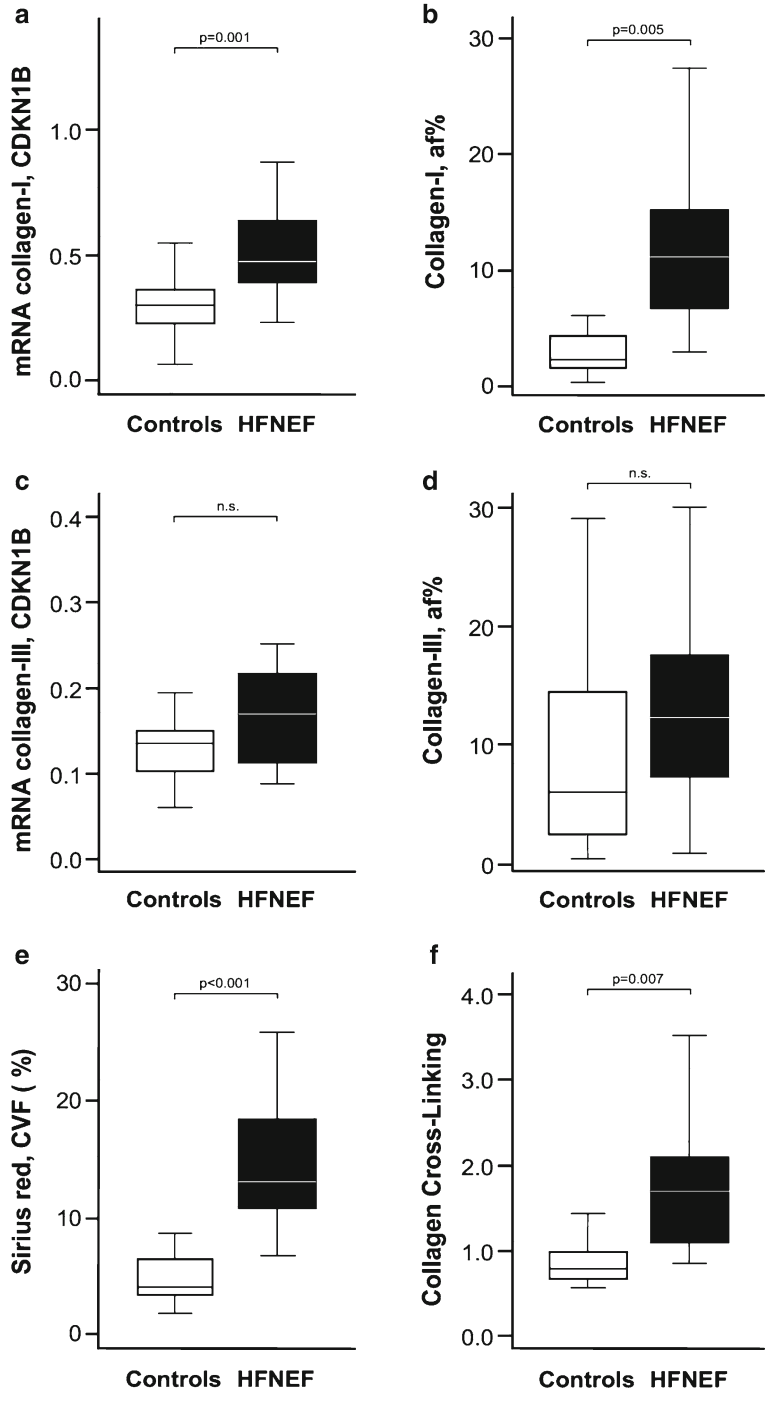

Fig. 13.3 Total collagen amount and collagen quality in patients with HFNEF versus controls. Expression of collagen type I is increased in patients with heart failure with normal ejection fraction (HFNEF) at both (**a**) mRNA and (**b**) protein levels, whereas there is no difference in collagen type III expression at (**c**) mRNA and (**d**) protein levels, compared with controls. Patients with HFNEF reveal increased collagen volume fraction (CVF) as shown by (**e**) Sirius red staining and (**f**) collagen cross-linking

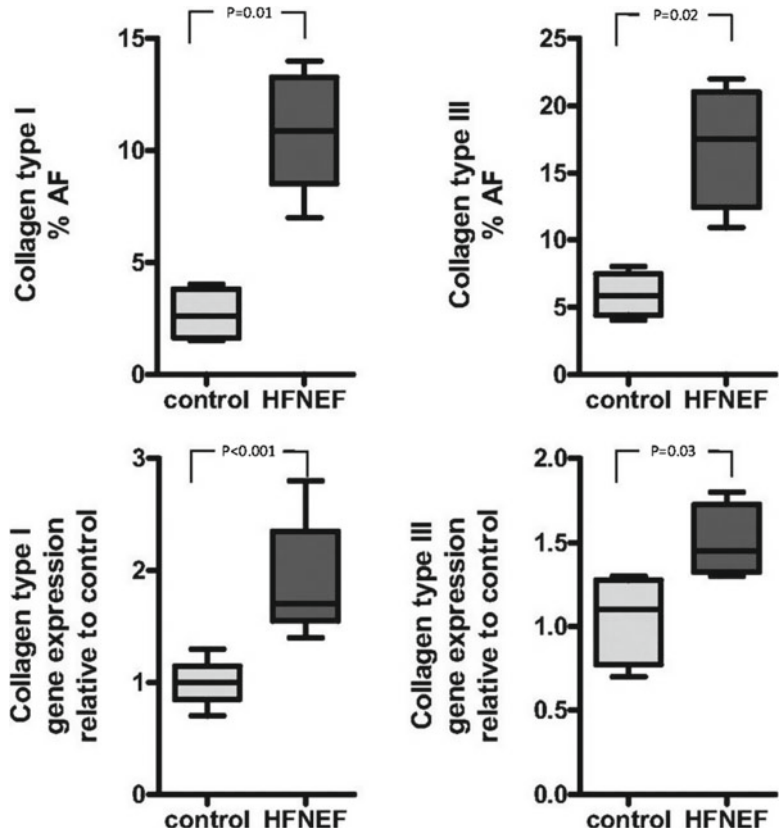

Fig. 13.4 Level of collagen in patients with HFNEF versus controls. Box-and-whisker plots showing increased levels of collagen types I and III proteins in endomyocardial biopsy samples from patients with HFNEF compared with controls. Increases in the collagen I–III ratio as well of collagen type I C-telopeptide were measured in serum. The mRNA abundance of collagen types I and III was increased in HFNEF compared with control subjects. AF indicates area fractions

especially interesting, because VCAM-1 is upregulated by angiotensin II, which may be increased in regard to known risk factors like hypertension and diabetes mellitus in HFPEF. Recently, it was shown that immunocompetent cells like T cells ($CD3^+$) can indeed alter tissue remodeling in vitro [45], and another study showed that cardiac inflammation is associated with excessive collagen accumulation in experimental diabetic cardiomyopathy in one animal model of HFPEF [46]. There is experimental and clinical evidence that inflammatory cells might modulate cardiac function in HF with reduced [47, 48] and normal EF [49, 50]. The direct effects of these cells are still under debate, but it has been suggested that increased inflammation is associated with the development of systolic heart failure by distinct changes in the ratio of MMP to TIMP [51, 52]. In line with these data, it could be demonstrated that these inflammatory cells express TGF-β in cardiac tissue and induce a pathological transdifferentiation from fibroblasts to myofibroblasts. This will not only stimulate gene expression of collagen but also induce a decline in MMP-1 activity and an increase in MMP-2 mRNA abundance, as well as paracrine TGF-β production (Fig. 13.7). Increased stiffness due to ECM accumulation will increase oxidative stress, suggested to be associated with increased endothelial activation. Together with increased MMP-2, which has been suggested to disrupt the basal membrane, this might induce a vicious circle fuelling inflammation leading to fibrosis and ultimately, to progression of the disease.

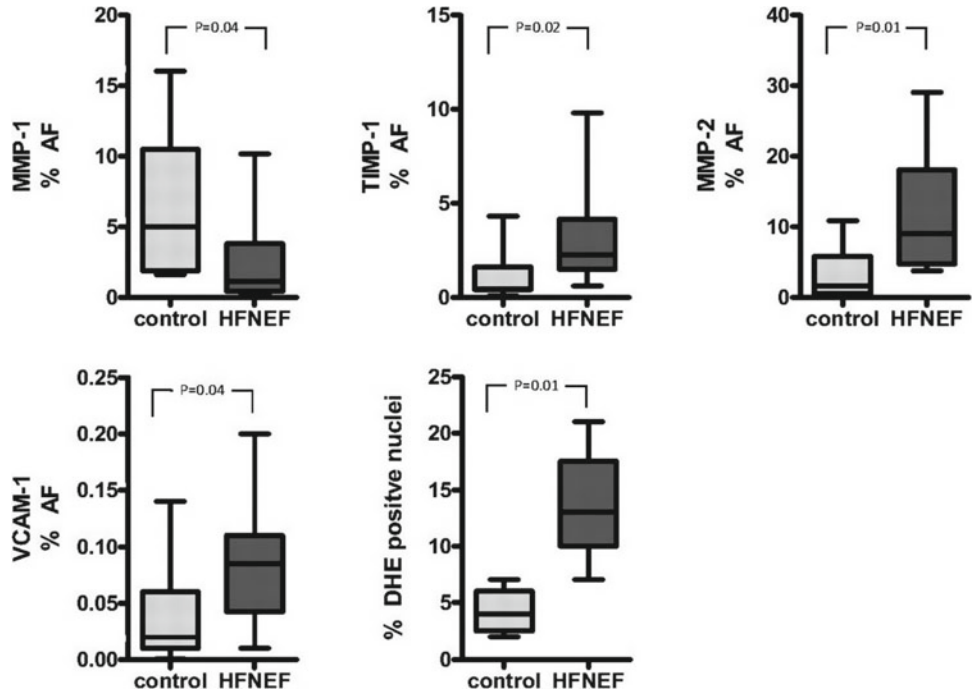

Fig. 13.5 Level of ECM protein in patients with HFNEF versus controls. Decreases in protein levels of MMP-1 and increases in levels of MMP-2 and TIMP-1 were found in endomyocardial biopsy samples from patients with HFNEF compared with controls. Increased oxidative stress by DHE staining was documented in HFNEF compared with control subjects. The adhesion molecule VCAM-1 was also increased in HFNEF compared with control subjects. AF indicates area fractions

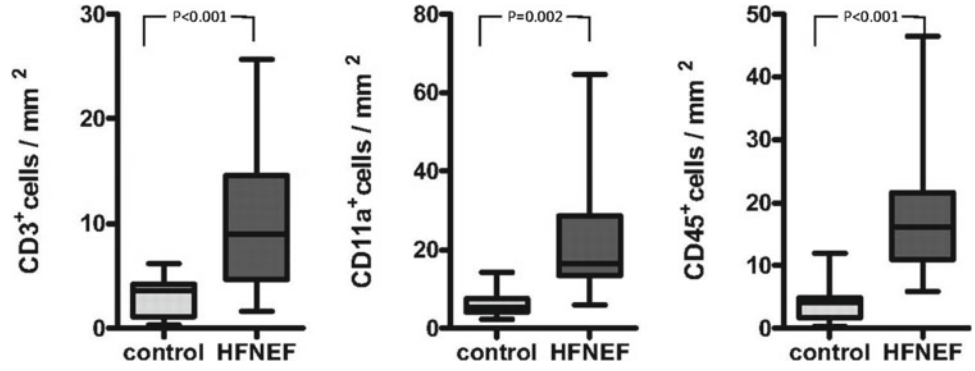

Fig. 13.6 Cardiac immune cell infiltration. Increased numbers of $CD3^+$, $CD11a^+$, and $CD45^+$ cells were found in endomyocardial biopsy samples from patients with HFNEF compared with controls

Therefore, LV chamber stiffness will be affected by the amount and quality of cardiac collagen, as previously shown indicating that changes in plasma levels of matrix metalloproteinase/tissue inhibitor of metalloproteinase and collagen propeptides reflect an increase in systemic collagen turnover [33, 51, 53–56].

Recent studies have also shed light on the origin and specific mechanisms underlying LV fibrosis. In human heart biopsies of patients with

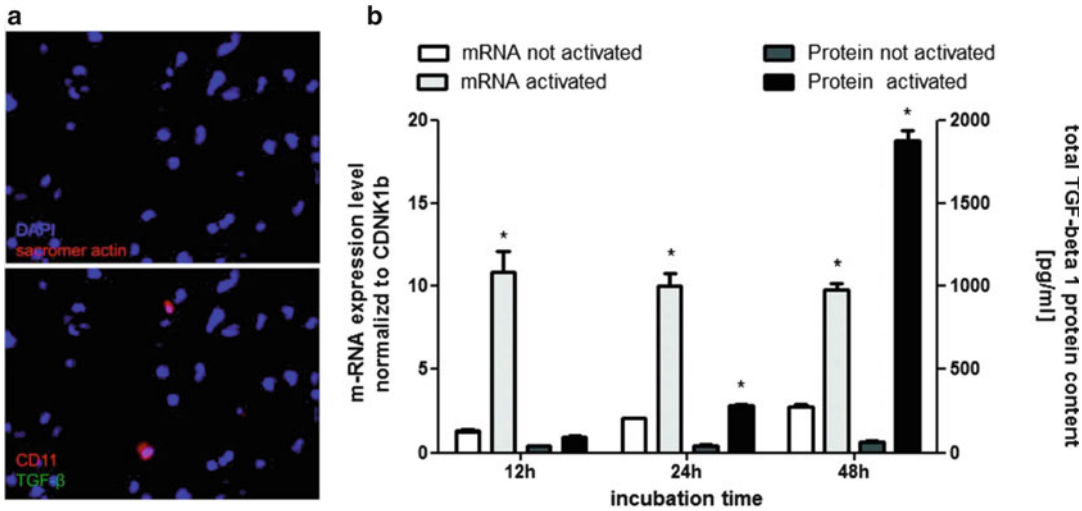

Fig. 13.7 TGF-β expression levels. (**a**) Representative histological image with double staining of CD11a$^+$ cells with the profibrotic growth factor TGF-β. (**b**) In vitro experiments with phorbol 12-myristate 13-acetate-activated monocytes (THP-1 cells) showed increased production of TGF-β mRNA and protein levels of TGF-β in a time-dependent manner. $^*P<0.05$ versus individual controls

severe diastolic heart failure, transforming growth factor (TGF)-β was shown to activate fibroblasts, releasing not only collagen but also chemokines (Fig. 13.7) [57]. In this way, activated fibroblasts (myofibroblasts) participate in a vicious cycle as inflammatory supporter cells, driving a cytokine cascade that triggers further vascular and tissue inflammation and fibrosis. Of note, the typical risk factors for HFPEF, such as obesity and diabetes, are known to induce oxidative and inflammatory stress responses that may trigger the key intracellular abnormalities involving endothelial activation and vessel rarefaction and extracellular regulation, thus contributing to increased LV stiffness and diastolic dysfunction. It is also important to consider pathophysiological mechanisms beyond LV diastolic dysfunction, at least in subgroups of patients with HFPEF (Fig. 13.2). Indeed, some studies have shown that mortality/morbidity rates were reduced [58, 59] without demonstrable improvement in echocardiographic LV diastolic function, while others have shown that improvements in echocardiographic LV diastolic function were unaccompanied by prognostic benefits in patients with HFPEF [60]. Potential pathophysiological mechanisms in HFPEF that deserve consideration include the role of intracellular calcium regulation (including the function of the late cardiac sodium current) [61], the autonomic nervous system [62], LV–arterial coupling [63], or mechanical dyssynchrony [64].

SPARC and Its Role in Collagen Processing

Diastolic dysfunction and increased cardiac stiffness as a key mechanism compromising the cardiovascular reserve in older patients results from changes in fibrillar collagen amount and assembly [65, 66]. Advanced age is associated with increased diastolic stiffness, increased collagen amount, and increased NaCl-insoluble collagen resulting in a limited ability to recruit Frank–Starling mechanisms to increase diastolic volume and enhance cardiac output. Interestingly, previous studies by Bradshaw and colleagues show an increased SPARC expression combined with a higher amount of mature cross-linked NaCl-insoluble collagen fibrils, increased fibrillar collagen content, and increased myocardial diastolic stiffness. Further, it could be demonstrated in SPARC-null mice that advanced age resulted in a

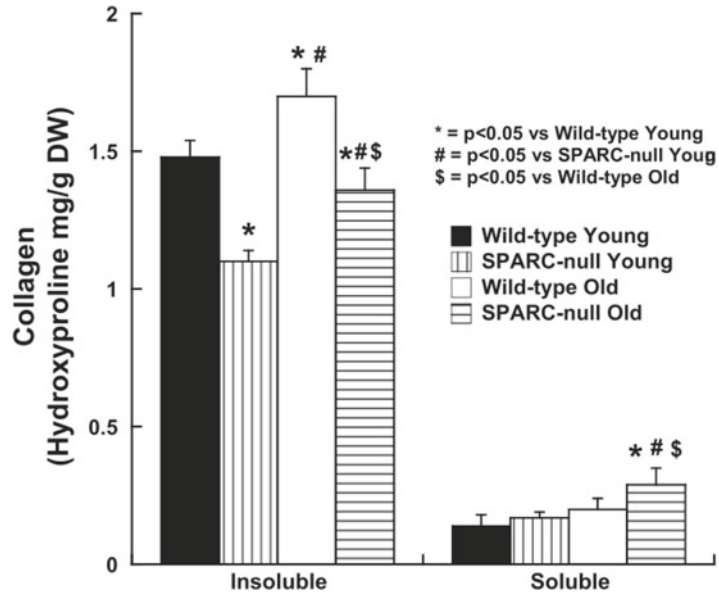

Fig. 13.8 Changes in collagen composition in hearts from old SPARC-null mice. The effects of the absence of SPARC on age-dependent changes in collagen composition are shown. Collagen composition was examined by measuring NaCl-insoluble collagen versus NaCl-soluble collagen by hydroxyproline quantification

significantly reduced increase in NaCl-insoluble collagen, collagen content, and myocardial stiffness than it did in wild-type mice (Fig. 13.8). The data support the hypothesis that a SPARC-associated increase in post-synthetic procollagen processing may be a factor that contributes to the ECM remodeling and diastolic dysfunction that occurs with advanced age [24].

Collagen homeostasis is influenced by three regulatory mechanisms: procollagen synthesis, post-synthetic procollagen processing, and the degradation of collagen [42, 67, 68]. The balance between synthesis, processing, and degradation determines the total fibrillar collagen content. Changes in these determinants are believed to play an important role in age-dependent alterations in ECM collagen and diastolic dysfunction. Moreover, additional studies that have suggested that the procollagen synthesis and the degradation of collagen may be increased in advanced age have found that some of these changes favored age-dependent collagen accumulation [42, 69, 70].

In aged cardiac tissue, levels of mRNA encoding collagen I and III were generally found to be decreased compared with young hearts [71–73]. Increased transcription of fibrillar collagen I and III in aged hearts is not likely to be the main contributor to elevated collagen content. SPARC has been hypothesized to enhance tissue collagen content by facilitating collagen deposition into the ECM. The loss of SPARC during aging did not appear to change the age-dependent increase in total collagen. There were no statistical changes between total collagen in the old WT versus old SPARC-null mice. Additionally, there was a similar increase in total collagen from young to advanced age in both WT and SPARC-null mice.

However, significant increases in collagen soluble in noncross-linked collagen were observed in the absence of SPARC expression [14, 31]. Although extraction of insoluble collagen with more stringent agents such as pepsin/acetic acid or cyanogen bromide releases a greater amount of cross-linked collagen from cardiac tissue, 1 M NaCl was used in these studies to monitor the amounts of noncross-linked collagen [31]. Increases in NaCl-soluble collagen in SPARC-null mice were similar to the response to transverse aortic constriction (TAC)-induced pressure overload. Increases in insoluble collagen associated with pressure overload resulted in similar increases in diastolic stiffness in TAC mice as those observed here in aged animals (Fig. 13.9) [20]. Likewise, the absence of SPARC

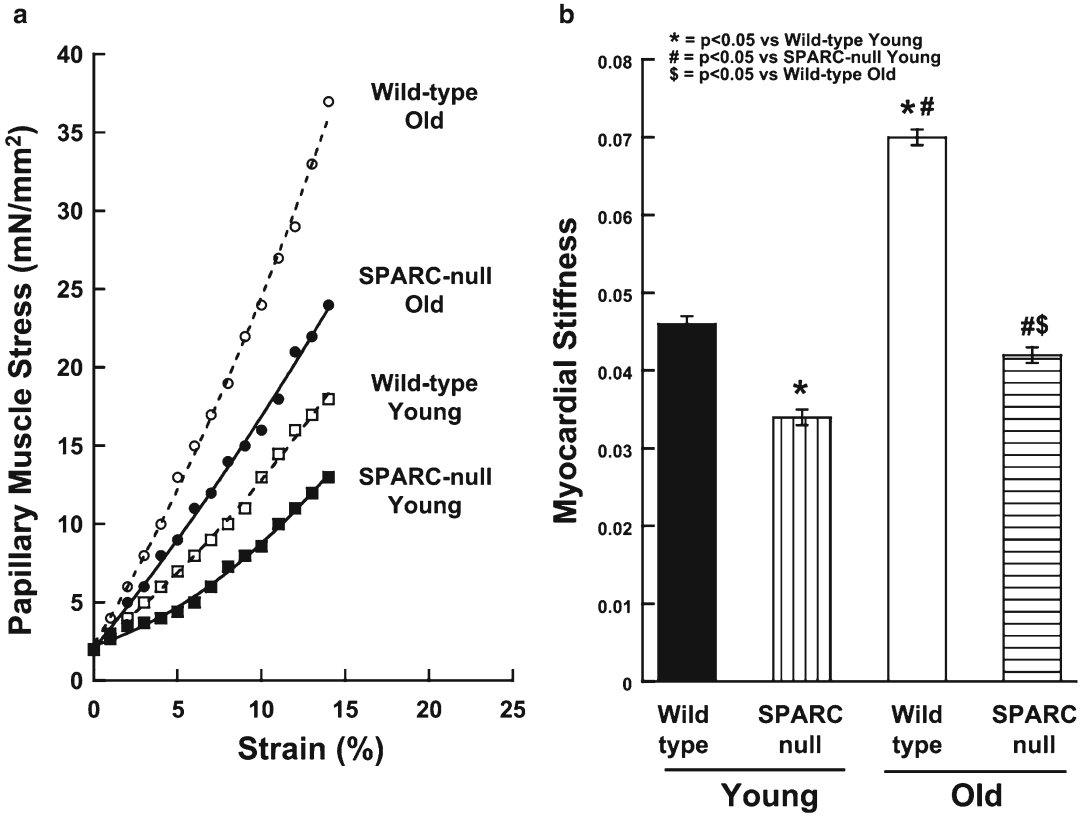

Fig. 13.9 Reductions in diastolic stiffness in aged papillary muscle of SPARC-null mice. (**a**) Examples of passive diastolic myocardial stress versus strain curves for the four groups of animals studied. (**b**) Mean ± SE values of the passive stiffness constant for the four groups of animals studied

decreased both collagen concentrations and diastolic stiffness associated with TAC comparable to the decreases shown here in the aged myocardium (Fig. 13.9).

The proteolytic determinants of collagen degradation appear to change in an age-dependent fashion in ways that favor less collagen degradation and more collagen accumulation [39]. Collagen-degrading enzymes, matrix metalloproteinases (MMPs), are generally decreased, and their endogenous tissue inhibitors [tissue inhibitors of metalloproteinases (TIMPs)] are generally increased as a function of advancing age. The balance between MMPs and TIMPs promotes a decrease in the degradative capacity of the aged myocardium [39]. As SPARC is a substrate for a number of different MMPs, we predict that the extracellular half-life of SPARC is likely increased in the aged myocardium due to decreases in specific MMP activity [34]. As SPARC is a collagen-binding protein, the increase in collagen content in old hearts might also increase the levels of extracellular SPARC through interactions with collagen in the ECM. Levels of mRNA encoding SPARC were not found to be significantly increased in old versus young hearts. Therefore, increased transcription of SPARC is not considered to contribute appreciably to more SPARC protein in the advanced-aged myocardium [27]. Current studies have shown that SPARC acts to increase the activity of certain MMPs, notably MMP-2, MMP-9, and MT1-MMP [2, 29].

Although SPARC is a primary secreted product of endothelial cells in culture, significant changes in the vascularity of SPARC-null tissues, including the heart, have not been demonstrated. Angiogenesis, as monitored in an implanted

sponge model, was enhanced in young SPARC-null mice [10]. However, similar experiments in old WT and SPARC-null mice revealed that the differences in angiogenesis disappeared with age [35]. Although subtle differences in endothelial biology and blood vessel ultrastructure cannot be ruled out in hearts of old SPARC-null mice, to date evidence that SPARC has overt effects on cardiac vascularity has not been found.

SPARC is a collagen-binding protein with counteradhesive activity that has been hypothesized to coordinate procollagen processing and facilitate collagen fibril assembly [19]. Although a number of activities have been ascribed to SPARC in vitro, including the modulation of growth factor activity, regulation of cell cycle progression, and gene expression, the function of SPARC in tissues appears complex as well as contextual [15]. The primary phenotypes characterized to date in SPARC-null mice involve aberrant ECM assembly [15]. Reductions in fibrillar collagen content of connective tissues have been observed, particularly in response to fibrotic injury.

The mechanism by which SPARC influences collagen deposition has been studied in vitro using primary dermal fibroblast cultures from WT and SPARC-null mice [36]. In the absence of SPARC, procollagen secreted from fibroblasts had a greater tendency to associate with and bind to the fibroblast cell surface, to undergo either degradation or premature, disordered processing, and did not efficiently or effectively develop into mature cross-linked insoluble collagen. If recombinant SPARC was added to SPARC-null primary fibroblasts cultures, then procollagen processing was restored toward normal and collagen association with the fibroblast cell surface was decreased [36]. These in vitro findings suggested that SPARC limits procollagen binding to cell surface receptors and promotes the processing of procollagen to mature collagen fibrils. In the absence of SPARC, the regulation of procollagen processing is disrupted, and the interaction of collagen with receptors is enhanced, leading to an increased degradation of procollagen at the expense of incorporation of processed collagen into insoluble collagen fibrils.

The balance between procollagen processing and procollagen degradation is a fundamental mechanism by which fibrillar collagen content is regulated. Moreover, a study [6] by Bishop and Laurent has suggested that a substantial portion of newly synthesized procollagen is degraded before complete processing and formation of or incorporation into a mature collagen fibril. Even in normal tissues, as much as 5–60 % of the newly synthesized procollagen is degraded [9]. Degradation of nascent procollagen was particularly high in the cardiac interstitium compared with levels in the skin. Therefore, even small changes in the balance between procollagen processing and procollagen degradation may act as a critical regulatory control mechanism effecting myocardial fibrillar collagen content. Age-dependent increases in SPARC altered this balance, increase procollagen processing, and are one mechanism responsible for the age-dependent increases in ECM fibrillar collagen. In summary, it was also shown that SPARC can play a key role in the changes in post-synthetic procollagen processing that occur in the aged myocardium.

Role of Comorbidities in the HFPEF Population

Despite several cardiac morphological changes in patients with diastolic heart failure, the rate of cardiac mortality is lower than seen in heart failure with reduced ejection fraction (HFREF). Age and comorbidities may have an important impact for the prognosis of patients with HFPEF [74]. Common comorbidities include anemia, chronic lung disease, chronic kidney disease, cancer, peptic ulcer disease, and hypothyroidism. These comorbidities may contribute to the high rates of noncardiovascular events in these predominantly elderly patients [75].

Anemia is frequently encountered in patients with HFPEF, particularly in hospitalized patients. Several studies have demonstrated worse outcomes in patients with HFPEF and anemia (increased symptoms, worse functional status, higher risk of heart failure admissions, and higher mortality). The value of intravenous iron or

enhancing erythropoiesis remains unclear in HFPEF [76].

Chronic obstructive lung disease is a common comorbidity in patients with heart failure and vice versa [77]. Recent studies have shown that even mild or subclinical obstructive lung disease may be associated with LV diastolic dysfunction [78, 79]. In fact, large community-based cohort studies suggest that airflow obstruction is related to future incident heart failure [80]. Furthermore, patients with HFPEF and chronic lung disease usually present with exertional dyspnea, leading to diagnostic difficulties [81]. When these two diseases coexist, one should recognize that the disease processes as well as the therapies may interact. It is important to establish the relative contribution of each disease to the symptom burden and optimally manage both conditions. Renal impairment and the cardiorenal syndrome are not uncommon in patients with HFPEF, and may relate to intrinsic renal pathology, renal venous hypertension, and reduced renal perfusion gradient. Renal artery stenosis is an important comorbidity to consider in patients with HFPEF, particularly in cases of protracted fluid retention, refractory hypertension, or recurrent episodes of flash pulmonary edema (more commonly encountered in bilateral atheromatous renovascular disease). Of note, the impact of renal dysfunction on prognosis appears to be greater in women than in men with HFPEF [82].

Concomitant cardiovascular risk factors also significantly influence outcomes in HFPEF. Atrial fibrillation is a frequent precipitant of acute HFPEF decompensation [74]. Current guidelines emphasize the importance of rate control of atrial fibrillation in the management of HFPEF. Intriguingly, sex-specific analyses from the I-PRESERVE study showed that atrial fibrillation was a greater risk factor for all-cause death and hospitalizations in women than in men with HFPEF [82]. This may be related to the higher rate of obesity in women than in men with HFPEF in the I-PRESERVE study. Obesity has been shown to influence LV geometry substantially more among women than men in the Strong Heart Study [83], suggesting a metabolic basis for LV hypertrophy in HFPEF especially among women. In fact, obesity is increasingly recognized as an inflammatory condition and a key risk factor in HFPEF. HFPEF, in turn, is increasingly recognized as a systemic syndrome involving multiple organ systems [80], rather than an isolated cardiac disease. These considerations are critical for the design of future therapeutic approaches.

Diabetes mellitus with clinical heart failure without coronary macroangiopathy but still preserved EF in the context of suspected small vessel disease or diabetic cardiomyopathy with only slightly reduced EF is a still poorly understood entity [84, 85], for which recently a pathophysiologically based new classification was proposed [84]. The role of specific diabetic drivers to the clinical phenotypes of heart failure with normal EF or confounders, such as hypertension, autoimmune factors, or inflammation with or without viral persistence, should be identified in each individual patient separately. In many cases hyperglycemia, hyperinsulinemia, and insulin resistance as well as lipotoxicity by free fatty acids (FFAs) are the factors responsible for diabetic cardiomyopathy and HFPEF.

Conclusion and Perspectives

HFPEF is a heterogeneous syndrome and is characterized by an increase in cardiac oxidative stress and inflammation, which triggers cardiac collagen accumulation by inducing collagen gene expression and inhibiting the cardiac degradation system.

Therapeutic strategies should not just target on reducing the amount of collagen but also on the reduction of collagen cross-linking to prevent the adverse impact of myocardial fibrosis on cardiac function in older patients with HFPEF.

Furthermore, it is reported that the ability of torasemide to correct both lysyl oxidase overexpression and enhanced collagen cross-linking results in normalization of left ventricular chamber stiffness in patients with heart failure [55]. However, the triggering mechanisms in the development and progression of HFPEF still remain unclear. To date there is no uniformly accepted approach and no proven therapy for HFPEF.

Previous attempts to extrapolate known therapies in HFREF to HFPEF have failed to improve outcomes in HFPEF, underscoring the need to reexamine our basic pathophysiological concepts in HFPEF. Pilot studies with aldosterone inhibitors, combination of angiotensin receptor and neutral endopeptidase (NEP) inhibitors, and/or physical activity are under investigation.

Patients with HFPEF are more frequently women, usually elderly with a history of hypertension, and commonly have multiple comorbidities including obesity, anemia, diabetes mellitus, and renal dysfunction. Each of these comorbidities may influence ventricular structure and function, provoking debate as to whether HFPEF is a distinct disease requiring specific therapy or an amalgamation of age-related comorbidities.

We conclude that oxidative stress and inflammation is one important trigger of myocardial fibrosis and plays a significant role in elderly patients with typical comorbidities and HFPEF. This suggests that cardiac inflammation by increased transendothelial migration and the accumulation and the adverse assembly of ECM are potent inductors of diastolic dysfunction and increased cardiac stiffness in patients with HFPEF. The inhibition of transendothelial migration of invading immune cells into cardiac tissue could be a future therapeutic concept in the older HFPEF population.

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14 Reperfusion and Vasodilator Therapy in Elderly Patients with STEMI and Heart Failure: Improving Outcomes

Bodh I. Jugdutt, Anwar Jelani, Seraj Abualnaja, Nakul Chander Sharma, and Joseph Szeman Wong

Introduction

The elderly population (aged ≥65 years) has been increasing worldwide [1]. Heart failure (HF) is also common and is increasing in the elderly [1] and therapy has been challenging [2]. Aging is associated with cardiovascular (CV) changes that predispose the elderly to HF [3–6]. Elderly subgroups aged 65–74 years and ≥75 years account for 7 % and 5 %, respectively, of the North American population in the 2010 update [7] and the problem persists in 2012/2013 updates [8, 9]. From the trend over the last few decades, the sizes of these subgroups can be expected to increase further [10]. In 2013, HF management in general remains challenging [11]. Comorbidities such as hypertension (HTN) and coronary artery disease with ST-segment-elevation myocardial infarction (STEMI) are more prevalent in the elderly and contribute to the development of diastolic and systolic HF with aging and in the elderly [2, 12]. Elderly patients with coronary heart disease and HTN are more challenging for healthcare providers [12]. That is partly because the "older-elderly" patients aged >75 years comprise more than one-third of all patients with acute myocardial infarction (MI) [13]. In fact, in North America and Europe, STEMI, HTN, and HF are more prevalent in the elderly [7]. Despite improved therapies, the CV death toll is highest in the elderly [14]. About half of all patients with HF die in 5 years [9]. Morbidity, hospitalizations, and costs associated with HF are higher in the elderly [15–18], threatening bankruptcy. The total cost of HF therapy (direct and indirect) is expected to increase from $30.7 billion to $69,8 billion by 2030 in the USA, and to increase faster for older than younger Americans, with a 3-fold increase occurring in those aged >65 years [11].

Honing in on the problem, STEMI is not only a major killer in both elderly and non-elderly (aged <65 years) patients [19], but the survivors of acute STEMI develop progressive dilative left ventricular (LV) that leads to chronic HF with low ejection fraction (HF/Low-EF) [2, 20, 21].

B.I. Jugdutt, MD, MSc, DM, FRCPC (✉)
2C2 W.C. Mackenzie Health Sciences Centre, Division of Cardiology, Department of Medicine, Mazankowski Alberta Heart Institute, University of Alberta and Hospitals, 8440-112 Street, Edmonton, AB, Canada T6G 2B7
e-mail: bjugdutt@ualberta.ca

A. Jelani, MBBS, SBIM, FACC
Department of Medicine, Section of Cardiology, King Abdulaziz Hospital, Alhasa, Saudi Arabia

S. Abualnaja, MDDS, FRCPC
Division of Cardiology, Department of Medicine, University of Alberta, Edmonton, AB, Canada

N.C. Sharma, MD, FRCP
Division of Cardiology, Department of Medicine, Mazankowski Heart Institute, WMC 2C2 8440-112 Street, Edmonton, AB, Canada T6B 287

J.S. Wong, MBBS, MRCP, FHKCP, FRCPC
Division of Cardiology, Department of Medicine, University of Alberta Hospital, 2C2, WMC, 727, Todd Landing NW, Edmonton, AB, Canada T6G 2B7

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In contrast, survivors of chronic HTN develop progressive concentric LV remodeling that leads to HF with preserved ejection fraction (HF/PEF) [2, 22]. Reperfusion and vasodilators play important roles in the therapy of STEMI [18, 23–26] and vasodilators in the therapy of HTN [27]. While reperfusion and vasodilators are attractive therapies in the elderly, cautionary measures are needed because of the aging-related changes [2–6, 23, 27] and because most clinical drug trials were not conducted in the elderly [2, 19, 20]. This chapter is focused on the roles of reperfusion and vasodilator therapies in the management of HF in elderly survivors of STEMI and chronic HTN and discusses some possible ways for improving outcomes.

Aging and Heart Failure

HF is considered to be a progressive disorder characterized by structural and functional changes that impair LV diastolic filling and LV systolic ejection that lead to typical symptoms and signs [15–18]. Population studies between 1980 and 2000 showed that HF is very common in the elderly, with many aged >80 years [28–30]. The risk of HF increases with age and severity of HTN [7, 14] and with antecedent MI and HTN [14]. Interactions with comorbidities such as HTN, MI, and diabetes fuel the march to HF [2, 31]. In the 2013 HF update, there were ~5 million patients with HF in the USA in 2012, and this number was expected to increase to ~8.5 million by 2030 [18]. The incidence of HF in the elderly approaches 10 per 1,000 and 75 % of cases have antecedent HTN [7, 14]. The diagnosis is often made after hospitalization and ~80 % of hospitalized HF patients are elderly [20]. The most common discharge diagnosis in the elderly is HF [14]. Outpatients with HF are more likely to utilize high-cost resources and rehospitalization rates are high in the elderly [14]. The total cost of HF for 2010 was estimated at $ 39.2 billion [14]. Healthcare providers and policy makers should be cognizant of these trends and prepare to address the problems and support prevention [2].

Heart Failure Groups

Clinically, HF has been defined as "a complex syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood; the cardinal manifestations of HF are dyspnea and fatigue which may limit exercise tolerance, and fluid retention which may lead to pulmonary and/or splanchnic congestion and/or pulmonary edema" [18].

As discussed before, HF is associated with high morbidity and mortality [15–18] and is a common cause of hospitalization and referral for consultation in hospital emergency departments among elderly patients in developed countries [32]. HF prevalence increases markedly with aging [10], being found in more than 10 % of the population aged 70 to 80 years, and 50 % of the patients diagnosed with HF die within ~5 years after the diagnosis [10, 33].

There are two broad groups of HF with distinct phenotypic profiles in the elderly [15–18]: (1) diastolic heart failure (DHF), also called HF with preserved ejection fraction (HF/PEF), HF with preserved systolic function (HF/PSF), or HF with normal EF (HF/NEF), and (2) systolic heart failure (SHF), also called HF with low EF (HF/low-EF). This phenotypic classification has important implications for HF management in the elderly. HF/PEF is best considered as a syndrome characterized by diastolic dysfunction with impaired rate of ventricular filling as well as slow myocyte relaxation, increased ventricular wall thickness, concentric ventricular remodeling, and increased extracellular matrix (ECM) deposition and fibrosis. Importantly, ~50 % of elderly patients have HF/low-EF, whereas ~50 % of all HF patients have HF/PEF and its prevalence is higher in the elderly [34, 35]. In a recent study of HF/PEF, all patients were aged >80 years and the mean age was 87 years [36].

Congestive heart failure (CHF) refers to a syndrome characterized by inadequate cardiac function to meet bodily demands. CHF results from a sudden decrease in stroke volume, causing an increase in systemic vascular resistance (SVR),

which, in turn, further reduces stroke volume and finally leads to pulmonary edema. The risk of CHF increases with age [37], and the most common acute HF syndrome in the elderly is CHF with preserved LV ejection fraction [38].

Aging and the Cardiovascular Continuum

It is important to remember that aging is a continuous biological process that leads to a host of CV alterations (Table 14.1 and Fig. 14.1) that result in LV dysfunction [3–6, 23, 39] and lead to progressive HF on the long term [19, 20]. The aging process is a key player in the CV disease continuum leading to HF and a key contributor in the march toward HF (Fig. 14.1). Consistent with the concept that progressive biological changes occurring during aging impact myocardial pathophysiology, several studies have documented that HF begins to increase after the age of 45 years [40].

Aging and the March Toward Heart Failure

In this scheme, CV risk factors (i.e., genetic factors, diet, cigarette smoking, sedentary lifestyle, dyslipidemia, HTN, obesity, diabetes, metabolic syndrome, and stress) contribute to myocardial pathologies that lead to HF. In parallel, common comorbidities during aging and particularly prevalent in the elderly (e.g., coronary artery disease, HTN, obesity, and type 2 diabetes) result in cardiomyopathies that accelerate the march toward HF, end-stage heart disease, severe disability, and death. In this construct, prevention must begin early, with measures applied throughout to halt progression [2].

Table 14.1 Physiological and pathophysiologic changes during aging

1.	↑ Systolic blood pressure and pulse pressure, LV mass
2.	↑ Incidence of CHD and atrial fibrillation
3.	↓ Early diastolic filling rate, maximal heart rate, maximum cardiac output, maximal aerobic capacity, exercise-induced augmentation in ejection fraction, reflex response in heart rate, beta-adrenergic, and endothelial-mediated vasodilation
4.	Cellular, enzymatic, and molecular changes in arterial vessel wall; arterial remodeling, ↑ arterial stiffness
5.	↓ Endothelial NO production; ↑ endothelial apoptosis and superoxide production; preserved response to non-endothelial-derived substances such as nitrates and nitroprusside
6.	Altered myocardial ECM in myocardium, with ↑ collagen, collagen fibril diameter, collagen cross-linking, collagen type I/III ratio, and fibronectin; ↓ elastin content
7.	Altered balance between MMPs and TIMPs → ↑ ECM production, development of atrial fibrillation
8.	↑ Collagen, elastin, and calcification conduction abnormalities, valvular calcification
9.	↑ Ventricular collagen and ECM → cell loss, myocyte hypertrophy, altered myocardial calcium handling, prolonged contraction, and relaxation
10.	↑ Fibrinogen, coagulation factors, platelet activity, PAI-1 and prothrombotic cytokines → ACS and development of atherosclerosis
11.	Altered autonomic nervous system function and ↓ β-adrenergic, α-adrenergic, and dopaminergic functions → ↓ baroreceptor response to stressors and ↑ sensitivity to parasympathetic stimulation
12.	↓ Ability to increase cardiac output in response to stress, ↓ ability to respond to myocardial injury; ↓ reserve capacity thereby lowering thresholds for symptoms

↑= increased; ↓ = decreased; → = leading to; *ACS* acute coronary syndrome; *CHD* coronary heart disease; *ECM* extracellular collagen matrix; *LV* left ventricular; *MMPs* matrix metalloproteinases; *NO* nitric oxide; *PAI-1* plasminogen activator inhibitor; *TIMPs* tissue inhibitors of metalloproteinases (reprinted from Jelani A, Jugdutt BI. STEMI and heart failure in the elderly: role of adverse remodeling. Heart Fail Rev 2010;15:513–521. With permission from Springer Science+Business Media)

Aging and HF Due to STEMI and Hypertension

In the USA, coronary heart disease is the leading cause of morbidity and mortality [14]. Importantly, coronary disease and MI are more common in the elderly and common causes of HF besides HTN [7, 41], the average age for MI being 64.5 years in men and 70.4 years in women [7]. In 2010, estimates are for 785,000 first coronary attacks; 470,000 recurrent attacks; and ~195,000 silent MIs. An estimated 74.5 million

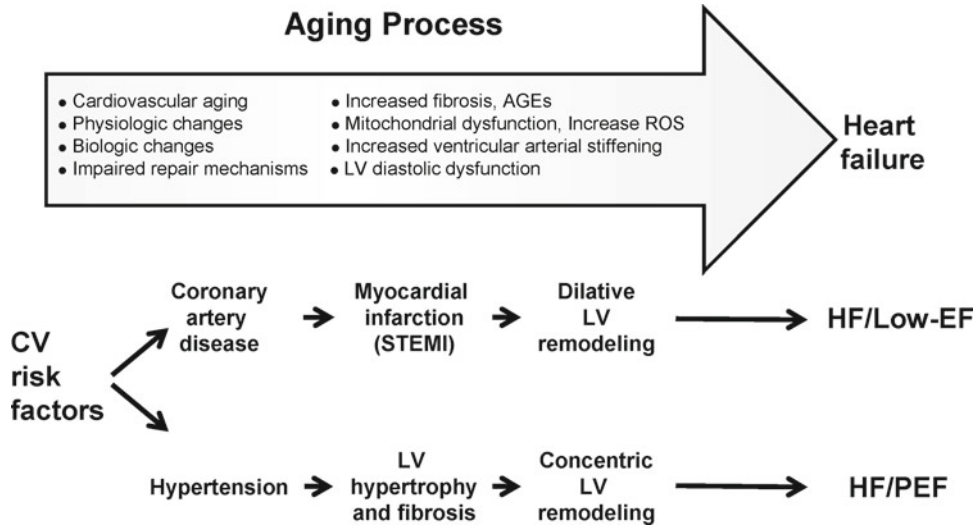

Fig. 14.1 Aging and the march to heart failure. *AGEs* advanced glycation end-products; *EF* ejection fraction; *HF* heart failure; *LV* left ventricular; *PEF* preserved ejection fraction; *ROS* reactive oxygen species (reprinted from Jelani A, Jugdutt BI. STEMI and heart failure in the elderly: role of adverse remodeling. Heart Fail Rev 2010;15:513–521. With permission from Springer Science + Business Media)

adults have HTN, with equal prevalence in men and women [14]. Improved CV disease therapies, especially those for MI, post-MI HF, and HTN, have improved survival and increased the number of non-elderly patients who survive into old age, thereby increasing the toll of HF-prone elderly patients [14–17].

In Canada, despite the declining mortality from CV disease and acute MI, HF prevalence is also high, with 350,000 reported cases in 1999 and one-year mortality between 25 % and 40 % [42], and greater prevalence and more hospitalizations in the elderly [39]. In Europe, the HF burden has also been increasing and is especially serious in the elderly [17].

Definition of STEMI

It is pertinent to note that the redefinition of acute coronary syndromes includes unstable angina, non-ST-segment-elevation MI (NSTEMI), and STEMI. Most STEMI patients have an occlusive thrombus and develop transmural or Q-wave MI, whereas most NSTEMI patients have a non-occlusive or mural thrombus and develop subendocardial, non-transmural, or non-Q-wave MI. However, transmural or Q-wave MIs, or STEMIs, result in more severe ventricular remodeling and dysfunction [43–45] and high mortality and morbidity [46]. In the reperfusion era, most MI trials focused on STEMI or Q-wave MI. Early and successful reperfusion interrupts the march to necrosis [47] and is thought to limit ventricular remodeling [48].

Models of Heart Failure

Early models of HF (i.e., cardiocirculatory, hemodynamic, and cardiorenal) emphasized key features such as pump dysfunction, decreased cardiac output and renal blood flow, and increased peripheral vasoconstriction. The subsequent neurohumoral model emphasized progression of asymptomatic to symptomatic HF, with initial injury leading to activation of the adrenergic nervous system, RAAS, and cytokine systems followed by secondary damage, with maladaptive remodeling and worsening of HF [49]. In the scheme of HF as a progressive disorder in the CV disease continuum (Fig. 14.1), coronary heart disease leads to STEMI and progressive dilative remodeling, eccentric LV hypertrophy, LV systolic

dysfunction, and HF/low-EF, while hypertensive heart disease leads to LV hypertrophy and fibrosis, concentric LV remodeling, LV diastolic dysfunction, and HF/PEF [2].

STEMI: A More Malignant Disease in the Elderly

HF is a recognized common secondary complication in survivors of STEMI [14, 46, 48–50], and the number of individuals who develop HF after a first STEMI increases with age [14]. In addition, most deaths after acute MI occur in the elderly [14]. Several clinical studies have shown that morbidity and mortality after STEMI are higher in elderly than non-elderly patients [19, 20]. STEMI is especially serious as it leads to more severe LV dysfunction, adverse remodeling, and HF in elderly than non-elderly patients [20, 21]. In-hospital and long-term mortality for elderly STEMI patients is significantly higher than for non-elderly patients. In a population-based study, patients aged 55 to 64 years were 2.2 times more likely to die during hospitalization for acute MI than patients aged <55 years, whereas patients aged 65 to 74, 75 to 84, and ≥85 years were at 4.2, 7.8, and, 10.2 times greater risk of dying, respectively [51].

Reperfusion Therapy in the Elderly with Acute STEMI

Early thrombolytic trials confirmed the adverse trend for immediate (within 30 days) or short-term (6–12 weeks) mortality in the elderly. In GUSTO-1, mortality of patients aged <65 years was 3 % compared to 20 % for patients aged 75–84 years at 30 days [52]. In the TIMI-III registry, risk of death with acute coronary syndrome at 7 weeks was four times for patients aged ≥75 years compared to the younger age group [53]. In the longer term, mortality at one year post discharge after a STEMI-related admission remained higher in patients aged over 70 years versus younger patients (19.1 % vs. 6–8 %, respectively) [54]. Overall, 60 % of STEMI-related deaths occur in patients aged ≥75 years [55]. Taken together, evidence indicates that the post-STEMI population segment aged ≥75 years is an especially high-risk group.

Risk of Heart Failure in STEMI Survivors

Elderly survivors of STEMI remain at increased risk for HF. Although management of elderly patients with acute coronary syndromes and STEMI as suggested in the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines [15] can reduce mortality, survivors may still increase the HF burden. In an observational study of elderly patients with first MI, 75 % of survivors developed HF in the subsequent 5 years [56]. However, in a Medicare study of elderly patients (mean age 78 years), the 30-day in-hospital mortality rate after acute MI declined slightly from 18.8 % to 15.8 % [57]. Also, data from STEMI trials of primary percutaneous intervention (PCI) versus fibrinolysis suggested a trend toward mortality benefit with PCI in the elderly [58–60]. However, even after successful PCI and medical therapy, STEMI patients develop persistent LV remodeling [61].

Reasons for Excess Mortality in Elderly Post-STEMI HF Patients

Twelve potential reasons why post-STEMI HF patients are at higher risk were reviewed previously [22]. It is important to consider these when treating the elderly with STEMI.

Lack of Representation in Clinical Trials

Elderly patients have been poorly represented in clinical trials due to enrolment biases. This has been recognized for several decades and strategies were proposed [62]. Enrolment of elderly patients in randomized clinical trials (RCTs) of acute coronary syndromes has been low [63].

Nearly 58 % of RCTs of acute coronary syndromes carried out between 1966 and 1990 had explicit age exclusion criteria although that improved to 40 % during 1991–2000 [64]. Enrolment of patients aged ≥75 years increased from 2 % during 1966–1990 to 9 % during 1991–2000, still well below their representation among all MI patients (i.e., 37 %) in the USA. Interestingly, women were also underrepresented, but enrolment rose from 20 % during 1966–1990 to 25 % during 1991–2000 [64]. This issue was also explored and emphasized nearly a decade before [65]. Since safety and efficacy of therapies can vary with age, enrolment biases can jeopardize delivery of optimal evidence-based care to elderly patients of cardiac patients including high-risk patients with post-STEMI HF.

Lack of Clinical Trial Data

There is a lack of clinical trial data exclusively in elderly patients for specific therapy of adverse remodeling post-STEMI and HF/low-EF or HF/PEF. Most recommendations of pharmacotherapies including reperfusion and vasodilators for the management of HF are based on studies done in younger populations. One recent PREAMI echo substudy [66] addressed the effect of the ACE inhibitor perindopril in elderly acute MI survivors with preserved LVEF (≥40 %). Of 1,252 patients (mean age 73 years) who were randomized, the placebo group showed persistent remodeling (increase in LV end-diastolic volume ≥8 %), whereas treatment with perindopril reduced the progressive remodeling [66].

Lack of Data on Aging and Post-STEMI Healing

Data on the impact of aging on remodeling during healing post-STEMI and HF is lacking. More data on pathobiology of post-MI healing and remodeling post-STEMI and clinical evidence of the beneficial effect of therapies on the healing and remodeling processes are needed. Previous studies have shown that post-STEMI remodeling impacts clinical outcomes [43, 48, 50]. However, those studies were mainly in the non-elderly.

Cumulative evidence suggests that optimal healing after injury is critical for survival with a favorable outcome, and the healing process may be different in older than younger hearts [20]. STEMI damages the muscle as well as the ECM and blood vessels. It triggers a host of biochemical, molecular, and cellular reactions that lead to concurrent dynamic processes of healing and remodeling over several weeks. An emerging concept is that timed release of proteins - such as chemokines, cytokines, matrix metalloproteinases (MMPs), other matrix proteins, and growth factors - leads to inflammation and remodeling of the ECM, under the modulatory influence of angiotensin II, oxidative stress, and other factors, and finally to a firm fibrotic scar. Degradation of ECM by matrix MMPs leads to cardiomyocyte slippage, cardiac enlargement, cardiac dysfunction, and HF.

Aging-Induced Delayed Healing and Adverse Remodeling Post-STEMI

Aging can potentially alter these processes, not only the extent of acute damage but also the subsequent healing and remodeling, and therefore outcome [20]. Aging is associated with increased LV angiotensin II – a regulator of ECM remodeling – and increased reactive oxygen species (ROS) and oxidative stress. Both these factors can participate in aging-induced impaired healing (Fig. 14.2). Aging-related impaired/defective healing can, in turn, augment or accelerate maladaptive remodeling, thereby, leading to progressive cardiac enlargement, fibrosis, disability, and death (Fig. 14.2). We hypothesized that aging-related defective healing involves dysregulation of inflammation and fibrosis pathways [20]. The aging-related neurohumoral, immunological, and oxidative stress changes have been reviewed before [20].

Evidence in the mouse model of reperfused MI suggested that aging results in suppressed inflammation, delayed repair, reduced infarct collagen, and adverse remodeling [67], providing

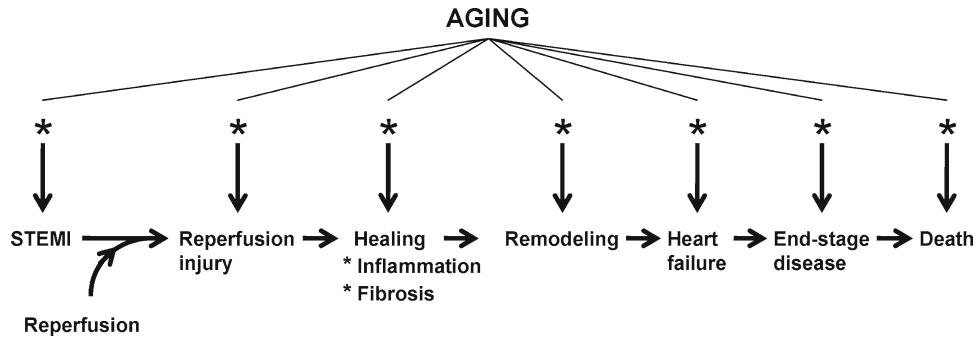

Fig. 14.2 Effects of aging on the march from STEMI to heart failure. (*asterisk*) Postulated sites at which aging may exert significant effects (reprinted from Jelani A, Jugdutt BI. STEMI and heart failure in the elderly: role of adverse remodeling. Heart Fail Rev 2010;15:513–521. With permission from Springer Science + Business Media)

a compelling argument for modifying post-STEMI therapy in the elderly [68]. Aging is associated with impaired immunity and comorbidities that contribute to impaired healing after MI [68]. To complicate matters further, aging is associated with attenuation of post-conditioning mediated cardioprotection [69], which may contribute to larger infarcts in the elderly. Anti-inflammatory agents such as nonsteroidal inflammatory agents (NSAIDs) and steroids [70] which are widely used for arthritis in the elderly also impair post-infarct healing.

To date, there is no therapy aimed specifically at improving post-STEMI healing in either the young or the old patients.

Severity of Coronary Artery Disease

Evidence suggests that the severity and extent of coronary artery disease increase with age. This may in part be due to the longer exposure to risk factors. As a result, a coronary event in the elderly is more likely to be associated with adverse outcomes. This is further compounded by aging-induced impaired post-conditioning and healing as mentioned above. In the National Registry of Myocardial Infarction (NRMI; http://www.nrmi.org), acute HF at time of presentation was observed in 11.7 % of STEMI patients <65 years versus 44.6 % of those who were older than 84 years [19].

Higher Early Post-STEMI Mortality with Reperfusion

In-hospital mortality post-STEMI is also significantly higher in elderly than younger patients. Regardless of the type of intervention for elderly patients presenting with STEMI, in-hospital mortality has been high and varied from 19.9 % to 32 % in different studies. In one study, 2,117 patients (aged >70 years) who received thrombolytic therapy for STEMI showed in-hospital mortality of 31.9 % [71]. Another study confirmed this observation and reported in-hospital mortality of 29.7 % in 706 patients with a first STEMI and aged >75 years [72].

Delayed/Atypical Presentations of the Elderly Post-STEMI

The high in-hospital mortality post-STEMI has been attributed to several other factors including atypical or delayed presentation and missed or delayed diagnosis. The symptomatology of the acute event may differ for elderly than non-elderly patients. It is not uncommon for elderly patients to present with atypical symptoms. In the National Registry of Myocardial Infarction (NRMI), only half of patients aged >84 years had chest pain (56.8 %), whereas the vast majority (89.9 %) of younger patients (<65 years) had "typical" symptoms. This not only interferes

with timely diagnosis of acute coronary events but also hinders the patient's awareness of having an acute problem for which they should seek immediate attention [19].

Cognitive and socioeconomic factors may contribute further to the delay [73–75]. These may be as simple as lack of transportation available to older patients residing either alone or in a long-term housing facility. This observation has been noted and emphasized in many studies carried out in North America [76, 77]. A delay in presentation after an acute event for older patients is a universal issue across different communities and countries. In a study from Singapore, only 59.6 % of elderly patients with an acute MI presented within the initial 12 h compared to 67 % of younger patients [78]. The median time of presentation after initial symptoms was 8 h for older patients compared to 5 h for younger patients [78]. Delayed presentation of elderly patients is not restricted to just the community population. Within the trial population, elderly patients were found to be presenting later than younger patients. This most likely subjected them to adverse effects associated with delayed presentation [51, 79]. Clearly this has implications on the type of treatment strategy chosen. The presence of left bundle branch block (LBBB) in one-third of ECGs of patients aged ≥85 years increases the chance of misdiagnosis [19]. Diagnosis may also be delayed due to the absence of typical chest pain in patients with diabetes.

Early Reperfusion Therapy in the Elderly with STEMI

Elderly patients do worse with reperfusion therapeutic strategies than their younger counterparts. For example, in the SHOCK trial, patients aged ≥75 years who were assigned to early revascularization had a mortality rate of 75 % at 30 days compared to 41.4 % in those aged <75 years [80]. Complications of an acute STEMI are also more catastrophic and more common in older patients than younger ones. Among these complications is LV free wall rupture, especially after an anterior MI, in the first 24–48 h. This usually develops with large transmural anterior MIs that involve >20 % of the LV. The incidence of this complication is overall very small; however, in the elderly, it is reported to be 7–9 % [81]. The risk of this often fatal complication increases with the use of thrombolytic agents. GISSI-2 reported an 86 % rate of cardiac rupture among autopsies performed on patients with electromechanical dissociation during hospitalization after receiving thrombolytic therapy [71]. In another study of the effect of thrombolytic therapy on the incidence of free wall rupture [72], of 706 patients (aged ≥75 years), those who received thrombolytic therapy had in-hospital mortality of 16.5 % compared to patients who had primary angioplasty (4.3 %) or who did not receive any reperfusion therapy. This complication might be avoided by refraining from use of agents that interfere with healing (NSAIDs, steroids, etc.) and using agents that attenuate rather than increase wall stress [82].

Lack of Evidence-Based Therapy for Elderly with Post-STEMI HF

As noted, improved therapies for CV diseases, especially those for STEMI and HTN, have increased the number of non-elderly patients who survive into old age, thereby increasing the toll of HF-prone elderly patients [14–18]. However, HF is also more common in elderly patients surviving STEMI. This is true for both HF/low-EF and HF/PEF [83, 84]. Large infarcts or STEMIs are not only common causes of post-STEMI HF [85, 86], but they are also subject to more severe adverse remodeling in elderly patients [20, 21]. Also, stroke and arrhythmias are more prevalent in the elderly [19]. Atrial fibrillation is more common after MI in elderly patients [87, 88]. All these comorbid conditions make management of elderly patients challenging. Anticoagulation for atrial fibrillation on top of antiplatelet agents, fibrinolytics, and GP IIb/IIIa and for long periods of time obviously increases the risk of bleeding.

The elderly commonly do not receive evidence-based therapies. In the Global Registry of Acute Coronary Events (GRACE), it was noted

that the rate of coronary artery bypass grafting in patients aged ≥75 years was 2.7 % versus 8 % in patients aged <75 years [89]. The possibility of not getting the appropriate, proven therapy increases with age. In the CRUSADE registry data, 5,557 patients 90 years or older with an acute coronary syndrome were compared with 46,270 patients aged 75–89 years [90]. The "older-elderly" were less likely than "younger-elderly" patients to receive guideline-recommended short-term therapies. These included heparin (75.1 % vs. 82.4 %), glycoprotein IIb/IIIa (12 % vs. 29.2 %), and statins (30.4 % vs. 45.7 %) in the crucial, initial 24 h. Eligible older-elderly patients were also less likely to have cardiac catheterization (10.8 % vs. 36.3 %) in the initial 48 h. Hence, the revascularization rate was also lower in this age group. The simplest forms of therapies are also delayed or even denied. This is true for the overall elderly patient group but more so for the "older-elderly" subgroup. For example, start of statins in the first 24 h – in patients who were not on statins before admission – was noted in 18.7 % of "older-elderly" versus 26.7 % of "younger-elderly" patients [90]. Cardiac catheterization was felt to be contraindicated in 59.8 % of the older subgroup versus 26.9 % of the younger subgroup. The most common contraindications for invasive procedure recorded were "advanced age" (40.6 %) and "do not resuscitate" (29.3 %) [90].

Physician Attitudes Toward the Elderly Post-STEMI HF Patient

There is a belief among healthcare providers that extrapolated evidence from younger patients to the elderly is not as safe. This is strictly correct for obvious reasons and this belief is reinforced by the guidelines issued by the ACC and AHA [19]. These guidelines clearly, and rightfully, suggest caution when treating the elderly with currently recommended therapies. From the evidence available at this time, it appears that the recommended treatment for the elderly patients carries benefits. Published guidelines therefore recommend the same therapies with proven efficacy in non-elderly HF patients for elderly HF patients but with certain caveats [15–18, 20, 21]. The therapies for HF/low-EF include mainly ACE inhibitors or ARBs, β-blockers, aldosterone antagonists or mineralocorticoid antagonists (MRAs) and the hydralazine-nitrate combination in patients intolerant to ACE inhibitors or nitrates or who are black Afro-American. Recent evidence suggests that MRAs may be useful in the elderly and very old, but hyperkalemia should be avoided [91]. Therapies for symptom control and morbidity benefit include diuretics and digoxin. Therapies for the two broad groups of HF patients have recently been reviewed [2, 17, 18].

Lack of Data on HF/PEF in the Elderly

Current knowledge of HF/PEF has also been reviewed [92, 93]. To date, clinical trials in HF/PEF patients have not shown mortality benefit so that management is focused on symptom relief and treatment of the underlying cause. In contrast to HF/low-EF, patients with HF/PEF are more likely to be elderly, female, and hypertensive and less likely to have STEMI or previous therapy with ACE inhibitors and angiotensin II type 1 receptor blockers (ARBs) [94]. However, mortality is similar to that with HF/low-EF. Although survival over time has improved for HF/low-EF, it has remained unchanged for HF/PEF. Due to the lack of clinical trial data to guide therapy in the elderly and non-elderly, management objectives are largely empirical and twofold: i) to treat the HF syndrome and ii) to manage underlying causes. Pharmacological therapy is limited as the results of small trials have been mostly inconclusive. ARBs have been tested based on the rationale that they decrease myocardial fibrosis. However, specific medical therapy for HF/PEF is lacking for both elderly and non-elderly patients.

Problems with Medical HF Therapy in the Elderly: Comorbidities and Polypharmacy

Treatment of HF in the elderly should be considered suboptimal. Therapy is more challenging because of aging-specific biological changes

(Table 14.1) and associated comorbidities and polypharmacy. Comorbidities not only aggravate HF and increase the HF burden but also complicate management. Polypharmacy may lead to drug interactions [95, 96]. The elderly may have blunted responses to diuretics, ACE inhibitors, β-blockers, and positive inotropes. They may show heightened sensitivity to renal dysfunction, impairment of sodium and water excretion, postural hypotension, aggravation of hypotension to treatments (i.e., ACE inhibitors, β-blockers, nitrates, hydralazine) besides cognitive impairment, and general frailty. In view of intrinsic physiological changes that occur with aging (Table 14.1), several precautionary measures are necessary with HF pharmacotherapy in the elderly. Therapy has to be individualized because of aging-related changes in physiology, drug metabolism, drug pharmacokinetics, drug tolerance, polypharmacy, drug-drug interactions, and the impact of comorbidities [1].

Elderly patients typically have multiple drugs prescribed. They are usually on these drugs at time of presentation. They usually use two to six prescription drugs and one to four nonprescription drugs on a regular basis [95]. When other drugs are added to their drug regimen, the possibility of adverse effects is substantially increased. It is estimated that the potential for an adverse effect from any drug increases by 6 % when taken with one drug, by 50 % when taken with five different drugs, and 100 % when taken with eight or more medications [96]. There has not been any scientific evaluation of pharmacokinetics of agents given simultaneously to elderly patients with acute STEMI, subacute STEMI, or HF, let alone in patients taking different medications at the time of presentation. The different aspects of drug pharmacokinetics (i.e., absorption, distribution, metabolism, and excretion) may be altered in the elderly due to age-related changes in the gastrointestinal tract, body fat and water content, and liver and renal functions. It is not possible to conduct an experiment, let alone a clinical trial, to find the results of every such combination.

Vasodilator Therapy for Heart Failure in the Elderly

Heart failure is prevalent in the elderly [7–19], and elderly patients with acute decompensated HF or CHF who are hypotensive with poor organ perfusion still have high mortality in the twenty-first century [97]. Vasodilators are used for treating acute exacerbation of systolic and diastolic HF, especially if patients cannot tolerate ACE inhibitors or ARBs. Vasodilators include nitrates, the hydralazine-nitrate combination, nitroprusside, and nesiritide. Also, if patients with HF are still symptomatic despite being on ACE inhibitors, β-blockers, and an ARB or spironolactone, addition of a vasodilator can alleviate symptoms. These therapies are recommended by the European, American, and Canadian guidelines [16–18, 23]. However, these guidelines were not designed specifically for the elderly or based on data obtained exclusively in the elderly. Whether improved strategies with the available vasodilators may produce similar mortality benefits in the elderly compared to younger HF populations needs study.

Vasodilator Era in Heart Failure Therapy

Until most of the 1960s, drug therapy of CHF consisted largely of digitalis preparations and diuretics. This combination produced symptomatic relief but no mortality benefit. Studies in the early 1960s identified outflow resistance [98] or afterload [99] as a determinant of cardiac performance. This opened the era of vasodilator therapy for CHF. In the 1970s, vasodilator drugs were proposed for the treatment of CHF on the basis of physiological studies on the hemodynamic modulation of cardiac performance [100–103]. These studies showed that acute administration of the drugs that decrease SVR and impedance to LV ejection improves ventricular performance and confirmed that ventricular performance is

dependent on impedance/afterload and SVR. Vasodilators differ depending on effects on arteriolar resistance vessels, arterial compliance vessels, and venous capacitance vessels and reflex neurohumoral control of the circulation [101]. Responses to drugs such as sodium nitroprusside underscored the role of inappropriate vasoconstriction on increased resistance to LV ejection [102]. Thus, in HF associated with acute MI, sodium nitroprusside reduced LV filling pressures from 23 to 11 mmHg and improved cardiac output [102]. Many more clinical studies established the benefits of short-term vasodilator therapy on LV performance, but further long-term studies were needed to establish mortality benefit.

Pertinent Pathophysiology and Mechanisms

Multiple hemodynamic and neurohumoral mechanisms contribute to increased vasoconstriction, SVR, and afterload and preload in HF [104 for review]. Documented abnormalities include i) reduced caliber of small arteries and arterioles, increased total SVR, reduced regional blood flow despite normal systemic arterial perfusion, and reduced peak reactive hyperemia in the extremity; ii) reduced compliance or distensibility of conduit arteries that contribute significantly to increased impedance and afterload; iii) increased vascular wall remodeling and vasoconstrictor tone; iv) venous vasoconstriction with increased venous vascular tone and decreased capacitance leads to increased central venous pressure and peripheral capillary pressure and edema, redistribution of blood volume centrally to cardiac chambers and pulmonary vessels, increased preload and pulmonary edema, and worsening of renal function; v) structural changes in the vascular wall due to increased sodium and water content as well as vascular smooth muscle (VSM) growth, hypertrophy, and remodeling lead to decreased arterial lumen area and wall distensibility; vi) maladaptive increase in activation of the sympathetic nervous system (SNS) with increased norepinephrine (NE) in synaptic clefts, increase in RAAS activation, and increase in angiotensin II, arginine vasopressin, and endothelin lead to increased SVR, wall stress, and myocardial oxygen demand and decreased stroke volume and cardiac output; vii) decrease in nitric oxide (NO) leads to endothelium-mediated vasoconstriction [104]; and viii) increased atrionatriuretic peptide (ANP) that is insufficient to counteract the increased vasoconstriction.

Vasodilator drugs may counteract these mechanisms through i) direct action on VSM to increase Na^+/K^+-ATPase or other cellular mechanisms and/or ii) indirect inhibition of the effects of neurohormone-mediated vasoconstriction, including SNS-mediated vasoconstriction by decreasing NE release or α_1-receptor blockade, vasopressin analogs, calcium antagonists, and agents that act via endothelium stimulation to increase NO release and cGMP-mediated vasodilation [105]. Vasodilator drugs therefore have the potential to reverse the hemodynamic abnormalities in HF by reducing SVR, improving arterial distensibility, and reducing LV wall stress and impedance to LV ejection. These in turn lead to augmentation of stroke volume and cardiac output, thereby, improving circulation in the short term and potentially attenuating the adverse remodeling process in the long term [106, 107].

Unlike the young, it is important to note that elderly people are more susceptible to develop HF under stress. At least four aging-related CV changes impair the ability of the elderly to respond appropriately to stress: i) reduced responsiveness to β-adrenergic stimulation; ii) increased vascular stiffness; iii) increased myocardial stiffness and reduced compliance leading to elevated diastolic pressure and left atrial stretch, thereby, predisposing to atrial arrhythmias such as atrial fibrillation; and iv) reduced performance of the mitochondria under stress. These changes predispose the elderly to develop CHF [23]. As discussed, the prevalence of such CV disease risk factors such as HTN, coronary heart disease, dyslipidemia, and diabetes fuels the march to CHF in this population [2, 17]. CHF was reported in 4 % of people aged 65 to 74 years and 6 % of people aged >75 years [32, 108]. Of those with CHF, 70–80 % could be attributed to HTN or coronary artery disease [108]. Valvular heart disease is the next most common

cause of CHF in the elderly, followed by non-ischemic cardiomyopathy (NICM) [17, 109]. With aging, increased collagen and collagen cross-linking in the arterial walls coupled with degradation of elastin fibers increase vascular stiffness [3–6], which results in increased resistance to LV ejection (afterload) and contributes to the development of systolic HTN in the elderly [20, 23]. The aging heart also becomes stiffer and less compliant, leading to impaired LV diastolic filling, reduced cardiac output, increased diastolic pressure, and increased left atrial stretch; LV hypertrophy contributes to increased afterload and myocardial oxygen demand. Age-related apoptosis develops [110]. Evidence suggests that these mechanisms are the precursors of DHF or HF/PEF. The lack of β-adrenergic response to stimuli ultimately results in reduced contractility. Poor β_2-adrenergic responsiveness impairs cardiac contractility, and β_2-mediated peripheral arterial vasodilation is impaired. Diminished adenosine triphosphate (ATP) production in response to cardiac demand also impairs contractility. Endothelial dysfunction results in diminished peak coronary flow and accelerated atherosclerosis. Together, these effects impair systolic function in the elderly and accelerate the onset of HF. Arterial stiffness in the elderly can be overcome with the use of ACE inhibitors, ARBs, and other direct vasodilators.

Factors Affecting Response to and Choice of Vasodilator Therapy

Several factors explain the differential effects of vasodilator drugs on arterial, venous, and regional beds and VSM [104 for review]. First, the dominant action of vasodilator drugs such as hydralazine and minoxidil is on arterioles whereas that of nitrates is on veins and conduit arterial vessels and less on arterioles, and RAAS inhibitors exert more balanced arterial and venous dilation. In the setting of coronary artery occlusion, nitroglycerin increases collateral blood flow [111], but the associated beneficial effects are blunted or offset by hypotension and the paradoxical J-curve effect [112, 113]. It is important to avoid excessive hypotension with vasodilators in the elderly [114]. Second, the major benefit from vasodilators in HF is via decreased impedance or the total force opposing LV ejection related to arterial compliance, arteriolar resistance, blood viscosity, and inertia. Of note, the calculation of SVR from mean cardiac output and mean arterial pressure overlooks the effect of compliance on impedance. Third, the state of the venous capacitance bed is important because vasodilator-induced venodilation with relaxation of the previously constricted venous capacitance bed in HF results in decreased ventricular preload and wall stress. However, as the LV in HF operates on a flattened Frank-Starling curve and very steep pressure-volume relation, a significant decrease in vasodilator-induced decrease in LV end-diastolic pressure (EDP) may be associated with a small change in end-diastolic volume (EDV) and force of contraction. Fourth, the vasodilator-induced effect on neurohumoral reflexes is important. In normal subjects, vasodilator-induced decrease in blood pressure (BP) triggers a cycle of SNS activation, increased NE, reflex tachycardia, reflex increase in contractility, and reflex vasoconstriction that counteracts the effect of the vasodilator. In HF patients, the neurohumoral reflex response to vasodilators drugs is attenuated or blunted. Infusion of nitroprusside is associated with minimal rise in NE and heart rate; an ACE inhibitor and ANP result in decreased NE levels and RAAS activity, while hydralazine induces a mild increase in plasma renin with no change in plasma NE. Fifth, since hydralazine is a predominant arteriolar dilator (i.e., decreases arteriolar resistance and SVR, with little change in LVEDP and right atrial pressure, and increase in cardiac output) [115] and isosorbide dinitrate (ISDN) a predominant venodilator (i.e., decreases LVEDP and right atrial pressure, increases arterial compliance, and modestly increases cardiac output) [116], the combination of hydralazine and ISDN (H-ISDN) was proposed for achieving dual arterial and venous dilation and optimizing benefits. Combined H-ISDN showed a decrease in arteriolar resistance, an increase in venous capacitance, and an increased arterial compliance equal to that produced by the balanced vasodilator nitroprusside [117].

Hydralazine-Nitrate Combination Therapy for Congestive Heart Failure

Further to the aforementioned short-term studies and others showing improved exercise tolerance and peak performance and ventricular function in patients with decompensated HF and reduced hospital admission rate in patients with worsening HF, mortality trials with long-term H-ISDN combination therapy were launched [104, 118 for review]. In patients with NYHA class III–IV HF, H-ISDN induced 36 % decrease in LV filling pressure, 58 % increase in cardiac index, and 34 % decrease in SVR [118]. At the same time, concurrent studies underscored the role of neurohumoral activation in HF patients [119]. V-HeFT I [120], which was conducted at a time when β-blockers and ACE inhibitors were not standard treatment, was the first study to show a mortality benefit with vasodilator therapy compared with placebo. In V-HeFT I [120], 642 men with LV systolic dysfunction and reduced exercise tolerance were treated with digoxin and diuretic and randomized to therapy with placebo, or prazosin (an α_1-adrenergic inhibitor), or H-ISDN. Mortality with placebo was 20 % per year while H-ISDN reduced mortality to ~12 % in the first year and remained lower at follow-up that averaged 2.5 years. There was a trend toward reduction of all-cause mortality (44.0 % vs. 38.7 %, $P=0.09$) which was significant at the prespecified 2-year end point (34 % relative risk reduction, $P<0.028$). Of note, prazosin did not exert a favorable effect on exercise tolerance, LVEF, or mortality, while H-ISDN showed an increment in exercise tolerance and improvement of LV ejection fraction compared to placebo.

In V-HeFT II [121], with a similar patient population of HF patients as in V-HeFT I, patients were randomized to H-ISDN or the ACE inhibitor enalapril. Both agents lowered the mortality rate but the reduction in mortality was greater with enalapril than H-ISDN, while H-ISDN was more effective in improving exercise performance and LVEF. The trend toward improved all-cause mortality with enalapril compared to H-ISDN (38.2 % vs. 32.8 %, $P=0.08$). Although there was no placebo arm, the mortality rates with H-ISDN were similar to those in V-HeFT I. The greater efficacy of ACE inhibition in improving survival was attributed to inhibition of neurohumoral activation including NE and angiotensin II [119].

The overall favorable effects of vasodilator drugs on LV function, exercise performance, quality of life, and mortality supported their retention for the pharmacological management of HF [122]. Although nitrate tolerance should be considered, this was not a limiting factor in V-HeFT I or II. While side effects of ACE inhibitors such as hypotension, azotemia, and cough are a concern, these were not seen with H-ISDN. New vasodilators continue to be developed and tested. On the basis of the V-HeFT data, BiDiL, a single pill equivalent to H-ISDN was developed [123]. The Food and Drug Administration (FDA) bureau in the USA ruled that the mortality benefit in V-HeFT I was marginal and H-ISDN was inferior to ACE inhibition in V-HeFT II [123].

Hydralazine-Nitrate Combination Therapy for Congestive Heart Failure in Blacks

Data in the 1990s suggested that HF in black-race patients had worse outcomes with higher all-cause mortality, pump-failure mortality, and combined death or hospitalizations than white-race patients. Retrospective analyses suggested that blacks had survival benefit with H-ISDN in V-HeFT I, whereas whites had better survival with enalapril than H-ISDN in V-HeFT II, with no difference with either therapy in blacks [123]. The FDA recommended a new prospective trial in blacks. In A-HeFT [124], blacks with advanced HF (NYHA class III-IV) and antecedent LV dysfunction within 6 months, LVEF ≤35 % or >45 %, LV internal end-diastolic diameter >2–9 cm/M^2, were randomized to placebo or H-ISDN. This patient population was on better medical therapy including diuretics (~90 %), digoxin (~60 %), ACE inhibitor (~69 %), β-blockers (~74 %), ARBs (~17 %), and aldosterone antagonists (~39 %). H-ISDN was given in a single pill (37 mg hydralazine and 20 mg ISDN) TID and uptitrated to 3 pills TID. After follow-up of 10

months when 1,050 patients were enrolled, this study was stopped due to significant relative mortality reduction (43 %) achieved with H-ISDN (10.2 % vs. 6.2 %, P=0.01). Improvement of quality of life and drop in hospitalization risk was also noted. Side effects included headache, hypotension/dizziness, and nausea. BiDiL was approved for HF in blacks.

Hydralazine-Nitrate Combination Therapy for Congestive Heart Failure in the Elderly?

In summary, vasodilators can affect the venous, arteriolar, or both sides of the circulation. A decrease in vascular resistance to LV ejection improves cardiac output and reduces LV size, wall stress, and myocardial oxygen demand. While excessive drop in arterial pressure can be detrimental, this is less likely with abnormal LV systolic function. Venodilators cause venous pooling and reduce venous blood pressure and decrease preload and cardiac output. This is particularly beneficial in ischemia-driven HF. A decrease in ventricular size and wall stress corrects the myocardial oxygen supply/demand ratio. Venodilators also decrease capillary hydrostatic pressure, thereby reducing development of edema. Vasodilators differ in their effects on arteriolar and venous beds. Some agents such as organic nitrates are predominant venodilators. Most currently available vasodilators cause vasodilatation by increasing intracellular cGMP. Hypotension is a contraindication to administration of vasodilators.

The ACC/AHA guidelines suggest that in HF patients with persistent symptoms on β-blocker and ACE inhibitor therapy, the addition of H-ISDN is reasonable [15]. It may also be considered in patients with hyperkalemia or severe renal dysfunction on ACE inhibitors or ARBs [15]. In black patients with NYHA class III and IV, the addition of isosorbide dinitrate and hydralazine to β-blockers and ACE inhibitors is beneficial [15, 114]. Unfortunately none of the H-ISDN trials separated their data regarding elderly patients so that firm conclusions cannot be drawn about possible benefits in the elderly with CHF [114, 123].

Race is considered a social construct [123], while age and elderly are socioeconomic constructs [1]. However, both blacks and the elderly have reduced NO bioavailability and impaired NO-mediated CV effects. ISDN is a NO-donor and hydralazine is an antioxidant, and H-ISDN prevents NO degradation. Aging is associated with increases in angiotensin II, ROS, and oxidative stress [20, 22, 68]. Subgroups of whites and women may benefit from H-ISDN [123]. In A-HeFT, women had a survival benefit over men [123]. H-ISDN is beneficial in acute decompensated HF which is associated with increased oxidative stress and disrupted NO signaling [123]. H-ISDN may benefit HF patients with pulmonary hypertension who have reduced NO availability [123]. The elderly with CHF may also benefit from H-ISDN and this deserves serious study.

Nitrates in HF

The role of nitrates as anti-ischemic and cardioprotective agents, for myocardial salvage and reverse remodeling, has been reviewed [125, 126]. As discussed, nitrates being predominant venodilators are effective in the treatment of pulmonary edema. They rapidly decrease pulmonary venous and ventricular filling pressures and relieve symptoms (dyspnea) and signs (pulmonary congestion) in acute HF. At higher doses, nitrates also act as arteriolar vasodilators, improving blood flow in epicardial coronary arteries. They also improve coronary blood flow in patients with active myocardial ischemia leading to HF. Availability of oral, sublingual, or spray formulation allows administration in patients without peripheral access to an emergency room. Treatment should be started sooner than later. The initial starting dose for intravenous nitroglycerin is 20 μg/min, with uptitration in as early as 5 min by doubling the dose; the goal is relief of symptoms or a drop in mean BP by 10 mmHg, keeping SBP above 100 mmHg. If SBP drops below 100 mmHg, the dose of the infusion should

be cut in half or discontinued if symptomatic hypotension develops. The use of nitrates was found to be suboptimal, especially in the USA (9 % of acute HF patients in USA vs. 38 % in Europe). The reasons remain unclear [17, 18]. The main drug interaction is with phosphodiesterase type 5 inhibitors (PDE5-I) such as sildenafil (used for erectile dysfunction) and a combination can lead to significant hypotension.

Sodium Nitroprusside in HF

Nitroprusside is most effective in hypertensive acute HF. It has a half-life of seconds to a few minutes. That makes it an ideal agent for hypertensive emergencies as well as patients with moderately severe mitral insufficiency presenting with acute HF. As a prodrug, nitroprusside is metabolized to NO and cyanide. It is a potent vasodilator with immediate action, hence its usage in hypertensive patients. If discontinued abruptly without tapering down, the risk of rebound HTN is a possibility. Despite its strong properties, it is not used commonly (1 % in patients with acute HF). This may be due to the requirement for invasive BP monitoring via an arterial line as well as the vasodilatory effect on intramyocardial coronaries resulting in a myocardial "steal phenomenon," inducing myocardial ischemia. Nitroprusside should be considered in patients presenting with low cardiac output and increased filling pressures with adequate blood pressure. Caution should be used in patients with ischemic heart disease. Once hemodynamic goals are achieved, oral vasodilator therapy with ACE inhibitors/ARBs or hydralazine and ISDN can be added to wean off nitroprusside. Side effects of sodium nitroprusside include nausea, dysphoria, and abdominal discomfort. These are related to cyanide metabolites. Cyanide poisoning potentially can occur if >1.5 mg/kg is administered over a few hours or >4 μg/kg/min for more than 12 h. An exposure of more than 2 days may result in cyanide poisoning which is treated with 12.5 g of intravenous sodium thiosulfate.

Nesiritide in HF

Nesiritide is recombinant human BNP that is a strong vasodilator that causes both venous and arteriolar vasodilation, resulting in a significant drop in venous and LV filling pressures. This in turn improves the clinical features of HF (relief of shortness of breath and some increase in cardiac output). It also has a natriuretic and diuretic effect, primarily mediated via the natriuretic peptide receptor A on VSM and endothelium and in the kidneys and adrenals. However, this "natriuretic" effect is not a substitute for diuretic agents in acute HF. Nesiritide has no direct inotropic effect. When administered intravenously [127], the effect is seen within minutes. It is reserved mostly for patients with decompensated HF with symptoms on minimal exertion or at rest (i.e., NYHA class III-IV). It reduces preload by reducing the pulmonary capillary wedge pressure and right atrial pressure almost immediately. It also improves cardiac output by reducing afterload. The VMAC trial of patients with acute HF demonstrated significant improvements in pulmonary capillary wedge pressure (PCWP) compared to placebo and nitroglycerin and significant improvements in dyspnea as compared to placebo [127]. Subsequent meta-analyses [128, 129] raised concerns about possible worsening of renal function and increased mortality with nesiritide. To address these safety issues, ASCEND-HF compared IV nesiritide versus placebo in addition to standard care in 7,141 patients with AHF and showed no effect on 30-day hospital readmission or death [130]. Nesiritide modestly improved shortness of breath but did not worsen renal function. The standard dosage is 2 μg/kg IV bolus followed by 0.01 μg/kg/min IV continuous infusion, although IV bolus is often omitted. It may be increased by 0.005 μg/kg/min every 3 h up to 0.03 μg/kg/min. The half-life is 18 min, although symptomatic hypotension can last for >2 h. It causes less headaches than nitrates. Hypotension is a contraindication for nesiritide.

Renin Inhibitors in HF

Renin catalyzes the key rate limiting step in the RAAS cascade and has been debated as a target since the 1990s. Renin inhibitors have actions which are mostly similar to those produced by ACE inhibitors and ARBs. First, they dilate arteries and veins by blocking angiotensin II formation. The resulting vasodilation reduces arterial pressure, preload, and afterload. Second, they downregulate sympathetic adrenergic activity by blocking the facilitating effects of angiotensin II on sympathetic nerve release and reuptake of NE. Third, they promote renal excretion of sodium and water (natriuretic and diuretic effects) by blocking the effects of angiotensin II in the kidney and by blocking angiotensin II stimulation of aldosterone secretion. This reduces blood volume, venous pressure, and arterial pressure. Fourth, they inhibit cardiac and vascular remodeling associated with chronic HTN, HF, and MI. The selective renin inhibitor aliskiren was approved for the treatment of HTN by the FDA in 2007. It is an orally active nonpeptide drug with a half-life of about 24 h and is dosed once per day. Because of its relatively long half-life, it takes about 2 weeks of dosing to achieve a near maximal antihypertensive effect. It is metabolized by the liver and excreted by the kidneys.

In patients with symptomatic HF, NYHA class II-IV, and history of HTN and who are aged 68 years, aliskiren added to an ACE inhibitor or ARB and β-blocker exerts favorable neurohumoral effects [131]. ASTRONAUT will test whether aliskiren on top of standard therapy will reduce post-discharge mortality and rehospitalization in patients with worsening HF/Low-EF [132]. ATMOSPHERE will test whether aliskiren added to or as an alternative to ACE inhibition in patients with chronic systolic HF improves outcomes [133]. In ASPIRE, adding aliskiren to standard therapy including a RAAS inhibitor in high-risk post-MI patients with LV systolic dysfunction did not result in further attenuation of LV remodeling and was associated with more adverse effects [134]. The ASPIRE HIGHER program will provide data on protection from target organ damage and CV morbidity/mortality in a range of cardiorenal conditions including HF, post-MI, and diabetic nephropathy [135]. AVOID showed that aliskiren may be renoprotective and reduced albuminuria in patients with type 2 diabetes, kidney disease, and HTN [136]. Several of those studies included elderly HF patients. ALTITUDE which aimed to test whether aliskiren on top of an ACE inhibitor or ARB therapy delays cardiorenal complications in patients with type 2 diabetes at high risk for cardiorenal events was stopped in 2012 because of no apparent benefit and an increase in adverse events including hyperkalemia (aliskiren 11 % vs. placebo 7 %) and hypotension (12 % vs. 8 %) [137]. Whether aliskiren might benefit the elderly with HTN and HF/PEF remains to be studied.

Dual-Action Molecules in Elderly Patients with HF/PEF

Dual inhibition of ACE and neutral endopeptidase (NEP) pathways in a single molecule such as omapatrilat (OMA) was studied in patients with HTN, but despite superior antihypertensive efficacy over ACE inhibition and equal antiremodeling efficacy in HF patients [138], the FDA did not approve OMA for patients with HTN because of troubling angioedema. The concept of dual-action molecules was revived with LCZ696, which combines neprilysin (NEP) and the ARB valsartan in a phase 2 trial, and was shown to be beneficial in patients with HF/PEF [139] and is being evaluated in patients with HF/Low-EF [139, 140]. Whether dual pathway inhibition may be a more effective strategy in elderly HF patients deserves study.

What to Watch for in Elderly?

While vasodilators are important tools for therapy of acute and chronic HF, especially in those intolerant to ARBs or ACE inhibitors as indicated in the ACC/AHA/ESC guidelines, these agents should be prescribed with clinical judgment to elderly patients, with close monitoring for adverse events. To date, clinical trials on the

effect of vasodilators in the elderly with HF have been done on limited numbers of individuals aged ≥65 years. As a result, drug therapy for the elderly is not significantly different from that recommended for younger patients except for caveats. Although a significant proportion of patients receiving nitrates are elderly, surprisingly little published work is available on the pharmacokinetics and pharmacodynamics of these agents in the elderly. Use of ISDN and nitroglycerin is preferred over isosorbide mononitrate (ISMN) since the latter is mainly secreted by the hepatic first-pass metabolism which is decreased in the elderly. As mentioned, a common side effect of vasodilators is hypotension which should be watched carefully in elderly who are more susceptible to it and are at risk of falls if it does occur. Headache often resolves within the first few days of therapy. Drug–drug interaction, especially with ACE inhibitors and PDE inhibitors, results in hypotension. Dosing often has to be three or four times daily, which may result in reduced compliance. Another entity among elderly is severe aortic stenosis, and the use of vasodilators among those patients may induce pre-syncope or CV collapse and therefore indicates need for caution. Future clinical trials with greater inclusion of patients aged ≥65 years will help to elicit the magnitude of benefits of optimal vasodilator therapy on mortality and morbidity rates in this population.

Conclusion

Heart failure is a common syndrome that has significant morbidity and mortality in the elderly population. There are many reasons for the increasing burden of HF in the elderly, both for HF/low-EF and HF/PEF. HF in the elderly does not usually occur as an isolated condition as in middle-aged patients; management is complicated by multiple comorbidities including HTN, diabetes, kidney failure, malnutrition, coronary artery disease, cognitive impairment, and depression. More research is needed to narrow the information gap in the biologies of post-STEMI remodeling and HF/low-EF as well as HF/PEF in the elderly. There has been a lack of clinical trial data exclusively in elderly patients for specific therapy of adverse remodeling, healing, and HF/low-EF post-STEMI and HF/PEF. While reperfusion has many benefits, aging may enhance reperfusion damage, impair healing, and enhance adverse remodeling after STEMI. While vasodilators are attractive agents for their LV unloading and anti-remodeling effects, caution is needed because of aging-related changes affecting the responses in the elderly. New paradigms and novel therapeutic approaches that specifically target the two major types of HF in the elderly are needed. It is likely that different therapeutic approaches for post-STEMI remodeling may be needed for these two types of HF in the elderly. Preclinical studies should test drugs in old as well as young animal models of the two disorders. Clinical studies should test drugs in both elderly and non-elderly patients with these disorders. More research and clinical trials are needed on finding strategies for optimizing HF therapies and improving outcomes in the elderly, especially in the older-elderly population segment aged ≥75 years.

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Erythropoietin Therapy for Heart Failure

15

Margarita Borovka and Mathew S. Maurer

A strong inverse correlation between hypoxia and anemia has been noticed both in scientific experiments and within the clinical realm since the late nineteenth century [1]. More than one hundred years ago, a French scientist observed increased red blood cell (RBC) count at high altitude, thereafter documenting for the first time the direct relationship between hypoxia and red blood cell count [2]. In 1948, Bonsdorff and Jalavisto identified "erythropoietin" (epo) as a curious humoral factor in the blood that when injected from hypoxic animals to untreated healthy animals caused a rise in RBC production [3]. Direct evidence for the presence of epo in blood to cause an increase in RBC count in anemia was obtained soon thereafter [4–6]. Then, only in 1977 did Dr. Takaji Miyake of Japan isolate 0.0003 of an ounce of epo from 675 gallons of urine from his patients [7]. That year, Miyake, working with American Dr. Eugene Goldwasser who isolated epo from rats, presented their discovery to Amgen [8]. In 1985, recombinant human epo (RHuEPO) was synthesized, and in 1989 the FDA approved the man-made hormone, Epogen, for use in patients with anemia associated with kidney failure [9, 10]. In less than one year, sales of epo reached more than $1 billion, and dialysis patients who had previously required frequent blood transfusions had reported improvements in their quality of life [8, 11]. Since then, erythropoietin analogues and erythropoietin-stimulating agents (ESAs) have become an epic drug of the biotechnology industry, and interest in their clinical application to other diseases has skyrocketed.

The explosion in the list of diseases to which epo can be applied is reflected in the literature and clinical trials of past and present. To date, over 550 clinical trials have been conducted in the application of epo to chronic diseases such as chronic kidney disease (CKD) and chronic heart disease (CHD) as well as cerebral malaria, bipolar disorder, and Friedreich's ataxia [10]. Today, epo is approved in the United States for treatment of patients who are anemic from chronic renal failure and may or may not be on dialysis, from cancer treatment with chemotherapy, and from zidovudine therapy in HIV-infected patients, as well as for the reduction of allogeneic blood transfusion in surgical patients [10]. Interestingly, with the growing burden of chronic diseases such as CKD, heart failure, and chronic coronary disease that are in large part the consequences of the progressive aging of the population, coupled with the rising prevalence of anemia with advanced age, there is a growing interest in the use of epo for older adult subjects with heart failure. Scientists have experimented and continue to delve into questions about epo administration, dose, and supplementation with iron in patients

M. Borovka, BA
University at Buffalo School of Medicine,
Staten Island, NY, USA

M.S. Maurer, MD (✉)
Department of Medicine, Columbia University
Medical Center, New York, NY, USA
e-mail: msm10@columbia.edu

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with heart failure [10]. These questions have culminated in an extraordinary literature on the subject of epo in heart failure in particular, totaling almost 250 articles with the majority of them having been published within the last 20 years [10]. While the list of diseases to which epo can be applied continues to grow, there is an increasing level of concern about its safety [10]. This has been coupled with additional insights into harnessing selective aspects of its biological function with epo analogues that may afford benefits while minimizing attendant risks [1].

In this chapter, we will focus on the older adult population with heart failure and

- Review the biological mechanisms underlying ESA production
- Characterize actions of ESAs related to their hematologic and non-hematologic effects
- Present data and analyses of clinical trials of ESAs in subjects with heart failure
- Delineate the efficacy of ESAs and the observed emerging risks from studies with ESAs
- Highlight new compounds that may have efficacy
- Delineate suggestions for management that may improve application of these new compounds to subjects with heart failure to improve safety and efficacy

Erythropoietin (Epo) Biological Mechanism

Epo is a glycoprotein growth factor that is the main stimulus for erythrocyte production [12]. Since erythrocytes have a limited life span, they must be continuously replaced by the body to ensure maintenance of normal oxygen delivery. The body adapts the rate of erythrocyte production to tissue oxygenation levels via a negative feedback mechanism, in which the amount of oxygen delivered to tissues determines plasma epo levels, and circulating epo levels in turn determine the number of erythrocytes by adjusting the rate of erythrocyte production [13]. For example, when oxygen delivery is decreased below normal, due to development of anemia after blood loss or in the setting of less atmospheric oxygen at high altitude, plasma epo levels increase, and the subsequent increase in circulating erythrocytes will return oxygen delivery to normal [14]. Similarly, when oxygen delivery is increased above normal, plasma epo levels will fall, erythrocyte counts will fall, and tissue oxygen delivery will also return to normal [14].

The kidney is the major site of epo production (90 %) and the liver to a lesser degree (10 %), both in response to reduced tissue oxygenation [13]. This was determined by Jacobson and colleagues who found that, of all other organs in the adult, only the removal of the kidney prevented the erythropoietic response [15]. In the kidney, epo is produced by peritubular, interstitial, fibroblast-like cells in the cortex of juxtamedullary nephrons [16]. These cells, termed REPOS cells for renal epo-producing and oxygen sensing cells, both detect blood oxygen levels and produce epo. In a kidney unstimulated to make epo, REPOS cells are found in the deep cortex and outer medulla. With increasing anemia, REPOS cells become more numerous and spread from the deep cortex and outer medulla into the superficial renal cortex [12]. Hepatocytes and Ito cells in the liver are the secondary source of epo in adults, but are the primary source of epo in the fetal and neonatal period [13, 16, 17].

Because hypoxia and hyperoxia can interfere with cell respiration and gene expression and can foster excessive production of tissue-damaging free radicals, tissue oxygenation must be tightly regulated [18]. What, then, renders the kidneys well suited to erythropoietin production? What sets the kidneys apart from other organs? Despite receiving 20–25 % of cardiac output [19], the renal arterial-venous oxygen difference is only 8 %, much less than other organs like the heart and brain [20]. Furthermore, this low oxygen consumption remains the same when renal blood flow (RBF) is increased or reduced by 30 % [18]. In a study by Leong, renal artery blood flow was altered by infusing rabbits with vasodilating and vasoconstricting agents, and arterial oxygen concentration was controlled by changing inspired oxygen concentrations [18]. Under normoxic conditions, GFR, tubular sodium reabsorption,

and oxygen consumption were closely linked, but renal oxygen consumption was not significantly changed and tissue oxygenation levels remained normal. Only when blood flow was reduced by more than 30 % did tissue hypoxia set in. This renal oxygen reserve that allows the kidney to maintain homeostasis within a wide range of blood flow is thought to be mediated by arterial-venous oxygen shunting [18]. The anatomical arrangement of renal blood vessels is such that it permits a large portion of arterial oxygen to be shunted to veins [20]. Variations in the amount of arterial-venous shunting are responsible for balancing changes in renal blood flow to maintain tissue oxygenation [18]. Tight control of renal tissue oxygenation is important because it allows the compartmentalization of two related kidney functions, separating renal blood flow and sodium reabsorption from tissue oxygen sensing and erythropoietin synthesis. Here, renal mechanisms regulating tissue oxygenation vary drastically from other organs because it is glomerular filtration and sodium reabsorption, the primary functions of the kidney, that regulate diameter of vessels supplying the kidney with blood, not tissue oxygen. The renal ability to maintain stable tissue oxygen levels despite large fluctuations in blood flow via shunting is the method by which it compensates for the fact that its primary determinant of blood flow, unlike other organs, is not tissue oxygen.

Within the kidney, prolyl-4-hydroxylase domain (PHD) enzymes are the oxygen sensors found in the nucleus and cytoplasm of REPOS cells [12]. Under normoxic conditions, a redox reaction occurs that results in repression of epo synthesis [16]. In the presence of oxygen, PHD is activated. One oxygen atom is used for the hydroxylation of HIF, hypoxia-inducible factor, and the other for oxidative decarboxylation of 2-oxoglutarate to form carbon dioxide and succinate [9, 16] (Fig. 15.1). Hydroxylated HIF increases the affinity for binding by Von Hippel-Lindau (VHL), a tumor suppressor protein. VHL, bound to HIF, is recognized by ubiquitin, and the entire HIF-VHL-ubiquitin complex is degraded. Degraded HIF cannot act as a transcription factor in epo mRNA synthesis and epo synthesis is halted [16]. Under hypoxic conditions, HIF is not hydroxylated [12] and acts as a transcription factor and activates many genes involved in the adaptation to decreased oxygen supply, including the epo gene. A subsequent increase in erythrocyte production will return oxygen delivery to oxygen-consuming tissues to normal [12].

Interestingly, the redox reaction described above is sensitive to reactive oxygen species (ROS) generated by the mitochondrial electron transport chain complexes or by NADPH oxidases [16]. Metabolic disturbances such as hypoglycemia and strong neuronal depolarization generate these ROS that may increase epo expression through HIF [21]. These findings illustrate that the regulation of epo production is a complex multifactorial process and that many factors other than simply hypoxia affect its synthesis and remain to be elucidated.

Epo production is affected by aging. The Baltimore Longitudinal Study of Aging reports that with normal aging, circulating epo levels increase quite dramatically after age 70 and that this rise represents a physiological response to maintain adequate red blood cell production [22]. This suggests that with aging red blood precursors may need more stimulation to differentiate to mature red cells as human age. Additionally, epo receptors outside of the hematopoietic system in the heart and in blood vessels may also require more intense stimulation to exert some of the positive non-hematopoietic effects on the body.

Hematopoietic vs. Non-hematopoietic Effects of Epo

The benefits of epo therapy are wide reaching, from stimulation of bone marrow to protection of the heart, blood vessels, and the brain (Table 15.1). Within the hematopoietic system, epo stimulates erythrocyte production. Epo binds to its receptor, EPOR, on the surface of committed erythroid progenitors within the bone marrow [23]. The activated receptor initiates a cascade that inhibits apoptosis of erythroid cells and increases their growth and development [23].

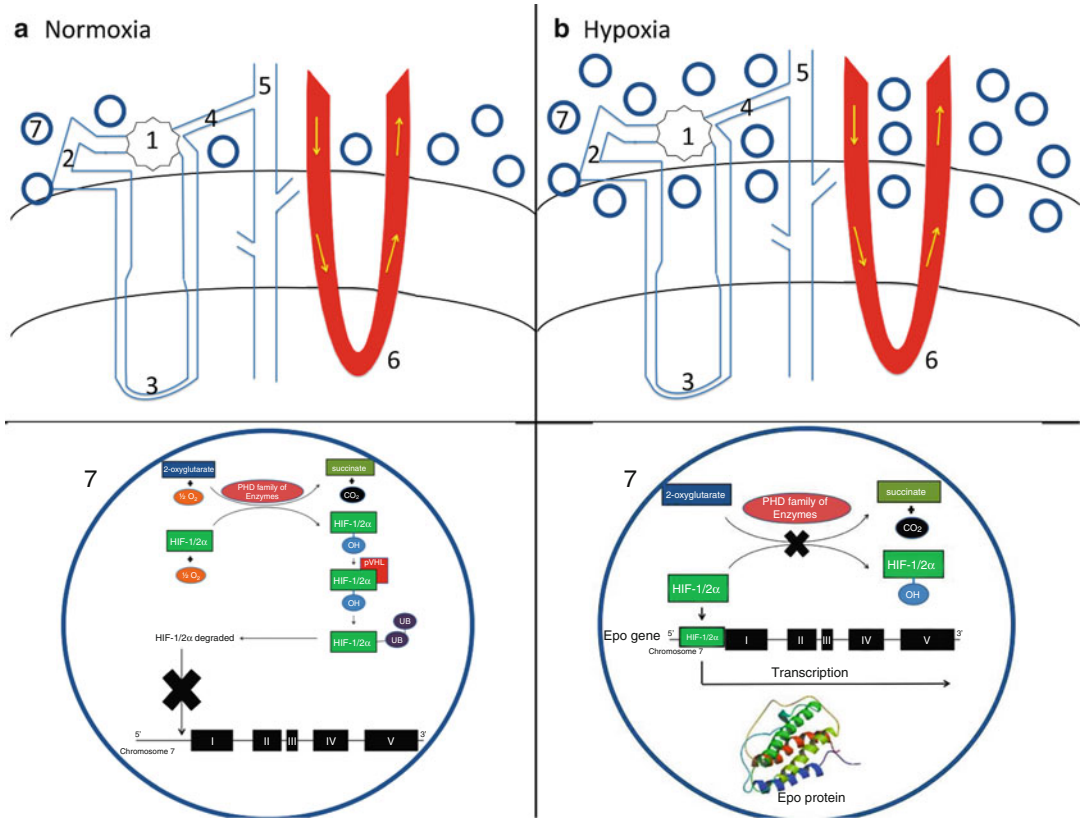

Fig. 15.1 Epo synthesis depends on presence of oxygen. Epo synthesis pathway [(1) Glomerulus, (2) proximal convoluted tubule, (3) loop of Henle, (4) distal convoluted tubule, (5) collecting duct, (6) Vasa recta capillaries, (7) REPOS cells]. (**a**) *Top panel* shows juxtaglomerular nephron. In normoxic conditions, REPOS cells are found in deep cortex. *Bottom panel* shows REPOS cell. In presence of oxygen, HIF is degraded and Epo is not made. (**b**) *Top panel* shows juxtaglomerular nephron. In hypoxic conditions, REPOS cells are more numerous and spread to superficial cortex and outer medulla. *Bottom panel* shows REPOS cell. In hypoxic conditions, HIF is not degraded. HIF acts as a transcription factor for the Epo gene. Epo protein is made (adapted from Wenger RH, Hoogewijs D. Regulated oxygen sensing by protein hydroxylation in renal erythropoietin-producing cells. American Journal of Physiology Renal physiology 2010;298:F1287–96 and Lin FK, Suggs S, Lin CH, et al. Cloning and expression of the human erythropoietin gene. Proceedings of the National Academy of Sciences of the United States of America 1985;82:7580–4)

Upon epo stimulation, red cell production can increase 4–5 times within a 1–2-week period [24]. When erythrocyte demands are high and plasma epo is high, large numbers of reticulocytes, immature erythrocytes, are released into blood to meet demand. At rapid erythrocyte production rates, more than 30 % of circulating erythrocytes are in the reticulocyte stage [25]. As new erythrocytes are produced, they move into the bloodstream and increase the oxygen-carrying capacity of blood. In normal human subjects, epo-induced increases in hematocrit do not significantly raise total blood volume because epo also causes a decrease in plasma volume. Epo downregulates the renin-angiotensin-aldosterone system, thereby reducing plasma volume [26], keeping the total blood volume nearly the same [27]. Plasma volume regulation may be especially important in heart failure patients, in whom a reduced plasma volume decreases preload and can normalize the hemodynamic workload of the heart.

The raised hematocrit that occurs with epo therapy also increases blood viscosity.

Table 15.1 Hematopoietic and non-hematopoietic actions of erythropoietin

Actions of erythropoietin	
Hematopoietic	Non-hematopoietic
Stimulate erythrocyte production	Promote cardiac development
Increase hematocrit	Promote endothelial progenitor cell homing to myocardium
Increase blood viscosity	Promote cardiomyocyte neovascularization
Stimulate leukocyte precursors	Prevent cardiomyocyte apoptosis
Increase platelet counts and platelet reactivity	Decrease reperfusion injury
Stimulate thrombopoiesis	Decrease fibrosis
	Decrease inflammatory cytokines
	Decrease oxidative damage
	Stabilize endothelium
	Improve recovery after stroke

Blood viscosity is estimated by the following formula: whole blood viscosity = $[0.12 \times h] + [0.17 \times (p - 2.07)]$, where h is hematocrit (%) and p is plasma protein concentration (g/dL) [28]. In one study, the blood viscosities predicted from this equation approximated closely the actual observed viscosities in 53 studied subjects [28]. While plasma protein concentrations as well as the charge and shape of plasma proteins determine blood viscosity [28], the hematocrit plays the more substantial role in determining viscosity (e.g., a 50 % increase in hematocrit at a constant protein concentration raises viscosity almost 20 times more than a fifty percent increase in plasma proteins at a constant hematocrit). From a clinical standpoint, high blood viscosity heightens risk of cardiovascular events including myocardial infarction and stroke. Hyperviscous blood reducing the heart's maximal cardiac output and in patients with heart failure can further deteriorate the pumping action of the heart [29].

In addition to stimulating erythrocytes, epo has also been shown to affect production of leukocytes [26]. A human study in which infants were treated with epo found that neutrophil progenitor counts did not fall, lending support to the idea that epo-mediated erythropoiesis does not divert pluripotent hematopoietic stem cells into the erythroid line at the expense of myeloid precursors [30]. In adults, epo stimulates an increase in CFU-GEMM, the precursor of granulocytes, platelets, red cells, and eosinophils, as well as CFU-GM, the precursors of granulocytes [31, 32]. Interestingly, epo also affects platelet reactivity and thrombopoiesis. In a human study, epo promoted the synthesis of increased numbers of platelets, elevating platelet count by 15 % [33]. The higher platelet count is probably induced by epo-induced stimulation of platelet progenitor cells, CFU-GEMM. Epo also enhances platelet reactivity, thereby highlighting the potential adverse effects of epo on patients with cardiovascular risk factors [33].

The effects of epo extend beyond its hematologic stimulation of erythrocytes to cardiovascular protection. From a developmental standpoint, epo is essential for blood vessel development and heart maturation. EPOR mRNA is expressed in vasculature and cardiomyocytes [34]. Deletion of epo or EPOR mRNA during embryogenesis leads to angiogenic defects and a lethal embryonic phenotype [35]. In blood vessels, epo stabilizes endothelial structures and strengthens cell–cell and cell–matrix contacts, thereby solidifying vascular integrity [36, 37]. EPOR is also necessary for normal cardiac development. Mice deficient for epo and EPOR exhibited cardiac structural impairment, including ventricle hypoplasia [38], an abnormal interventricular septum [39], and unattached myocardial leaflets [39], while expression of human EPOR in the same mice restored normal heart development [40]. This study suggests that expression of human EPOR can rescue organ defects observed during embryogenesis. Whether epo signalling is abnormal in various human congenital heart diseases (e.g., hypoplastic left heart syndrome (HLHS)) has not to our knowledge been adequately investigated and whether therapy has any role awaits further investigation.

Not only is epo invaluable in development, but it also targets some of the pathophysiological cardiac changes associated with normal aging. Data from longitudinal studies of humans such as the Baltimore Longitudinal Study of Aging (BLSA) have provided vital insights into normative

age-related cardiovascular changes [41]. On a cellular level, the number of ventricular myocytes declines with normal aging. This is the result of apoptosis that results from alterations in mitochondrial pathways, such as the cytochrome c-mediated pathway, in which proteins form complexes that cause large-scale DNA fragmentation and chromatin condensation [42]. Mitochondria both release free radicals that damage tissues directly and fall victim to free radical damage that they themselves generate, leading to mtDNA injury, dysfunctional proteins in electron transport chain complexes, and generation of more free radicals [42]. Indeed, the concentration of mitochondrial antioxidant enzymes in heart tissue increases with age, suggesting an adaptive response to chronic reactive oxygen species exposure and lending support to the importance of mitochondria and free radicals in age-related myocardial changes [42].

Due to the magnitude of cardiac cell loss, during which the initial ventricular myocyte population decreases by almost 30 % as the heart ages, remaining myocytes hypertrophy [43] without concomitant increase in blood supply. Here, cells increase in size, yet their growing need for oxygen may not be met. Myocyte hypertrophy contributes to altered myocardial structure, namely, left ventricular hypertrophy. Increases in interstitial collagen content and amyloid depositions also contribute to impaired left ventricular (LV) relaxation [43, 44]. The rate of early diastolic filling decreases [44], increasing reliance on atrial augmentation of ventricular filling, such as more active atrial emptying [45]. Importantly, distinguishing between disease-induced and age-related changes in the heart is essential but often difficult to do practically because of the confounding effects of the development of disease and effects of lifestyle changes on the aging cardiovascular phenotype. Epo targets pathophysiological changes in older adults regardless of whether the changes were caused by heart failure or by normal aging.

Epo may improve cardiac function in older adults mainly by two closely tied mechanisms: promotion of blood vessel development and protection of cardiomyocytes from apoptosis. Epo protects the ischemic and infarcted mouse heart by inhibition of programmed cell death, thereby preserving myocardial cells in ischemic zones of the heart and enhancing contractile function [46], mitigating permanent muscle damage and accelerating LV remodeling [47]. Markedly high levels of proteins AKT and STAT3 have been identified in cardiomyocytes highly resistant to apoptosis. Epo administration has been shown to result in a positive transactivation loop between two signaling pathways involving the proteins, AKT/NF- κB and Jak2/Stat3, promoting higher levels of AKT and STAT3 and thereby affording cardioprotection [48]. These cardiac benefits of epo treatment have sparked enthusiasm in discerning the molecular pathways involved in regulating the processes involved in myocardial and vascular signaling that occur with normal aging or during a cardiac insult, especially for older adults who exhibit a phenotype that is characterized by a marked susceptibility to the development of heart failure [49]. Because myocardial infarctions (MIs) are a major cause of heart failure, excitement surrounding epo use in heart failure initially emerged from studies of epo administration in the setting of a myocardial infarction aimed at reducing myocardial damage. A study by van der Meer and colleagues found that epo treatment immediately post MI induced neovascularization and reduced infarct size, while treatment 3 weeks post MI once every 3 weeks improved cardiac performance [50]. When myocardial cells hypertrophy without proportional increase in blood supply, epo can increase VEGF and endothelial progenitor cell (EPC) homing to the myocardium, thereby improving blood supply according to increased demand [51]. Here, while it is unclear whether heart function is improved by protecting cardiomyocytes or by stimulating coronary blood vessel development and fortification alone, it is most likely the combination of both mechanisms that has protective effects on the cardiovascular system.

Another proposed mechanism of improvement of cardiovascular function is mitigation of cytokines and inflammation. In a recent study, epo treatment during post-MI heart failure improved heart function in a murine model by

reducing inflammatory cytokines and oxidative damage through activation of the PI3K/Akt and Jak/Stat cellular signaling pathways [52]. Increased inflammatory cytokines and oxidative stress are correlated with poor prognosis after MI and are also involved with continuous myocardial remodeling post-MI which contributes to heart failure [53, 54]. Furthermore, epo attenuates post-MI reperfusion injury and fibrosis by reducing levels of one particular cytokine, TGF-β1 [52], sustained expression of which may lead to LV remodeling, heart failure [55], and heart tissue fibrosis [56]. Despite high expectations generated by these findings from basic studies, however, epo failed to reduce infarct size in human trials [57]. These results were particularly disappointing because not only was epo ineffective, it increased adverse outcomes experienced by patients, including doubled incidence of microvascular obstruction and increased LVEDV and LVESV [57]. While these reports indicate that epo trials in this setting for MI will probably not be repeated due to safety concerns, interest in the use of lower doses of epo post-MI shows promise [58].

Brain cells produce epo and express EPOR [59]. While astrocytes are the main producers of epo, both astrocytes and neurons express epo mRNA in response to hypoxia [60]. Studies in animal models have shown that brain epo contributes to neuron survival in ischemic conditions [61]. Interestingly, epo mediates its neuroprotective effects via both local and systemic infusion. In a study in which the middle cerebral artery in mice was occluded to simulate stroke, epo infusion into cerebroventricles slowed some of the hallmarks of loss of brain function, such as cortical infarction and place navigation disability [62], a mechanism by which animals orient themselves in novel environments using only proprioception and vestibular receptors [63]. Intraperitoneal epo treatment in animal models with spinal damage and retinal ischemia–reperfusion injury also produced neuroprotective effects [64, 65]. These experiments speak to the permeability of the blood brain barrier to epo. Given the role of epo in neuroprotection, interest in the drug's role in reducing risk of dementia has soared. A study by Kumar and colleagues found that epo reversed learning and memory deficits that were induced in rats by administration of DNA damaging agents [66]. The mechanism by which epo may improve learning and memory is hypothesized to be by regulating the plasticity of the neuronal synapse [67]. In a randomized double-blinded placebo-controlled human study of 40 patients in which epo was administered within 8 h of onset of stroke, patients treated with epo had significantly better functional outcomes, marked by improvements in the NIH and Scandinavian stroke scales, as well as less pronounced neurologic damage, marked by improvements in a marker of brain injury [68]. The effects of epo on the brain hold promise for treatment of neurologic and psychiatric disease and suggest that epo may in the future be approved as a therapy for neurologic emergencies. Moreover, although epo is best known for its hematopoietic properties, the extensive list of its non-hematopoietic actions, including those on the central nervous system, warrants further research into its pleiotropic actions (Table 15.1).

Restricted exercise capacity is one of the chief manifestations of heart failure and varies directly with severity of disease [69]. As such, measurement of exercise capacity provides clinicians with information about the maximum ability of the cardiovascular system to deliver oxygen to muscle and for muscle to extract oxygen from blood. Exercise capacity is quantified by peak VO_2, or the maximal oxygen uptake [69]. Several clinical trials with epo in patients with anemia and heart failure found significantly increased peak VO_2 [70, 71]. However, questions remain about physiological mechanisms that mediate increased exercise capacity and the relative contribution of each process to the increased VO2. Does epo boost exercise capacity via its hematopoietic effects, like increased oxygen delivery from increased hemoglobin concentration, or are non-hematopoietic mechanisms the dominant mechanisms by which exercise capacity is increased? Mancini and others found that increased oxygen delivery, not muscle oxidative capacity and vessel vasodilatory function, accounted for increased peak VO_2 [72]. Data from a 2012 animal study suggest that epo

may have muscle-protecting effects in normal mice during exercise. Epo-deficient mice, who had subnormal exercise capacity and a significantly lower VO_2 than controls, also experienced expression changes in genes related to muscle hypoxia, suggesting that physiological epo concentrations may have a muscle protective effect via the action of pathways not yet determined [73]. Epo-induced improvements in exercise capacity are likely mediated by both hematopoietic and non-hematopoietic factors. Increased hemoglobin levels may decrease oxidative stress, thereby improving endothelial cell function, increasing cardiac perfusion, and improving oxygen delivery to cardiomyocytes. Correction of anemia, counteraction of harmful effects of neurohormonal and inflammatory pathways, and enhancement of cardiac contractile function may all underlie the beneficial effects of epo on exercise tolerance.

Results of Clinical Trials

Many trials have evaluated the use of erythropoietin in patients with heart failure (Table 15.2). Trials are of modest size (subject range $n=23$ to $n=319$ people), usually with oral or IV supplementation of iron. While it appears that these studies encompass patients with a wide range of ages and ejection fractions and include trials with different primary outcomes, several trends emerge from these studies. All of the clinical trials, except one, are in patients with systolic heart failure (e.g., HFLEF), and only one trial to date has been conducted specifically in the population with heart failure and a normal/preserved EF (e.g., HFNEF/HFPEF, aka DHF). The disproportionately high number of studies on systolic heart failure (Table 15.2) to date has left the role of erythropoietin-stimulating agents for subjects with HFPEF, which accounts for more than 50 % of persons with chronic heart failure [74], an underinvestigated clinical arena. Not only are there fewer published data concerning the incidence of heart failure among patients with HFPEF, but the average age of the patients enrolled in trials of epo to date is middle age, with those over the age of 75 years not typically enrolled. Thus, despite the fact that the average age of patients with heart failure being >75 years, none of the ten completed trials in systolic heart failure had a recruited population that was on average 75 years of age, and only one trial reported how many patients were older than 75 (Table 15.2).

Most of the studies conducted to date evaluated the effect of epo on cardiovascular health and quality of life by addressing both clinical and echocardiographic endpoints (Table 15.2). While the primary outcomes often vary, the essential question to be answered is this: does epo exert a positive effect on patients with heart failure and anemia? Several studies have found that epo positively impacts clinical outcomes, such as exercise tolerance and NYHA class. Palazzuoli [75] noted improvements in NYHA functional status, duration of exercise and distance walked, as well as oxygen use during exercise in patients treated with epo and oral iron compared with oral iron alone. The study by Ghali et al., however, the largest randomized double-blind study to date to determine the efficacy of anemia treatment in CHF, did not find increased exercise tolerance [76]. Others evaluated echocardiographic estimates as evidence of epo efficacy and found improved ejection fraction, reductions in end-diastolic volume and end systolic volume, pulmonary artery pressure, and mitral regurgitation, among others. Most studies agree that epo has a significant effect on functional capacity, ventricular structure, exercise tolerance, and quality of life.

Meta-analyses have confirmed that patients with systolic heart failure and anemia can benefit from epo therapy. In Kotecha's meta-analysis, in which 11 randomized controlled trials were studied, epo treatment significantly improved exercise duration by 96.8 s [95 % CI 5.2–188.4], 6-min walk distance by 69.3 m [95 % CI 17.0–121.7], peak oxygen consumption by 2.29 mL/kg/min, reduced NYHA class by 0.73 points, increased ejection fraction by 5.8 %, decreased BNP by 227 pg/mL, and improved quality of life assessments [77]. The authors also show that the potential clinical impact of epo is similar to that of other therapies shown to improve ejection fraction, like carvedilol, an alpha/beta blocker,

Table 15.2 Endpoints and outcomes of prospective, randomized, placebo-controlled trials in heart failure

Results of trials on erythropoietin treatment of patients with heart failure and anemia											
Study	Type of trial	Trial design	Number of patients	Age (average)	Ejection fraction (% average)	Iron	Follow-up time	Primary endpoint	Primary outcome	Secondary endpoint	Secondary outcome
HFREF											
Cleland 2005 [87]	Prospective	Randomized placebo controlled	63	73	33	none	71 days	Change in [Hb]	No change in Hg after 40 days with two 0.75 μg/kg IV doses given 29 days apart. Sustained increase in Hb after 40 days with one 2, 3, or 5 μg/kg SC dose	Pharmacokinetics	Exposure to epo (measured with area under serum concentration curve), clearance (CL/F), peak serum concentration (C_{max}), time of peak serum concentration (T_{max}), half life ($T_{1/2}$) over dose range of 0.75 μg/kg to 5 μg/kg similar in CHF and healthy patients
Cosyns [100]	Prospective	Randomized placebo controlled	28	68	31	None	NR	Mitral regurgitation	Decreased mitral regurgitation as measured by effective regurgitant orifice area, E/Em ratio	LV remodeling	Decreased LVEDV, LVESV Increased LVEF, LV systolic performance (as measured by LV dP/dT)
Ghali [76] (STAMINA-HeFT)	Prospective	Randomized placebo controlled	319	69 ± 11	36 ± 10	Oral	52 weeks	Exercise duration at 6 weeks	Increase in treadmill exercise duration in treatment group as compared to placebo group (24.7 vs. 12.5 s increase, respectively) that was not significant	NYHA class Quality of life	No decrease in NYHA class in treatment compared to control group (−0.19 vs. −0.13 decrease, respectively) No improvement in quality of life in treatment compared to control group (Patient Global Assessment of Change 71 % vs. 71 %; Minnesota Living with Heart Failure Questionnaire −9.3 vs. −7.1 decrease, respectively)

(continued)

Table 15.2 (continued)

Results of trials on erythropoietin treatment of patients with heart failure and anemia										
Study	Type of trial	Trial design	Number of patients	Age (average)	Ejection fraction (% average)	Iron	Follow-up time	Primary endpoint	Primary outcome	Secondary endpoint	Secondary outcome
Kourea [70]	Prospective	Randomized placebo controlled	41	69.1	27	Oral	3 months	Quality of life	KCCQ functional increased in treatment as compared to control group (21 vs. 2 point score increase, respectively) and KCCQ overall (21 vs. 5 point increase, respectively)	Emotional stress	Decrease in BDI in treatment as compared to control group (−5 vs. −2 point decrease, respectively) Decrease in SDS in treatment as compared to control group (−9 vs. +5 point change, respectively)
Mancini [72]	Prospective	Randomized placebo controlled	23	58.3	23	Oral	3 months	Exercise tolerance	Peak VO_2 increased in treatment as compared to control group (1.7 vs. $^{-}0.5$ $mL \cdot kg^{-1} \cdot min^{-1}$ change, respectively) and 6MWD increased in treatment as compared to control group (67 vs. −83 m change, respectively)	Mechanism of change in exercise tolerance	No change in NIR recovery time in treatment compared to control group (−3 vs. 6 s, respectively) No change in $T_{1/2}$ VO_2 recovery time in treatment compared to control group (−4 vs. −2 s, respectively) No change in post-ischemic forearm resistance in treatment compared to control group (0.4 vs. 0.3, respectively)
Palazzuoli [75]	Prospective	Randomized placebo controlled	40	73.4	28	Oral	12 months	Not specified (cardiac function)	Increased exercise distance in treatment as compared to control group (78 vs. −19 m change, respectively) Increased peak VO_2 in treatment as compared to control group (2.3 vs. −0.5 mL/kg change, respectively)	Not specified (serum creatinine, creatinine clearance, BNP)	Decreased serum creatinine in treatment as compared to control group (−0.8 vs. −0.2 mg/dL change, respectively) Increased creatinine clearance in treatment as compared to control group (7 vs. 2 mL/min increase, respectively) Decreased BNP in treatment as compared to control group (−297 vs. −89 pg/mL decrease, respectively)

Palazzuoli [88]	Prospective	Randomized placebo controlled	56	73.0	32	Oral	12 months	Improved LV dimensions	Decreased LVSD in treatment as compared to control group (−2.3 vs. 0.7 mm, respectively) Decreased LVSV in treatment as compared to control group (−6.7 vs. 2.6 ml/m [2], respectively)	Cardiac events (sudden death, hospitalization, myocardial infarction) LVEF LVM	Decreased cardiac events in treatment as compared to control group (4 vs. 8, respectively) Increased LVEF in treatment as compared to control group (4.5 % vs. −1.3 %, respectively) Decreased LVM in treatment as compared to control group (−7.9 vs. 2.6 g/m [2], respectively)
Parissis [71]	Prospective	Randomized placebo controlled	32	71.0	27	Oral	3 months	Exercise tolerance	Increased 6MWD in treatment as compared to control group (31.7 % vs. −21.9 % change, respectively)	Cardiac function	Increased LVEF in treatment as compared to control group (23.8 % vs. –9 % change, respectively) Increased RVEF in treatment as compared to control group (15.6 % vs. −4.4 %, respectively) Decreased ESWS in treatment as compared to control group (−21.4 % vs. −4.8 %, respectively)
Ponikowski [89]	Prospective	Randomized placebo controlled	41	71 ± 7	NR	Oral	26 weeks	Exercise tolerance	No increase in exercise duration or peak VO_2 in treatment as compared to control group	Quality of life	Increased PGA in treatment as compared with control group (79 % vs. 41 % increase, respectively)
Silverberg [90]	Prospective	Randomized placebo controlled	32	73.8	NR	IV	12 months	Cardiac function	Increased LVEF in treatment as compared to control group (5.5 % vs. −5.4 % change, respectively)	NYHA class	Decreased NYHA class in treatment as compared with control group (−42.1 % vs. −11.4 % decrease, respectively)

(continued)

Table 15.2 (continued)

Results of trials on erythropoietin treatment of patients with heart failure and anemia

Study	Type of trial	Trial design	Number of patients	Age (average)	Ejection fraction (% average)	Iron	Follow-up time	Primary endpoint	Primary outcome	Secondary endpoint	Secondary outcome
RED-HF	Prospective	Randomized placebo controlled	2278	72	30	Oral (73 %), IV (5 %)	60 months	Composite of death from any cause or hospitalization for worsening heart failure	1.01; 95 % confidence interval, 0.90 to 1.13; $p = 0.87$	Secondary outcomes were death from any cause, the composite of death from cardiovascular causes or first hospitalization for worsening heart failure and the change from baseline to 6 months in the Overall Summary Score and Symptom Frequency Score on the Kansas City Cardiomyopathy Questionnaire (KCCQ)	No significant between-group difference in any of the secondary outcomes. Fatal or non-fatal stroke occurred in 42 patients (3.7 %) in the darbepoetin alfa group and 31 patients (2.7 %) in the placebo group ($p = 0.23$). Thromboembolic adverse events were reported in 153 patients (13.5 %) in the darbepoetin alfa group and 114 patients (10.0 %) in the placebo group ($p = 0.01$). Cancer-related adverse events were similar in the two study groups

HFPEF											
Maurer [98]	Prospective	Randomized placebo controlled	56	77	58	Oral	6 months	LVEDV	Changes in end-diastolic volume (–6 ± 14 versus –4 ± 16 mL; $p = 0.67$) at 6 months did not differ between epoetin alfa and placebo	Exercise tolerance (as measured by peak VO_2, 6MWT), quality of life (as measured by KCCQ), LV structure (volume and mass), LV function (stroke volume, cardiac output), adverse outcomes (hospitalization)	Declines in stroke volume (–5 ± 8 versus 2 ± 10 mL; $p = 0.09$) without significant changes in left ventricular mass were observed with epoetin alfa. Changes in 6-minute walk distance (16 ± 11 versus 5 ± 12 m; $p = 0.52$) did not differ. Although quality of life improved by the Kansas City Cardiomyopathy Questionnaire and the Minnesota Living with Heart Failure Questionnaire in both cohorts, there were no significant differences between groups. Among those able to exercise peak VO2 increased in epoetin alfa (+1.0 ± 0.5 versus −1.2 ± 0.6 mL/kg per minute; $p < 0.03$; 95 % confidence interval, 0.67 to 3.73 ml/kg/min)

E/Em ratio = early mitral inflow velocity compared to peak mitral annulus velocity, *ESWS* End systolic wall stress, *KCCQ* Kansas City Cardiomyopathy Questionnaire, *LVEF* Left ventricle ejection fraction, *LVDV* Left ventricle diastolic volume, *LVDD* Left ventricle diastolic diameter, *LVSV* Left ventricle systolic volume, *LVSD* Left ventricle systolic diameter, *LVM* Left ventricle mass, *NIR* Near-infrared spectroscopy, determines rate of skeletal muscle oxidative capacity, *RVEF* Right ventricle ejection fraction

and reduce BNP levels, similar to enalapril, an ACE inhibitor [77]. Here, epo targets several manifestations of heart failure, not anemia alone. Another meta-analysis also found that epo therapy leads to a significant increase in exercise capacity (as measured by 6MWD and peak VO_2) and quality of life (as measured by MLHFQ and KCCQ scores) [78]. Ejection fraction and patient global assessment (PGA), a patient's ranking of how one feels overall, were both improved. Ejection fraction increased by 7.55 %, [95 % CI 3.20, 11.89] and PGA increased by 2.55 points [95 % CI 0.98, 6.641] [78]. Clinical and functional echocardiographic measures suggest a beneficial effect of epo in subjects with systolic heart failure and anemia. However, these results were not confirmed in the RED-HF trial which did not show a clinical benefit of aranesp in systolic heart failure [79].

Hazards of Erythropoietin Use

A popular physician database reports the serious adverse effects of ESAs to be increased mortality, tumor progression, thromboembolism, myocardial infarction, stroke, congestive heart failure, hypertension, seizures, hypersensitivity reaction, and pure red cell aplasia [80]. The warnings are reflective of a wave of apprehension over results of clinical trials on ESA use in anemic CKD patients that showed elevated risk of cardiovascular events, such as stroke and all-cause mortality [81, 82]. These findings were so disturbing that in 2011, the US Food and Drug Administration recommended more conservative dosing guidelines for ESA use in CKD patients with anemia and added modified recommendations for the drug's administration in the boxed warning and other sections of the package insert. The package insert warns that ESAs increase the risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events [83].

Since then, however, the positive effects of ESAs on heart failure patients have also provoked researchers to examine the drug's hazards in this new population, contributing to a large data set on hazards of ESAs in CKD and heart failure populations. These serious adverse events and their frequency of occurrence per 100 person years in placebo-controlled studies are shown in Table 15.2. Data for CKD patients is obtained from TREAT study, the only large placebo-controlled ESA study ($n=4{,}038$). Pooled adverse effects for nine heart failure studies [74, 75, 81, 89–92] ($n=647$) are also shown.

In the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), a large placebo-controlled analysis of 4,038 individuals with CKD not on dialysis, patients were assigned to either ESA or placebo groups (ESA group target hemoglobin 13 g/dL) [81]. The primary endpoints were the composite outcomes of death or a cardiovascular event (nonfatal MI, CHF, stroke, or hospitalization for myocardial ischemia) and of death or end-stage renal disease. The results showed that not only did epo use not reduce the risk of death, a cardiovascular event, or a renal event, but it was associated with an increased risk of stroke [81]. In the treatment group ($n=2{,}012$), 101 patients had a stroke, as compared to the placebo group ($n=2{,}026$) in which only 53 people had a stroke [81]. Although hypertension, myocardial infarction, and mortality were associated with both the treatment and control groups, stroke was the only adverse outcome in which ESA-treated patients had greater risk as compared to placebo-treated patients (Table 15.3). Additional analysis of the TREAT trial [84] has suggested that hypo-responders to ESA therapy, which more often occurs in older adult women with evidence of chronic inflammation, are the population that is more likely to suffer adverse consequences from therapy with ESAs, particularly stroke.

Another important trial that raised doubts about epo's safety of use was Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR), one of the earliest randomized controlled trials of epo use in CKD patients. In this non-placebo-controlled CKD 3-year clinical trial, anemic CKD patients not on dialysis with hemoglobin <11 g/dL were assigned to either an 11.3 g/dL or 13.5 g/dL target hemoglobin group. Patients in the higher target group were found to

Table 15.3 Hazards of erythropoietin use in patients with chronic kidney disease and heart failure

Adverse events reported in placebo-controlled trials with ESAs				
	Chronic kidney disease trials[a]		Heart failure trials[b]	
Adverse event	ESA (events/100 person years)	Placebo (events/100 person years)	ESA (events/100 person years)	Placebo (events/100 person years)
Hypertension	6.0	5.6	48	6
Exacerbation of heart failure	2.5	2.8	106	262
Renal failure	4.2	4.1	15	0
Stroke	1.3	0.7	2	2
Myocardial infarction	1.6	1.6	2	13
Mortality	5.1	4.9	57	82
Ischemic attack (transient and myocardial)	0.5	0.6	2	58

[a]TREAT data only
Event rate per 100 person years was obtained in the following way. Number of events in each group per 100 people, *n*, was divided by the length of each study. Event rates from all nine studies were added to obtain events/100 person years
[b]Pooled data from nine randomized, placebo-controlled trials [72, 73, 78, 87–92]

have increased relative risk of all-cause mortality [82], and CHOIR researchers were forced to terminate the prematurely. The initiation of this study without a control group speaks to the confidence with which epo was administered and the lack of knowledge about its adverse effects. One subsequent analysis of CHOIR [85] found that epo dosing was an important variable in the trial. Many patients in higher hemoglobin target groups also received higher doses of drug because they responded to the drug more slowly than other patients in the same group, bringing to the forefront the issue of safe dosing algorithms for treatment. Other analyses of CHOIR that focused on heart failure found that within the higher target hemoglobin group, patients with heart failure did not experience increased risk of all-cause mortality [86, 87]. It is interesting that while the higher target hemoglobin group had more exacerbations of heart failure as a whole, subgroup analysis showed that patients with heart failure in low and high target groups had similar occurrence of heart failure exacerbation [86]. This seems to suggest that certain comorbidities such as heart failure mitigate risk of drug administration and underscore the need for trials of epo in heart failure populations.

Trials in which epo is prescribed to target heart failure patients fail to identify an absolute risk of death or serious adverse cardiovascular effects to date (Table 15.3). Epo was well tolerated in all studies [71, 72, 75, 76, 88–91]. Nonserious effects experienced included gastrointestinal disorders [88], injection site reactions [88], neurologic symptoms [89, 90], breathing abnormalities [76, 88], headache [88], connective tissue [89], and musculoskeletal symptoms [89]. None of the studies reported a significant difference between controls and treatment groups in death or serious adverse events in individual analyses. Serious adverse effects were considered not related to epo administration because they were experienced in both placebo and treatment groups. Meta-analyses support these findings. Kotecha found a reduction in all-cause mortality, as well as no significant increase in adverse events and a trend of lower MI and other thromboembolic events [77]. Jin also found a lower trend of mortality in epo-treated groups [78]. Pooled data show that ESA and placebo groups had similar (exacerbation of heart failure, MI, mortality) and in some cases identical (stroke) effects on patients (Table 15.3). Interestingly, only hypertension was shown to be of increased risk in treated patients. Hypertension increased risk by an impressive 8 times more events/100 person years in the ESA group as compared to placebo. This finding upon pooled examination that was not found in individual analyses is not surprising, but rather indicative of the relatively small patient pool in which ESA

hazards have been evaluated ($n=647$, 1 year maximum study length) as compared with TREAT, a 4-year study with more than 4,000 patients. Such findings are supported by the results of RED-HF which demonstrated no significant difference in fatal or nonfatal stroke but a higher rate of thromboembolic adverse events in the darbepoetin alfa group compared to placebo. Table 15.3 elucidates that on average the risk of adverse outcomes is much higher in heart failure population than among subjects with CKD, but that some of the dangers of therapy observed in CKD populations may not be present in the heart failure population. Such findings are supported by the results of RED-HF which demonstrated no significant difference in fatal or nonfatal stroke, no effect on heart failure hospitalizations but a higher rate of thromboembolic adverse events in the darbepoetin alfa group compared to placebo.

Emerging Erythropoietin Analogues

An emerging clinical application of epo is attainment of epo-mediated cardioprotection without increase in hemoglobin levels. As previously described, in addition to its hematopoietic effects, epo possesses pleiotropic effects besides correction of anemia, and EPOR has been detected in several non-hematopoietic tissues including the heart [34] and brain [59] . The impact of epo on improvement of cardiac function in heart failure is detailed in Table 15.2. However, it is possible that the epo-induced increase in hemoglobin may counteract the beneficial effects of epo by raising viscosity, increasing resistance to flow, and inducing hypertension, thereby confounding cause and effect relationships. Two non-hematopoietic derivatives of epo have been developed to mediate tissue protection without some of the unwanted effects on hematocrit.

Asialoerythropoietin (asialoEPO) is a non-hematopoietic derivative of epo that is produced by removing sialic acid moieties from the molecule [92]. These moieties are responsible for epo's delayed clearance [92], and their removal modifies epo's half-life such that asialoEPO cannot significantly stimulate hematopoiesis [92]. Accelerated clearance, however, does not interfere with asialoEPO's tissue-protective effects. In a recent study [93] in mice who underwent nephrectomy that caused renal dysfunction, anemia, and cardiac dysfunction and who were administered either saline, epo, or asialoEPO, both epo- and asialoEPO-treated mice had significantly less left ventricular dilation, hypertrophy, as well as fibrosis, leukocyte infiltration, and oxidative damage. However, only epo-treated animals had increased hemoglobin post drug administration [93]. This study demonstrated the cardioprotective effects of asialoEPO and emphasized that improved cardiac function was not mediated through rise in hemoglobin. Within the heart failure realm, asialoEPO has also been shown to improve capillary density and therefore establish itself as an attractive agent for cardioprotection in this context [94].

Implementation of epo derivatives with different affinity for EPOR is an alternate approach to harnessing the non-hematopoietic effects of epo. CEPO, or carbamylated erythropoietin, is one such epo derivative, which binds to EPOR with low affinity, reduces its erythropoietic and procoagulant activity [92], and provides ample opportunity to determine whether epo bears hematopoiesis-independent cardioprotective effects. One study [95] found that mice and rats treated with CEPO post-MI daily for 1 week at a dose adjusted for body weight did not experience increase in hematocrit, but had reduced cardiomyocyte loss and LV wall stress without increases in LVEDP. In vitro, apoptosis induced in mice models was significantly attenuated by 35 %, an effect comparable to that of epo [95]. These findings indicate that epo-mediated prevention of cardiomyocyte apoptosis without increase in hemoglobin may explain epo's role in cardioprotection.

Non-erythropoietic derivatives of epo, such as asialoEPO and CEPO, have generated enthusiasm about safer and more effective alternatives for treatment of cardiovascular diseases in the clinical setting. Future experiments to pinpoint precisely the role of epo-mediated cardioprotection without increase in hemoglobin levels are a highly active area of study.

Potential Methods to Enhance Safety of ESA Administration in Heart Failure

The interest in the epo administration for heart failure will likely contribute to a growing database about its benefits and hazards, particularly focused on older adults who constitute the vast majority of subjects with heart failure. Accordingly, a consideration of trial design aimed at minimizing risk of ESA exposure, methods to identify patients at higher risk for adverse effects from ESAs, and greater attention to ESA dosing in clinical practice that mimic algorithms in clinical trials collectively could contribute to the principle of delivering the "right drug to the right patient at the right time."

Previous studies have highlighted that a significant percentage of subjects in clinical trials may be hyporesponsive to ESA therapy, and among such subjects the risks of therapy are higher than among responders. While randomized controlled trials aim to provide clinically relevant evidence to physicians, they may fail to identify this cohort of hypo-responders and thus expose patients to the risks of ESAs without potential benefits. The use of pre-randomization run-in periods in randomized clinical trials can be employed to identify a cohort of subjects who respond to therapy (e.g., a >1 g/dL increase in hemoglobin after 4 weeks of therapy). Only such subjects would be permitted to enroll in the randomized portion of the clinical trial. Such designs can be employed in trials of ESA to eliminate long-term exposure to those subjects who do not respond to therapy and have been shown to have the potential to be harmed [84]. This is particular appealing with a therapy such as ESAs that are associated with particularly high costs. Obviously, these benefits need to be weighed against the loss of applicability and the effect on estimates of treatment effect [96].

Alternatively, identification of hypo- or nonresponders to epo therapy prior to its administration would be a vital exclusion for enrollment in a clinical trial. Unfortunately, while hyporesponders to therapy are more likely to be women, to have a history of cardiovascular disease, to be treated with aldosterone antagonists, and to have a lower serum potassium level and higher CRP level than patients with a better initial response [84], none of these factors have enough sensitivity nor specificity to be used as exclusion criteria for a clinical trial of ESAs. However, since a significant percentage of subjects with systolic heart failure have a hemodilutional basis of their anemia (e.g., an expanded plasma volume in the absence of a true red cell deficit) [97] and similar data may apply to subjects with HFPEF [98], it is possible that blood volume analysis would be useful in this regard. Hypo- or nonresponders could be patients who, despite the presence of low hemoglobin concentrations that meets the definition of anemia, have no red cell deficit but rather simply an expanded plasma volume, characteristics of a hemodilutional anemia. Preliminary data from a retrospective analysis of a recent study in older adult subjects with heart failure and preserved ejection fraction [99] suggests that a large proportion of patients, almost one third of total enrolled subjects, are hemodiluted and that blood volume analysis can be used to identify this fairly large nonresponsive cohort at baseline. Since no trial has yet identified a target hemoglobin level, epo dose, or dosing strategy that does not increase risks of epo therapy, and because anemic CKD patients with poor initial response to epo therapy have been shown to have higher rates of serious cardiovascular events and death with epo administration [84], recognition of patients nonresponsive to therapy is a potential method to mitigate the hazards of epo use.

Another consideration in epo administration is dosing of the drug. When the FDA recommended more conservative dosing of epo in patients with CKD to improve the safety of use of these drugs based on results of clinical trials like TREAT, the epo package insert warned of targeting hemoglobin level to greater than 11 g/dL [100]. Typically dosages in excess of 10,000 units may be prescribed on a weekly or biweekly basis in clinical practice. However, review of heart failure trials completed to date (Table 15.2) suggests that much lower dosages were required (range of 2,000 IU to 6,000 IU). Additionally, while it is reasonable to assume a dose-response effect of ESAs such that a higher dose raises hemoglobin to a greater extent, as it did in one study [88], all studies do

not support this phenomenon. For instance, a 6,000 IU dose twice a week increased hemoglobin by 1.25 g/dL from baseline at 12 months [75] in one study, but a dose of 4,000 IU dose administered once a week raised hemoglobin by 2.6 g/dL at 12 months [91]. Thus, there is much to be learned from the appropriate dosing algorithms in subjects with heart failure and concomitant anemia who receive ESAs. In general, dosing algorithms that adjust the dose based on body size, the absolute hemoglobin level, and the rate of rise from week to week [101] are most likely to achieve a similar effect and safety profile to what has been reported in recent large-scale trials.

Conclusions

Heart failure is a major challenge in medicine today. The number of people diagnosed with heart failure grows every year because people are living longer as medical care undergoes restructuring and improvement, and advances are made in the treatment of many medical conditions. However, despite the great strides that have been made in heart failure treatment with ACE inhibitors and beta-blockers, thousands of older adults live with severe progressive heart failure, a high mortality rate, frequent hospitalizations, and symptoms of severe fatigue and dyspnea. Because anemia is recognized as a common comorbidity in patients with heart failure, the use of erythropoietin within this cohort has been entertained as a potential therapy for improving quality of life. However, for this hope to be realized for older adults with heart failure, much needs to be learned including appropriate dosing algorithms and the definition of the mechanisms of erythropoietin action that are essential to clinical benefit while minimizing the effects that are harmful.

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Role of Resistin in Heart Failure in the Elderly

16

Yasuchika Takeishi

Multiple Biological Functions of Resistin

Adipose tissue is not only a store of excess energy but also a highly active endocrine organ [1–4]. Adipose tissue secretes bioactive peptides, termed "adipocytokines," which act on the function and structural integrity of various tissues through autocrine, paracrine, and endocrine mechanisms [1–4]. Increased production of adipocytokines impacts on multiple functions such as energy balance, immunity, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism, inflammation, and hemostasis, all of which are closely linked with cardiovascular diseases. Leptin, a 167-amino-acid protein, is expressed exclusively by adipose tissue. Leptin is a fundamental signal of satiety to the brain and a regulator of insulin and glucose metabolism. Adiponectin, one of the most abundant adipocytokines, is a 244-amino-acid protein produced by the apM1 gene, highly expressed in human adipose tissue. Adiponectin has anti-atherogenic and anti-inflammatory properties. Resistin is a novel cysteine-rich secretory 12.5-kDa polypeptide [5–9]. Resistin was initially identified in the adipose tissue and derived almost exclusively from fat tissue in rodents. However, it is now recognized that resistin is produced from other types of cells including macrophages [10]. Adipose expression and serum levels of resistin are elevated in animal models of obesity and insulin resistance [9]. Although functional roles of resistin are not clearly established, high serum levels of resistin impair glucose tolerance and induce insulin resistance in rats [11]. On the other hand, mice deficient in resistin are protected from obesity-associated insulin resistance [12]. A clinical study has demonstrated that plasma resistin levels are correlated with markers of inflammation and are predictive of coronary atherosclerosis in humans [13]. In addition, resistin concentrations are correlated with renal dysfunction [14] and adverse prognosis in patients with atherothrombotic ischemic stroke [15].

Circulating Concentration of Resistin in Patients with Heart Failure

Several inflammatory biomarkers including C-reactive protein, interleukin-6, tumor necrosis factor-α, and pentraxin 3 are associated with increased risk of heart failure [16]. Similarly, it has been reported that insulin resistance is observed in heart failure. Heart failure is the major and increasing health problem with a high mortality rate, because of the increase in aging population and high prevalence of heart failure in the elderly [17–19]. However, the relationship

Y. Takeishi, MD, PhD (✉)
Department of Cardiology and Hematology,
Fukushima Medical University,
1 Hikarigaoka, Fukushima, Japan
e-mail: takeishi@fmu.ac.jp

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between resistin and heart failure has not been fully understood.

Takeishi et al. initially reported the association between circulating concentrations of resistin and heart failure [20]. We prospectively enrolled 126 consecutive patients with chronic heart failure (76 men, mean age 67 ± 13 years) admitted to our hospital. Blood samples were obtained at admission to measure serum resistin levels in 126 patients with heart failure and 18 control subjects. Serum resistin concentrations were measured by a sandwich enzyme-linked immunosorbent assay (ELISA, Phoenix Pharmaceutical, Inc., Belmont, CA, USA). The etiologies of heart failure were dilated cardiomyopathy in 48 patients, ischemic heart disease in 34 patients, valvular heart disease in 20 patients, and hypertensive heart disease in 12 patients. Patients were followed up (mean follow-up 645 ± 644 days, range 29 to 1,080 days) after discharge to register (1) cardiac death, defined as death from worsening heart failure or sudden cardiac death, and (2) worsening heart failure requiring readmission. Serum resistin levels increased with advancing New York Heart Association (NYHA) functional class. Normal upper limit of resistin levels was defined as mean + 2SD value of 18 control subjects (14.1 ng/mL). There were 32 patients with high resistin level (>14.1 ng/mL) and 94 patients with low resistin level (≤14.1 ng/mL). Serum resistin levels were not correlated with body mass index and blood glucose. Serum resistin levels were not different between patients with and without diabetes mellitus. There were 31 cardiac events including 10 cardiac deaths and 21 rehospitalization due to worsening heart failure during the follow-up period. Cardiac event rate was significantly higher in patients with high resistin than in those with low resistin levels (43.8 % vs. 18.1 %, $P < 0.0036$ by chi-square test). Kaplan–Meier survival analysis also demonstrated that high resistin group showed significantly lower event-free rate than low resistin group ($P = 0.0041$ by log rank test). Next, patients were divided into four groups based on the serum resistin levels: first quartile (1.7–6.6 ng/mL, $n = 31$), second quartile (6.7–10.1 ng/mL, $n = 31$), third quartile (10.2–14.0 ng/mL, $n = 31$), and fourth quartile (14.1–60.2 ng/mL, $n = 33$). The highest fourth quartile of resistin was associated with the highest risk of cardiac events compared to other three groups (first quartile 16.1 %, second quartile 16.1 %, third quartile 22.6 %, and fourth quartile 42.4 %). To determine risk factors to predict cardiac events, we performed the Cox proportional hazard regression analyses. In the univariate analysis, serum resistin level (per one SD increase, hazard ratio [HR] 1.357, 95 % confidence interval [CI] 1.061–1.746, $P = 0.014$) as well as age, body mass index, B-type natriuretic peptide and the use of loop diuretics were associated with cardiac death and rehospitalization. Among those variables with P value of less than 0.05 in the univariate analysis, the multivariate Cox proportional hazard regression analysis demonstrated that resistin was an independent predictor for cardiac events in patients with chronic heart failure (HR 1.439, 95 %CI 1.017–2.059, $P = 0.041$). We concluded that resistin is useful for risk stratification of patients with chronic heart failure and may represent a novel link between metabolic signals and heart failure.

Although patients with heart failure develop metabolic derangements including increased adipokine levels and insulin resistance, the relation of resistin with body mass index, blood glucose, and diabetes mellitus was not evident in a study by Takeishi et al. [20]. Recently, Schulze et al. measured plasma resistin levels and homeostasis model assessment of insulin resistance (HOMA-IR) in acute decompensated heart failure ($n = 44$), chronic stable heart failure ($n = 26$), and 21 control subjects [21]. Resistin was elevated in chronic stable heart failure and increased further in acute decompensated heart failure compared to control. Similarly, HOMA-IR was increased in chronic stable heart failure and increased further in acute decompensated heart failure. HOMA-IR correlated positively with resistin levels in heart failure patients. They concluded that acute decompensated heart failure is associated with worsening of insulin resistance and elevation of resistin compared to chronic stable condition.

Association of Resistin with the Incidence of New-Onset Heart Failure

Frankel et al. have reported the association of resistin with the incidence of heart failure in 2,739 participants in the Framingham Offspring Study [22]. During 6 years of follow-up, 58 participants developed new-onset heart failure. In proportional hazard models adjusting for age, sex, blood pressure, antihypertensive treatment, diabetes, smoking, cholesterol, prevalent coronary heart disease, valvular heart disease, left ventricular hypertrophy, and estimated glomerular filtration rate, the hazard ratios for heart failure in the middle and top thirds of resistin levels were 2.89 (95 %CI 1.05–7.92) and 4.01 (95 %CI 1.52–10.57) compared to the lowest third. In the maximally adjusted model including C-reactive protein and B-type natriuretic peptide, one SD increment in resistin level (7.45 ng/mL) was associated with a 26 % increase in heart failure risk (95 %CI 1–60 %). Interestingly, concentrations of adiponectin were not related to heart failure. This was the first report demonstrating that increased circulating levels of resistin were associated with incidence of new-onset heart failure, even after accounting for prevalent coronary heart disease, obesity, insulin resistance, and inflammation.

Resistin as a Risk of Heart Failure in the Elderly

Heart failure is a common disease in the elderly [17, 18]. Its incidence approaches 10/1,000 annually after age 65, and 80 % of patients hospitalized with heart failure are older than 65 years. Butler et al. reported common clinical variables to predict incident heart failure risk in the elderly [23]. Despite the increasing incidence of heart failure and aging population in the USA, there were no useful prediction models for incident heart failure in the elderly. In the Health, Aging, and Body Composition (Health ABC) study, 3,075 well-functioning, community-dwelling individuals aged 70–79 years were enrolled. Among them, 140 participants had heart failure and 82 had missing data on heart failure at baseline. These participants were excluded, and 2,853 elderly participants were studied (mean age 73.6 ± 2.9 years, 47.9 % men, 58.6 % white). Incident heart failure developed in 258 (8.8 %) participants during 6.5 ± 1.8 years of follow-up. Independent predictors of incident heart failure included age, history of coronary disease and smoking, baseline systolic blood pressure and heart rate, serum glucose, creatinine, and albumin levels, and left ventricular hypertrophy. A heart failure risk score was developed from these factors: age (−1 to 1), history of coronary disease (0–5) and smoking (0–4), baseline systolic blood pressure (−4 to 6), serum fasting glucose (−1 to 5), creatinine (−2 to 6), and albumin (−3 to 3) levels, and left ventricular hypertrophy (0 or 2). They defined four risk groups (low, less than 2 points; average, 3–5 points; high, 6–9 points; and very high, more than 10 points) based on this risk score. The actual 5-year incident heart failure rates in these groups were 2.9 %, 5.7 %, 13.3 %, and 36.8 %, respectively. A simple point score was able to predict risk for incident heart failure in well-functioning elderly.

The same research group of Butler et al. examined the association between serum resistin concentrations at baseline and development of new-onset heart failure among older persons in the Health ABC study [24]. Out of 3,705 participants enrolled in the Health ABC study, participants with heart failure or missing data for heart failure at baseline were excluded, and 2,902 participants without prevalent heart failure who had available data of serum resistin concentrations were investigated. Their mean age was 73.6 ± 2.9 years with 48.1 % men and 58.8 % white. Mean resistin concentration was 20.3 ± 10.0 ng/mL. They also measured serum concentrations of inflammatory markers (C-reactive protein, interleukin-6, and tumor necrosis factor-α), insulin resistance (fasting insulin and hemoglobin A_{1C}), and adipokines (leptin and adiponectin). Total fat mass was assessed by whole-body dual X-ray absorptiometry, and abdominal visceral and subcutaneous adipose tissue areas were measured

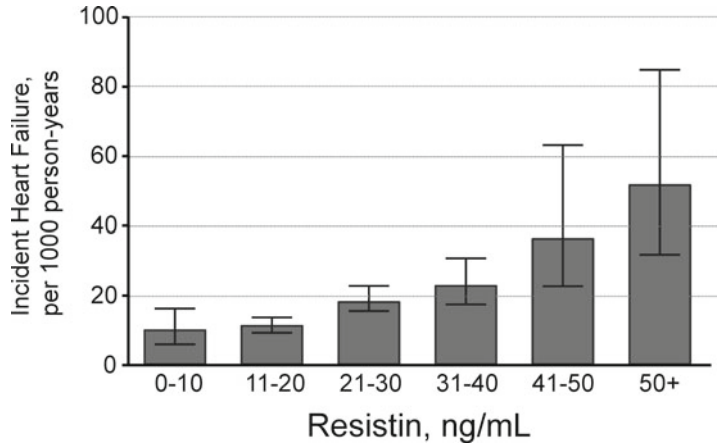

Fig. 16.1 Baseline resistin concentrations and incident heart failure rates (per 1,000 person-years) among participants without prevalent heart failure at baseline in the Health ABC Study. Error bars represent 95 % confidence interval (adapted from Butler J, Kalogeropoulos A, Georgiopoulou V, Rekeneire N, Rodondi N, Smith AL, et al: Serum resistin concentrations and risk of new onset heart failure in older persons. Arterioscler Thromb Vasc Biol 2009; 29: 1144-1149. With permission from Wolter Kluwers Health)

with computed tomography. During median follow-up of 9.4 years, 341 participants (11.8 %) developed heart failure. Figure 16.1 shows the observed heart failure incidence in the cohort in relation to baseline resistin concentrations. Incident heart failure rates (per 1,000 person-years) elevated with increasing baseline resistin concentrations. In addition, resistin was strongly associated with risk for incident heart failure in Cox proportional hazard models controlling for clinical variables, inflammatory biomarkers, and measures of adiposity (HR 1.15 per 10.0 ng/mL increase, 95 %CI 1.05–1.27, $P=0.003$). They concluded that serum resistin concentrations are independently associated with risk of heart failure in older persons.

Zhang et al. have recently reported the prognostic significance of resistin in ambulatory patients with stable coronary heart disease [25]. This was performed as a sub-analysis of the heart and soul study, and they evaluated whether resistin was predictive of worse cardiovascular outcomes in 980 patients with documented coronary heart disease and stable condition. After a mean follow-up period of 6.1 years, 358 were hospitalized for myocardial infarction or heart failure or had died. As compared to the lowest quartile, patients with resistin levels in the highest quartile were associated with an increased risk of heart failure (HR 2.06, 95 %CI 1.26–3.39) and death (HR 1.56, 95 %CI 1.11–2.18). However, resistin levels were not associated with a risk of nonfatal myocardial infarction. Resistin was associated with higher risk for heart failure and death, but not myocardial infarction, in ambulatory patients with stable coronary heart disease.

In the Framingham Offspring cohort, Rienstra et al. recently studied the relations between circulating concentrations of resistin and incident atrial fibrillation or atrial flutter (AF) [26]. Out of 2,487 participants, 206 individuals developed incident AF during a mean follow-up of 7.6 years. Natural logarithmically transformed concentrations of plasma resistin were significantly associated with incident AF. Multivariate-adjusted hazard ratio was 1.17 per one SD increase (0.41 ng/mL) of logarithmically transformed resistin (95 %CI 1.02–1.34, $P=0.028$). However, further adjustment for C-reactive protein, the resistin-AF association was attenuated (HR 1.14, 95 %CI 0.99–1.31, $P=0.073$). In this community-based longitudinal study, higher concentrations of resistin were associated with incident AF, but the relation was attenuated upon adjustment for CRP. Incident AF increased in the elderly, and tachycardia due to AF is one of the

major causes of heart failure, especially heart failure with preserved ejection fraction. Patients of heart failure with preserved ejection fraction are increasing and common in the elderly. Thus, circulating resistin level may have important clinical implications in older population.

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17 Role of Coronary Artery Calcium in Cardiovascular Risk Stratification and Management in the Aging Population

Craig R. Butler and Paolo Raggi

Introduction

The risk of coronary heart disease (CHD) increases sharply over the age of 60, and establishes ischemic cardiomyopathy as the most important cause of systolic heart failure in the elderly [1]. Elderly individuals are more likely to present with heart failure as their first manifestation of CHD, and they are more likely to develop heart failure after their index CHD event than younger individuals [2–4]. Cardiovascular computed tomography (CT) has evolved over the last two decades to become a very powerful tool to noninvasively image coronary atherosclerosis and to assess the risk of future coronary events and may therefore be of help in risk stratifying elderly patients. Risk stratification is fundamental to preventing CHD and subsequent ischemic cardiomyopathy, and can be significantly refined through the use of coronary calcium scores. Accurate risk stratification of elderly individuals using coronary calcium scoring attains the potential dual benefit of allocating proven therapies to those who will receive the most benefit and avoiding unnecessary polypharmacy in lower-risk individuals. In this chapter we review the current literature on use of coronary artery calcium imaging for risk stratification in the elderly patient population.

C.R. Butler, MSc, MD (✉) • P. Raggi, MD
Division of Cardiology, Mazankowski Alberta Heart Institute, Department of Medicine, University of Alberta Hospital, 8440-112 Street, Edmonton, AB, Canada T6G 2B7
e-mail: crbutler@ualberta.ca

Pathophysiology of Coronary Heart Disease

Coronary atherosclerosis is a chronic, inflammatory process that progresses slowly over many years and is highly prevalent in older populations. Deposition of lipid and inflammatory cells in the walls of the coronary arteries begins as fatty streaks in young adulthood and develops into more complex atheroma with aging. Enlarging atheroma can encroach the lumen of the coronary artery (i.e., negative remodeling) causing a restriction of blood flow to downstream myocardium and thereby produce clinical symptoms of exertional angina. Alternatively, enlarging atheroma can expand away from the arterial lumen (i.e., positive remodeling) without causing any restriction of blood flow for a prolonged period of time, although ultimately it may encroach on the vessel lumen as well. Overlying each atheroma is a cap that is either thick (i.e., composed of collagen and smooth muscle) or thin (thin layer of collagen heavily infiltrated with inflammatory cells and absent smooth muscle cells). Plaques that have extensive positive remodeling, a large lipid core, and a thin fibrous cap are termed high-risk plaques as they are prone to rupture producing acute thrombotic

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occlusion of the coronary arteries, the so-called acute coronary syndrome.

Invasive coronary angiography has been the mainstay to evaluate coronary artery disease for decades but is principally useful in identifying negatively remodeled atheroma implicated in angina and acute coronary syndromes. However, invasive coronary angiography does not provide information on plaque composition or positive vessel remodeling that often hides unstable plaques as explained above. Direct identification of the high-risk, unstable plaque is the holy grail of preventive cardiovascular medicine in old and young populations alike, but currently there is no imaging modality with sufficient spatial resolution to visualize vulnerable plaques directly.

Calcification of the growing coronary atheroma is a spontaneous process that occurs from the early phases of disease although it may not be possible to visualize plaques in the early stages due to the low amount of calcium. As calcium accumulates over time, it facilitates the identification of atheroma with radiological techniques, and most specifically with non-contrast cardiac CT. The signaling mechanism for calcium deposition is incompletely understood, but the process of deposition is similar to that of developing bone. Calcified coronary atheroma is believed to represent 20 % of the total volume of coronary atheroma (i.e., calcified plaque + noncalcified plaque) (Fig. 17.1) and is tightly correlated to total plaque burden. More calcified plaque is a marker of a larger plaque burden which in turn suggests the presence of a larger number of unstable high-risk plaques and an increased likelihood of experiencing an acute coronary event.

Coronary calcium is quantified most commonly using the Agatston score which is calculated as the product of plaque volume and a coefficient based on peak plaque attenuation [5]; the resulting numerical score (coronary artery calcium score) has been used extensively in observational and prospective studies to assess the value of coronary calcium as a marker of cardiovascular risk.

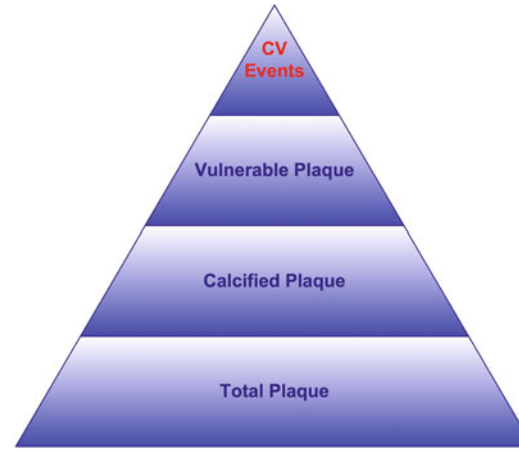

Fig. 17.1 Relationship between subtypes of coronary atherosclerotic plaque. While calcified coronary plaque is only a subset of total coronary plaque, it predicts the presence of a subset of high-risk plaques that can produce acute coronary syndromes

Risk Stratification

Elderly individuals receive significant benefit from intensive management of CHD risk factors such as cholesterol lowering [6, 7], hypertension [8], and lifestyle modification [9]. In fact, elderly individuals may receive greater benefit from treatment of risk factors than younger individuals [10]. Despite ongoing efforts to educate physicians about the importance of risk factor management in the elderly, proven preventive therapies are still underutilized in elderly populations because of misconceptions about clinical ineffectiveness, lack of cost benefit literature, and concern regarding medication side effects [11]. Providing patients with their coronary artery calcium scores has been shown to improve smoking cessation rates and promote weight loss [12] and should motivate physicians to pursue treatment of risk factors in older patients more aggressively.

Treatment goals for preventive therapies are intimately linked to a patient's individual level of risk. Target cholesterol levels, for example, are different depending on an individual's level of risk; in fact, as outlined in the 2009 Canadian Cholesterol guidelines and the Third Report of

the National Cholesterol Education Program (NCEP), individuals at higher risk have lower low density lipoprotein (LDL) targets [13, 14]. Similarly, daily aspirin use is contingent upon a patient's baseline risk so as to minimize the risk of gastrointestinal bleeding while optimizing prevention of myocardial infarction [15]. Thus accurate risk prediction is central to applying evidence-based therapies to prevent CHD, acute coronary syndromes, and ultimately ischemic cardiomyopathy.

The most popular tool to evaluate 10-year risk of developing coronary heart disease is the modified Framingham/ATPIII risk score [14]. This tool categorizes adults into low- (<10 %), moderate- (10–20 %), and high-risk (>20 %) groups based on their sex, age, cholesterol profile, blood pressure, antihypertensive use, and smoking. However, Framingham risk-based models have several limitations in their application to older patients since they were modeled on middle-aged populations and the attributable risk of cardiovascular risk factors decreases with age [16–20]. Age is also weighted heavily in the traditional CHD risk models such that, for individuals over the age of 50, chronologic age becomes the dominant risk factor [21].

The association between increased age and increased risk of adverse coronary events exists because of the cumulative effects over time of known and unknown risk factors for the development of coronary atherosclerosis. Advanced chronologic age is a proxy measure for increased burden of coronary atherosclerosis, which ultimately confers the increased risk of adverse coronary events. The difficulty in using age as a risk predictor is that it represents the average risk for people of a given age and does not incorporate the individual heterogeneity in coronary atherosclerotic burden. Sir William Osler wrote in 1911 that "you are as old as your arteries"; this concept—later embraced by Grundy [22]—is an extension of the biologic versus chronologic theory of aging, and it acknowledges individual variation of a risk factor within an age group. Nonetheless, direct measurement of coronary atherosclerotic burden is a more refined assessment of risk than chronologic age and allows greater individualization of preventive therapies [22, 23].

Coronary Artery Calcium Score and Cardiovascular Risk

The degree of coronary artery calcification is proportional to the total burden of coronary atheroma and has been shown to be highly predictive of future cardiovascular events for men and women of diverse ages and ethnicity [24–27]. Calcium scores range from zero (no identifiable calcium) to several thousand, with each increment in score being associated with an increase in mortality (Fig. 17.2) [27]. The multiethnic study of atherosclerosis (MESA) demonstrated that coronary artery calcium independently improved the prediction of a coronary event among Whites, Blacks, Chinese, and Hispanics [24]. Participants in the MESA study with coronary calcium scores of more than 100 had a sevenfold increase in risk of a future cardiovascular event compared to those without coronary calcium even after controlling for age and other known cardiovascular risk factors.

Several large registries have established average values of coronary calcium scores stratified by sex and age [28–30]. It is clear that the degree of coronary calcium varies widely between adults in the same age group, even among the elderly age groups. Hoff et al. showed that among 540 asymptomatic men between 70 and 74 years of age, 25 % had calcium scores below 64 and 25 % had scores above 1,774 [28] (Fig. 17.3). This heterogeneity in the degree of coronary atherosclerosis explains why arterial age (i.e., chronologic age adjusted for degree of coronary artery calcification) is a much better predictor of incident CHD events than chronologic age [31].

There is a growing body of literature that demonstrates that coronary artery calcium scores have similar predictive power for mortality and cardiovascular events in older age groups as it does in younger age groups [32–35]. Raggi et al. evaluated coronary artery calcium scores in over 35,000 asymptomatic individuals, 3,570 of whom

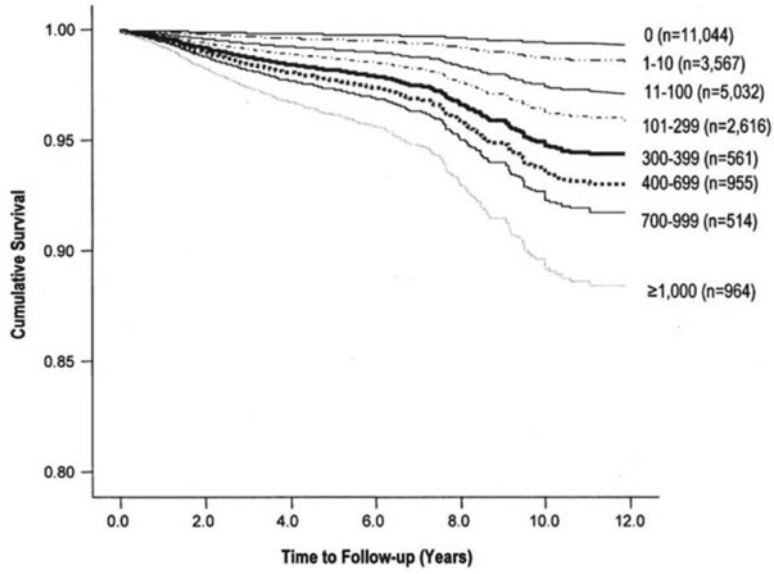

Fig. 17.2 Cumulative survival by coronary artery calcium score. Outcome data for over 25,000 self-referred individuals demonstrating a statistically significant decrease in survival with increasing coronary calcium scores (adapted from Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, Flores FR, Callister TQ, Raggi P, Berman DS. Long-term prognosis associated with coronary calcification: Observations from a registry of 25,253 patients. J Am Coll Cardiol. 2007;49:1860-1870. With permission from Elsevier)

	Age (yrs)								
	<40	40–44	45–49	50–54	55–59	60–64	65–69	70–74	>74
Men (25,251)	3,504	4,238	4,940	4,825	3,472	2,288	1,209	540	235
25th percentile	0	0	0	1	4	13	32	64	166
50th percentile	1	1	3	15	48	113	180	310	473
75th percentile	3	9	36	103	215	410	566	892	1,071
90th percentile	14	59	154	332	554	994	1,299	1,774	1,982
Women (9,995)	641	1,024	1,634	2,184	1,835	1,334	731	438	174
25th percentile	0	0	0	0	0	0	1	3	9
50th percentile	0	0	0	0	1	3	24	52	75
75th percentile	1	1	2	5	23	57	145	210	241
90th percentile	3	4	22	55	121	193	410	631	709

Fig. 17.3 Age and sex stratified coronary artery calcium scores. Age and sex stratified coronary calcium score quartiles for over 35,000 asymptomatic individuals illustrating substantial heterogeneity in the distribution of coronary calcium scores within chronologic age groups, including patients over 60 years (adapted from Hoff JA, Chomka EV, Krainik AJ, Daviglus M, Rich S, Kondos GT. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. Am J Cardiol. 2001;87:1335-1339. With permission from Elsevier)

were over the age of 70 years. Comparison between those with calcium scores over 400 and those with scores between 1 and 10 yielded consistently higher hazard ratios for death across age groups ranging from 50 to 79 years [33]. Coronary artery calcium scores of zero were found in 16 % of individuals over the age of 75 and were associated with an excellent (98 %) 5-year survival rate [35].

Coronary Artery Calcium Scores and Risk Reclassification

While there is a clear association between increasing cardiovascular risk and increasing calcium, the real clinical utility of coronary artery calcium scoring lies in its ability to correctly reclassify an individual into a different cardiovascular risk

Framingham Refitted 10-Year Risk Categories	Framingham Refitted + CAC 10-Year Risk Categories			n (%) Reclassified
	<10%	10%–20%	>20%	
<10%				
n = 1,438	1,278 (88%)	156 (11%)	4 (1%)	160 (12%)
Observed risk (95% CI)	0.03 (0.02–0.05)	0.13 (0.08–0.20)	NA	
10%–20%				
n = 451	134 (30%)	216 (48%)	101 (22%)	235 (52%)
Observed risk (95% CI)	0.09 (0.05–0.16)	0.14 (0.10–0.20)	0.29 (0.20–0.41)	
>20%				
n = 144	7 (5%)	42 (29%)	95 (66%)	49 (34%)
Observed risk (95% CI)	0.49 (0.15–0.94)	0.13 (0.05–0.31)	0.31 (0.21–0.44)	

Fig. 17.4 Reclassification of individuals by combining Framingham risk scores with coronary artery calcium scores. Data from a study of over 2,000 older adults followed for 9 years demonstrating that adding coronary artery calcium scores to calculated Framingham risk correctly reclassified 52 % of patients predicted to be at moderate risk by Framingham risk alone (adapted from Elias-Smale SE, Proenca RV, Koller MT, Kavousi M, van Rooij FJ, Hunink MG, Steyerberg EW, Hofman A, Oudkerk M, Witteman JC. Coronary calcium score improves classification of coronary heart disease risk in the elderly: The rotterdam study. *J Am Coll Cardiol*. 2010;56:1407-1414. With permission from Elsevier)

group. Risk reclassification is a key concept in the evaluation of new cardiovascular risk markers and refers to a test's ability to improve risk prediction over and above traditional risk assessment such as the Framingham risk score. A systematic review by Peters et al. recently evaluated the impact of subclinical atherosclerosis imaging to improve prediction of cardiovascular events [36]. The investigators found that coronary artery calcium scores demonstrated the highest improvement in predictive value (range of c-statistic improvement 0.05–0.13) and net reclassification index (14–25 %) compared to flow-mediated arterial dilation and carotid intima-media thickness. Yeboah et al. also showed that coronary artery calcium scores correctly reclassified more individuals than ankle-brachial index, high-sensitivity C-reactive protein, and family history of cardiovascular disease [37].

Coronary artery calcium score is particularly effective at reclassifying cardiovascular risk in elderly populations [26, 33]. Elias-Smale et al. performed coronary artery calcium scoring in 2,028 asymptomatic elderly patients (mean age 70 ± 6 years) and collected data on adverse cardiovascular outcomes for more than 9 years [26]. They reported that the incorporation of coronary artery calcium scores into their Framingham-based risk prediction models allowed 52 % of individuals originally classified as moderate risk to be correctly reclassified as high (22 %) or low risk (30 %) (Fig. 17.4). Raggi et al. made a similar observation in a group of individuals aged 70–79, in whom half of the participants could be reclassified to a lower-risk group utilizing coronary calcium scores in risk prediction models [33]. Raggi et al. also reported that the cost to identify one new high-risk patient was most favorable in older populations (i.e., $405 for individuals over 70 and $247 for individuals over 80).

One important consideration in the relationship between coronary artery calcium and risk reclassification is what coronary calcium score thresholds should be used to identify high-, moderate-, and low-risk groups. A sizeable amount of data suggests the presence of a strong inflection point for increased risk of cardiovascular disease above a calcium score of 400; by convention—therefore—calcium scores over this threshold are considered as evidence of high risk. However, there is a paucity of studies with sufficient duration of follow-up to reliably assess the 10-year event rates associated with each coronary calcium score cut point. In their prospective study with one of the longest follow-up periods to date (median of 9 years), Elias-Smale et al. modeled

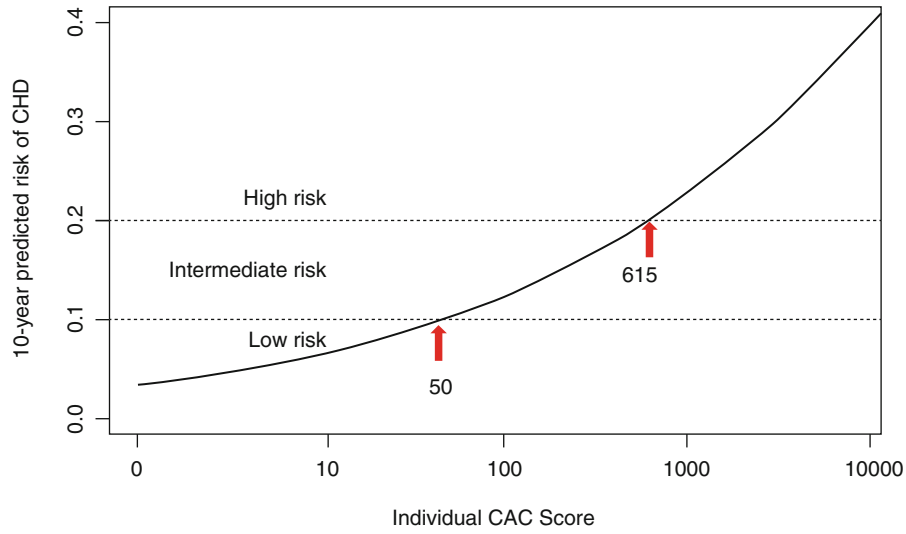

Fig. 17.5 Coronary artery calcium score thresholds for low and high cardiovascular risk in older individuals. The coronary calcium score threshold to identify low (<50), moderate (51–614), and high (>615) 10-year coronary heart disease risk in older individuals may be higher than for younger age groups, which typically treats scores of over 400 as high risk (adapted from Elias-Smale SE, Proenca RV, Koller MT, Kavousi M, van Rooij FJ, Hunink MG, Steyerberg EW, Hofman A, Oudkerk M, Witteman JC. Coronary calcium score improves classification of coronary heart disease risk in the elderly: The rotterdam study. *J Am Coll Cardiol*. 2010;56:1407-1414. With permission from Elsevier)

actual cardiovascular event rates with baseline calcium scores [26]. The authors reported that baseline calcium scores over 615 were the best markers of high risk (i.e., >20 % 10-year risk) of cardiovascular events, and scores below 50 predicted a low risk of events (Fig. 17.5).

Improvement in risk prediction through risk reclassification allows preventive therapies to be focused on those individuals most likely to benefit from them, while avoiding polypharmacy in lower-risk groups where the numbers needed to treat are too large to attain a cost-effective benefit.

Coronary Artery Calcium and Left Ventricular Systolic Dysfunction

Elevated coronary calcium scores clearly identify individuals at increased risk of coronary events, which in turn lead to left ventricular systolic dysfunction and ultimately clinical heart failure. In 2001 the American Heart Association proposed a heart failure classification scheme (stages A through D) that incorporated both pathophysiology and symptomatology [38]. Stage A heart failure is populated by individuals who have risk factors for the development of heart failure, but who do not have overt ventricular dysfunction or symptoms. Stage B heart failure is composed of individuals who have asymptomatic structural heart disease. A recent study estimates that 81 % of patients aged 65–84 years had subclinical heart failure (stage A or B) and that a large proportion of these patients did not have adequate control of their cardiovascular risk factors [39].

Coronary artery calcium imaging is a simple tool that can help identify and tailor preventive therapies to individuals at risk for heart failure though it has not yet been incorporated into clinical guidelines. Leening et al. recently evaluated the ability of coronary artery calcium to independently predict the development of heart failure in an elderly population [40]. They measured coronary artery calcium scores in 1,897 older individuals (mean age 70 years) without a history of CHD or congestive heart failure and prospectively documented index cardiac events. The authors reported that a first diagnosis of congestive heart failure was preceded by a CHD event in

only 18 % of patients and that heart failure was the first cardiac event 40 % of the time. Furthermore, a calcium score over 400 conferred a threefold increased risk of developing heart failure independent of overt clinical CHD events.

Coronary Artery Calcium and Frailty

Frailty is a clinical syndrome of reduced resistance to physical stressors characterized most often as reduced physical strength, slow gait speed, and physical inactivity. It is estimated that 27–50 % of elderly patients admitted to cardiology wards with advanced coronary artery disease are frail [41]. There has been a call to better understand the relationship between atherosclerotic disease and frailty [42]. Investigators from the Cardiovascular Health Study reported that frailty was strongly associated with clinical CHD but was most prevalent in those with a history of congestive heart failure [43]. Frailty also independently confers a worse prognosis in heart failure patients, outperforming New York Heart Association Class in predicting risk of mortality [44].

It has been speculated that the poorly understood chronic inflammatory state that is involved in coronary plaque development also adversely affects muscle mass and contributes to frailty [45]. Frailty has also been shown to be associated with subclinical atherosclerosis, in the form of increased carotid intima-media thickness and peripheral vascular disease (i.e., reduced ankle-brachial index) [43]. Coronary calcium score is associated with two key metrics of frailty, specifically lower self-reported levels of physical activity [46] and slower gait speeds [47]. It appears, therefore, that coronary calcium scores may identify patients at risk of developing frailty; however more research in this area is needed.

Conclusion

Ischemic cardiomyopathy remains the most common etiopathogenetic mechanism of heart failure among the elderly despite important advances in the prevention and management of coronary heart disease. Controlling cardiovascular risk factors for coronary heart disease is the most effective way to reduce the burden of ischemic cardiomyopathy in elderly populations. Appropriate application of proven preventive therapies relies on accurate estimation of cardiovascular risk. Currently favored risk prediction models place a disproportionate emphasis on chronologic age resulting in the misclassification of risk in many elderly individuals. Coronary artery calcium scoring is a simple test that can be used to estimate the burden of coronary atherosclerosis and help "personalize" the approach to treatment of cardiovascular risk independent of chronologic age. Coronary artery calcium scores accurately predict cardiovascular events in older patients and effectively reclassify risk in elderly individuals with subsequent alteration of treatment goals. The improvement in risk prediction that coronary artery calcium offers promotes the use of preventive therapies in individuals who will receive the most benefit, while avoiding polypharmacy in those who would receive the least benefit.

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18 Aging and Remodeling of the RAS and RAAS and Related Pathways: Implications for Heart Failure Therapy

Bodh I. Jugdutt

Introduction: Statement of the Problem

Human aging is a natural biological process that is progressive and is associated with cardiovascular (CV) and other biological changes that impact disease expression and response to injury and therapy [1–10]. As expected, progress, prosperity, and improved health care have been accompanied by prolonged longevity with an increase in people aged ≥65 years in industrialized developed countries and most developing countries are following this pattern [11, 12]. As reviewed in the first two chapters of this book, the definition of elderly by the chronological age ≥65 years was driven by pension legislations in the Europe of the 1870s, presumably to reduce the socioeconomic burden and political pressure when very few people were expected to survive to that age. This nearly 150-year-old definition has persisted into the twenty-first century despite the changing demographics, increased longevity, progress in medical therapies, and prosperity [13–16] and certainly mandates upward adjustment in keeping with modern trends. Progress and prosperity over these years have been accompanied by expansion of an elderly population burdened with cardiovascular disease (CVD) including hypertension (HTN) and coronary heart disease (CHD), comorbidities that impact the CV system, and heart failure (HF), the known ultimate result of CVD [1, 14, 17]. While medical progress and clinical trials since the mid-1970s have improved therapy of CVDs in the non-elderly (aged <65 years), there is an alarming knowledge gap about the pathobiology and pathophysiology of CVDs and their therapy in the elderly people aged ≥65 years. The negative impact of that knowledge gap is already clearly apparent. The burden of CVD and HF is known to be greatest in the elderly, with escalating morbidity/mortality and related healthcare costs [18–24].

One reason for this global problem is that therapies for the non-elderly may not be optimal for the elderly because aging may result in remodeling of major pathways leading to CVD [6, 10, 17, 25, 26]. This chapter focuses on the aging-related remodeling of the renin–angiotensin system (RAS) [27] and related pathways including the renin–angiotensin–aldosterone system (RAAS) which play central roles in the pathophysiology and pharmacotherapy of CVDs and HF.

Aging and the RAS

Population studies have shown that myocardial infarction (MI), HTN, and HF are more prevalent in the elderly [6, 11, 24, 28]. The healthcare costs

B.I. Jugdutt, MD, MSc, DM, FRCPC (✉)
2C2 W.C. Mackenzie Health Sciences Centre,
Division of Cardiology, Department of Medicine,
Mazankowski Alberta Heart Institute,
University of Alberta and Hospitals, 727, Todd Landing NW, Edmonton, AB, Canada T6G 2B7
e-mail: bjugdutt@ualberta.ca

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for post-MI HF in the elderly are high and increasing [6, 11, 17–19, 28]. While the RAS has critical functions in CV physiology, an upregulated RAS leads to CV pathology in both non-elderly and elderly populations [6]. Accordingly, components of the RAS have become important targets for CVD and HF pharmacotherapy since the mid-1980s [6, 28, 29]. Angiotensin II (AngII) is the primary effector molecule of the RAS. Since the 1990s, AngII inhibitors have formed the basis of therapy for both elderly and non-elderly HF patients [6, 29]. However, several clinical studies indicate that elderly post-MI patients are at higher risk for adverse events despite recommended therapy with RAS/AngII inhibitors compared to younger patients [6, 28]. Aging is associated with increased AngII and other components of the RAS [6, 30–33]. Emerging evidence suggests that the RAS may also become further upregulated and/or dysregulated during aging [6, 9, 29]. This adverse remodeling of the RAS may account for poor outcome and increased HF burden in the elderly despite conventional therapies [27].

Aging and Remodeling of the RAS and Left Ventricle Post-MI and Post-HTN

Aging of the CV system is associated with fundamental physiological, biological, and structural changes that lead to increased extracellular matrix (ECM) and fibrosis, increased ventricular-arterial stiffening, left ventricular (LV) diastolic dysfunction, and HF associated with preserved ejection fraction (HF/PEF) [6, 7, 17] (Fig. 18.1). The aging process is progressive and marches in parallel with the CVD continuum towards HF [7, 17]. In this aging-HF continuum [14], CVD risk factors and comorbidities as well as the upregulated RAS [27] and other related pathways can fuel progression towards HF in the elderly (Fig. 18.1). It is important to recognize that the biological changes during aging lead to profound structural remodeling of the CV system that impact cardiac reserve. Even in the absence of CVD, the progressive changes during aging can themselves lead to HF. However, exposure to CV risk factors and interaction

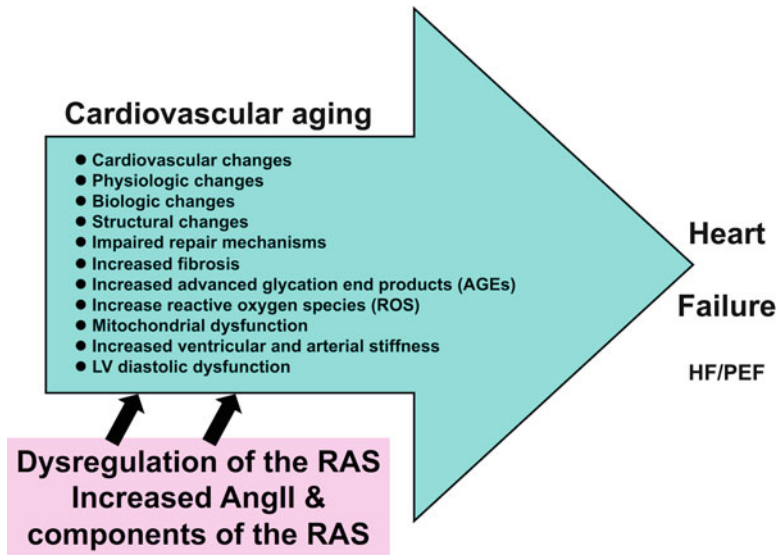

Fig. 18.1 Cardiovascular aging and role of the RAS in the march to heart failure. While age is considered to be a nonmodifiable risk factor, the age-related changes in cardiovascular vascular structure and function and associated physiological, biochemical, cellular/subcellular, and pathophysiological changes provide the substrate for heart failure with preserved ejection fraction (HF/PEF). Dysregulation of the RAS and related pathways and other unrelated pathways influence the aging-related changes and can be modified by appropriate interventions. *RAS* renin–angiotensin system; *AngII* angiotensin II

with comorbidities during aging together with the effect of increased RAS and reactive oxygen species (ROS) tend to accelerate progression to both categories of HF, namely, HF associated with low ejection fraction (HF/low EF) and HF/PEF in the elderly (Fig. 18.2).

Upregulation of the RAS is especially pertinent to the two major categories of HF (i.e., HF/low EF and HF/PEF) that contribute nearly equally to the HF burden in the elderly [7, 17] (Fig. 18.3). Some studies suggest that the prevalence of HF/PEF in the elderly is higher than 50 %, especially the very old [34–36]. Based on evidence suggesting that aging is associated with increased AngII and other components of the RAS [30–33], it is reasonable to speculate that remodeling of the RAS with aging may play a critical role in increased fibrosis in elderly hearts [37, 38] as well as hypertrophic remodeling and enhanced fibrosis in HF/PEF associated with hypertensive disease and enhanced dilative remodeling and HF/low-EF post-MI (Fig. 18.3).

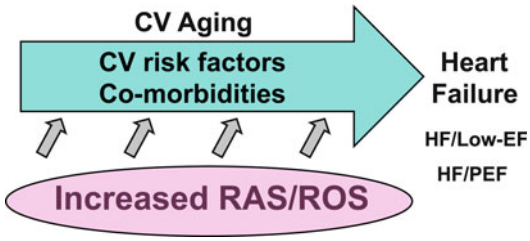

Fig. 18.2 Role of risk factors, comorbidities, ROS, and RAS in heart failure. Interactions between cardiovascular (CV) risk factors, comorbidities, and increased ROS and RAS spur the march to heart failure during CV aging. *RAS* renin–angiotensin system; *ROS* reactive oxygen species

Additionally, increased AngII with aging can also lead to amplified pro-inflammatory and pro-remodeling effects after injury. Aging has been shown to result in impaired repair mechanisms after reperfused MI [6–9]. Increased RAS/AngII and oxidative stress/ROS with aging [6] aggravate myocardial and matrix damage post-MI [9] and exacerbate adverse LV remodeling and dysfunction post-MI and progression to HF/low EF [7–10, 17]. Taken together, the aging-related increase in AngII, other components of the RAS, ROS, and oxidative stress may explain both the increased fibrosis in elderly hearts and HF/PEF and the enhanced postinfarction adverse LV remodeling and associated HF/low EF [6, 10].

It follows that there is need for a paradigm shift in HF management, going beyond targeting the RAS with respect to HF therapy for the elderly. There is need for identifying new therapeutic targets and strategies through translational research for optimizing HF therapy in the elderly. Because responses to major causes of HF such as

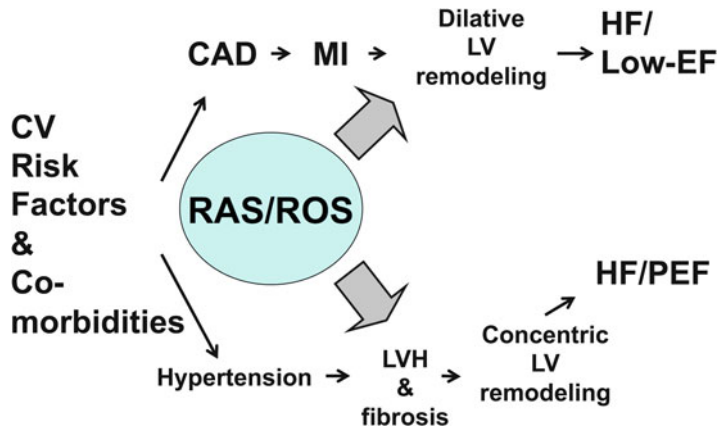

Fig. 18.3 The two major categories of heart failure in the elderly. Role of risk factors, comorbidities, ROS, and RAS. Aging-related increase in RAS and ROS play major roles in dilative and concentric LV remodeling, leading to the two main categories of heart failure. *CAD* coronary artery disease; *CV* cardiovascular; *EF* ejection fraction; *HF* heart failure; *LV* left ventricular; *LVH* LV hypertrophy; *MI* myocardial infarction; *PEF* preserved EF; *RAS* renin–angiotensin system; *ROS* reactive oxygen species

HTN and MI may be amplified in the elderly, different therapeutic strategies may be needed in the elderly compared to the young. Because biological changes with aging may alter responses to therapies that were tested in mostly young and non-elderly patients with HF, caution should be exercised and appropriate adjustments of medications (i.e., type, dosage, and timing) should be done when applying those in the elderly.

Aging and AngII, AT_1/AT_2 Pathways

Traditional concepts of RAS inhibition have been based on research studies that were done in predominantly young animals and humans. While the fundamental concepts and pathways are similar, there are some important differences with evidence of aging-related RAS dysregulation that may profoundly impact therapy of HF in the elderly.

Pharmacology of the RAS/RAAS in the Young and Non-elderly

The pertinent aspects of RAS/RAAS pharmacology have been reviewed elsewhere [39]. Briefly, the RAS/RAAS regulates blood volume and systemic vascular resistance, thereby modulating cardiac output and blood pressure (BP) through a cascade of events (Fig. 18.4). Renin, released primarily from the kidneys, cleaves circulating

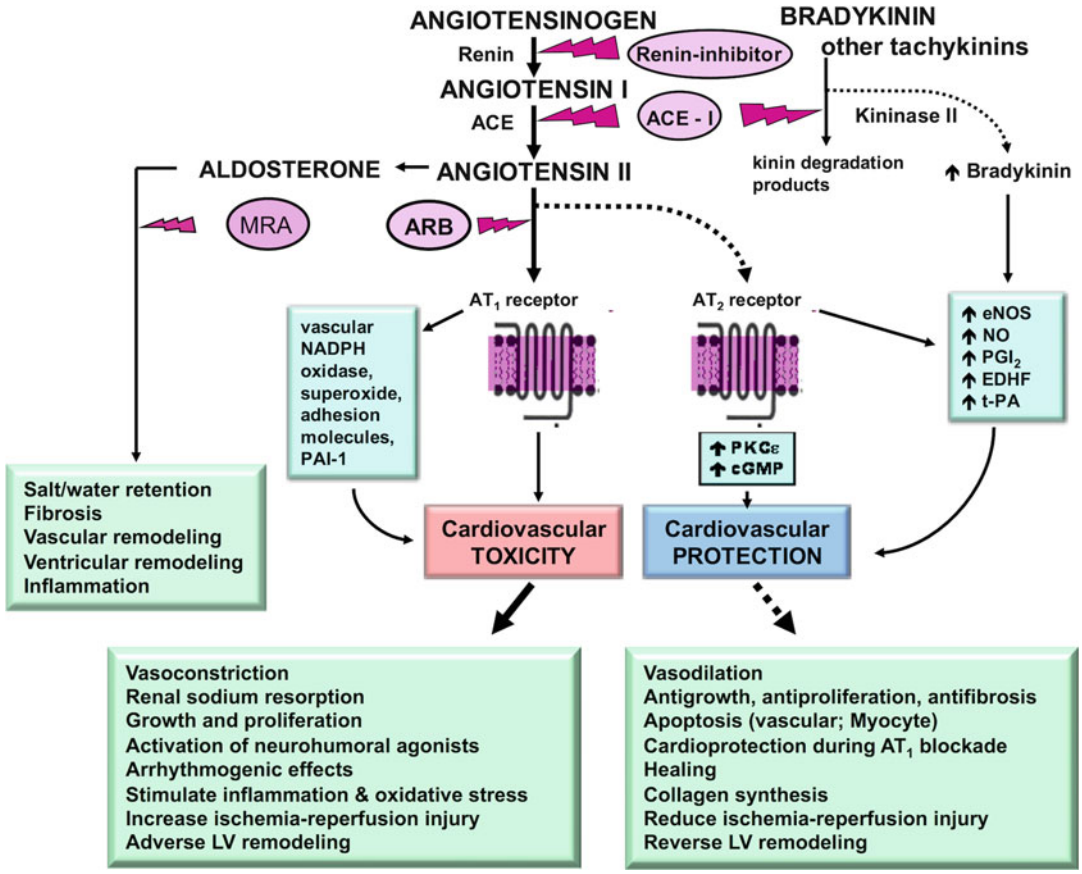

Fig. 18.4 The major pathways in the RAS and RAAS cascades. *ACE* angiotensin-converting enzyme; *ACE-I* ACE inhibitor; *ARB* angiotensin receptor blocker; *cGMP* cyclic guanosine 3′ 5′ monophosphate; *EDHF* endothelin-derived hyperpolarizing factor; *eNOS* endothelial nitric oxide synthase; *MRA* mineralocorticoid receptor antagonist; *PAI-1* plasminogen activator inhibitor-1; PGI_2 prostacyclin; *PKCε* protein kinase Cε; *RAS* renin–angiotensin system; *RAAS* renin–angiotensin–aldosterone system; *t-PA* tissue plasminogen activator

angiotensinogen to the decapeptide angiotensin I (AngI), which is further cleaved by the angiotensin-converting enzyme (ACE), found primarily in pulmonary vascular endothelium, to the octapeptide molecule AngII. The latter is considered to be the major effector polypeptide molecule of the RAS/RAAS. It is also a pleiotropic cytokine that exerts several important physiological actions, including vasoconstriction, release of neurohumoral agonists (such as aldosterone, vasopressin, and norepinephrine), drinking, secretion of prolactin and adrenocorticotropic hormone, and glycogenolysis. AngII also plays a critical role in the pathophysiology of CVD. Thus, chronically increased AngII induces increased vasoconstriction (leading to high BP and HTN), stimulates growth (leading to cardiac and vascular hypertrophy), contributes to LV dysfunction and progression of HF, mediates adverse structural cardiac and vascular remodeling [40], and causes deleterious activation of other neurohumoral agonists including endothelin. Sodium and water homeostasis becomes dysregulated, especially in the elderly. Since high AngII levels and low cardiac output stimulate thirst, the elderly patient with high AngII, HF, and low cardiac output is prone to develop hyponatremia despite reduced water intake.

While the RAS was initially regarded as an endocrine system, a steady flow of new evidence since the 1990s has expanded the paradigm into that of a multifunctional endocrine, paracrine, and intracrine system with circulating and local/tissue components [40–42]. While AngII is produced in the circulation and tissues and acts on the AngII type 1 (AT_1) and AngII type 2 (AT_2) receptors [39, 41], most of the effects of AngII are normally mediated through the AT_1 receptor. However, in the presence of CV pathology—such as cardiac hypertrophy, vascular injury, MI, HF, and wound healing—the AT_2 receptor is upregulated and may mediate some CV effects of AngII through AT_2. Since there is a decrease in AT_1 and an increase in AT_2 receptors in HF, it was proposed that the antiproliferative and vasodilatory effects of AT_2 counterbalance the growth-stimulating and vasoconstricting effects of AT_1. In that construct, it follows that an AT_1 receptor blocker (ARB) would completely block effects of AngII via AT_1 and result in unopposed AT_2 receptor stimulation that might augment its beneficial effects [43]. Although, there is controversy about the role of AT_2 in humans [44], it may be important in the elderly. However, the role of AT_3 and AT_4 receptors with aging remains unclear and needs study.

Cardioprotective Effect of RAS Inhibition: Role of Kallikrein–Kinin System

Cumulative evidence supports the view that the cardioprotective effects of ACE inhibitors are due not only to the inhibition of AngII formation via ACE but also to inhibition of breakdown of bradykinin and other tachykinins related to ACE's kininase II activity. In this construct, ACE inhibition decreases the amount of AngII that is presented to both AT_1 and AT_2 receptors, at least initially, so that decreased but balanced AT_1 and AT_2 effects is expected. However, increased bradykinin during ACE inhibition leads to stimulation of nitric oxide (NO), prostaglandins such as prostacyclin (PGI_2), endothelial-derived hyperpolarizing factor (EDHF) and tissue-thromboplastin activator (t-PA), thereby contributing to vasodilation, CV protection, and other favorable CV effects of ACE inhibitors [45]. The increased bradykinin also contributes to the hypotensive effect of ACE inhibitors which may be pertinent for the elderly.

In contrast to ACE inhibitors, the cardioprotective effect of ARBs is mediated through at least three pathways: (1) the primary pathway involves selective AT_1 receptor blockade, (2) a secondary pathway involves AT_2 receptor activation, and (3) a third pathway involves the release of kinins and stimulation of kinin B_1 or B_2 receptors [46–49] and/or direct AT_2-mediated signaling via protein kinase C (PKCε), NO, and cyclic guanosine monophosphate (cGMP) [50–53]. Coupling between the AT_2 receptor and kallikrein during AT_1 blockade has been demonstrated in young mice with myocardial ischemia–reperfusion injury [49].

However, while kinins contribute to the protective effects of ACE inhibitors and ARBs

acting through the AT_2 receptor and NO contribute to myocardial and vascular protection, the kinin system is also involved in inflammation and the pathogenesis of inflammatory diseases such as arthritis ([54], for review). The kinins are known to act as mediators of inflammation by promoting maturation of dendritic cells which activate the body's adaptive immune system and thereby promote inflammation. This may also be pertinent in elderly HF patients.

Role of Chymase and Other Non-ACE Pathways in Angiotensin II Generation

The discovery, in the 1990s, of non-ACE pathways that can generate AngII during ACE inhibition [55–60] has important implications for optimal therapy of HF in both non-elderly and elderly patients. Data in mostly non-elderly patients indicated that ACE inhibitors do not block all AngII formation. This includes AngII from AngI via the serine protease chymase and other non-ACE enzymes and/or that from angiotensinogen via non-renin pathways. Several studies showed that AngII levels persist during long-term ACE-inhibitor therapy, suggesting incomplete RAS blockade or the so-called ACE-inhibitor escape due to a reactive rise in active plasma renin [57–60]. This finding not only supported the use of ARBs for blocking the effects of AngII at the AT_1 receptor but also fueled the push for using combined ACE inhibition and AT_1 receptor blockade for more complete blockade of the deleterious effects of AngII and therefore anticipated greater benefits. However, support for the concept of dual ACE and AT_1 receptor blockade came from experimental [61] and clinical [62] studies that were done in mostly the young with HF. For example, in young rats with post-MI HF, the ACE inhibitor fosinopril combined with the ARB valsartan resulted in suppression of histopathologic evidence of remodeling and normalized collagen I, macrophages, and myofibroblasts [63].

Two additional findings deserve emphasis. First, the AngII-forming capacity of chymase from AngI was found to be 20-fold higher than that for ACE [55, 56]. Second, chymase was also shown to activate the Kallikrein–kinin pathway [64, 65]. These findings imply that the combination of a chymase inhibitor with either an ACE inhibitor or an ARB may potentially double the beneficial effects through decrease of AngII and increased kinins. Dual chymase and ACE inhibition was proposed for HTN and HF to boost the efficacy of ACE inhibition and prevent *ACE-inhibitor escape*.

In fact, chymase inhibitors have been tested in young experimental animal models. They were shown to improve diastolic LV function and prevent fibrosis in a canine model of tachycardia-induced HF [66], reduce arrhythmias and LV dysfunction after MI [67, 68], attenuate LV remodeling in a mouse model of intermittent hypoxia [69], and decrease infarct size after ischemia–reperfusion through attenuation of matrix metalloproteinase (MMP)-9 and pro-inflammatory cytokines in a porcine model of reperfused MI [70]. In the mouse model of intermittent hypoxia, decrease in LV hypertrophy and fibrosis was associated with decrease in LV chymase, AngII, oxidative stress, interleukin (IL)-6, tumor necrosis factor (TNF)-α, and transforming growth factor (TGF)-β [69]. In a hamster model of post-MI HF, combined ACE and chymase inhibition decreased infarct size and LV remodeling and dysfunction compared to ACE inhibition alone [71]. In the canine model of LV volume overload due to mitral regurgitation, the anti-remodeling effect of chymase inhibition appears to be in part due to inhibition of MMP and kallikrein activation and fibronectin degradation [72], thereby attenuating loss of ECM and cell-ECM connections, and cell death. The multiple actions of chymase on tissue remodeling support its role in adverse LV remodeling and HF post-MI [73–75] atherosclerosis [76–79].

Whether the AngII generation by non-ACE pathways is increased with aging and in elderly HF patients needs investigation. Whether chymase inhibitors might be beneficial in older animals and patients with HF needs study. Recent evidence indicates that chymase is upregulated in coronary and renal arteries of diabetic patients [80] and implicates chymase in the intracellular

formation of AngII in cardiomyocytes, fibroblasts, and renal mesangial and vascular smooth muscle cells under hyperglycemic conditions [81]. This finding may be especially pertinent in the context of aging as diabetes is a major comorbidity in elderly patients with HF.

Interactions Between the RAS and the Endothelin System

Extending the concept of dual inhibition one step further, the ARB valsartan combined with the endothelin (ET) blocker bosentan was shown to produce added benefits on neurohumoral activity and LV loading and performance end-points in pigs with HF induced by rapid atrial pacing [82]. Both the RAS acting through AngII and the endothelin system acting through ET-1 produce powerful vasoconstrictor and vasopressor effects that promote adverse LV remodeling and progression of HF ([83–85] for review). As AngII, both circulating and myocardial tissue ET levels are increased in animals and humans with HF, interactions between the RAS and ET system have been described [83]; AngII stimulates ET production through transcriptional regulation while ET inhibits renin synthesis and stimulates aldosterone secretion. Both AngII and ET stimulate matrix synthesis. In animal models of HF, both nonselective ET-A and ET-B antagonists and selective ET-A antagonists exert beneficial CV effects. However, ET-A antagonist therapy in experimental HF results in augmentation of the RAS and sustained sodium retention [86]. Furthermore, in patients with HF, short-term ET antagonist therapy improved hemodynamics but long-term therapy did not improve combined morbidity/mortality end-points [87]. In the EARTH trial, the ET antagonist darusentan as an add-on to an ACE inhibitor, β-adrenergic blocker, or aldosterone antagonist in patients with chronic HF failed to improve LV remodeling, clinical symptoms, or outcomes [87]. Long-term trials of the ET antagonist bosentan in HF were prematurely terminated due to increased adverse events [88]. Despite anecdotal evidence of success with bosentan in the subgroup of patients with pulmonary artery hypertension secondary to HF, a recent trial showed no improvement [89]. Despite further anecdotal reports of short-term benefit in patients with severe pulmonary hypertension awaiting heart transplantation, the routine use of ET antagonists is not recommended by the World Health Organization (WHO) Pulmonary Hypertension group 2 [90]. Whether ET antagonists may have an application in elderly HF patients has not been studied.

Role of the Counter-Regulatory ACE2 and Ang-(1–7) Arm of the RAS

While the RAS became recognized as a central regulator of CV and renal function with a major role in pathophysiology of CVD and HF, the discovery of angiotensin-converting enzyme 2 (ACE2) in 2000 [91, 92] further modified the traditional concepts about the RAS. Subsequent studies viewed ACE2 as an essential regulator of cardiac function [93] and several studies underscored the importance of AngII degradation by the carboxypeptidase ACE2 to Ang-(1–7), a vasodilator, antitrophic and antifibrotic heptapeptide that functions as an endogenous inhibitor of AngII [94, 95]. Both ACE2 and Ang-(1–7) were demonstrated in rat and human cardiomyocytes. Later, ACE2/Ang-(1–7) was also demonstrated in other tissues, including blood vessels, kidneys, lungs, and brain, and was implicated in CV homeostasis.

Experimentally in rats, ACE inhibition decreased AngII formation and increased Ang-(1–7), while AT_1 blockade increased AngII and Ang-(1–7) [96]. The increase in Ang-(1–7) with ACE inhibition was attributed to increased AngI and inhibition of Ang-(1–7) metabolism, while the increase with AT_1 blockade was attributed to formation from increased AngI [96]. After MI in rats, AT_1 blockade was shown to upregulate ACE2 [97], which may contribute to its cardioprotective effect via Ang-(1–7) formation as verified by Ang-(1–7) infusion [98]. In the late phase of LV dysfunction after MI in rats, the ACE inhibitor enalapril was shown to attenuate downregulation of ACE2 [99]. In hypertensive rats, the ARB telmisartan attenuated aortic hypertrophy through modulation of ACE2 [100].

Preliminary data from our laboratory showed that the ARB candesartan and the vasopeptidase inhibitor omapatrilat attenuated LV remodeling and dysfunction during healing after reperfused MI in rats through modulation of ACE2 as well as MMP-9, inflammatory cytokine IL-6, TNF-α, TGF-β, *N*-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP), collagens, and fibrosis [101]. In that study, increased ACE2 and Ang-(1–7) levels, associated with enhanced AT_2 receptor signaling and suppression of TGF-β_1 and smad-2 signaling, inflammatory cytokines, and AngII signaling via AT_1 receptors, effectively limited fibrosis, adverse remodeling, and dysfunction during healing after reperfused MI [101]. Recent evidence suggests that the ACE2-Ang-(1–7)-Mas receptor can counter-regulate remodeling effects of AngII and inhibit hypertrophy and fibrosis [102].

It appears that whereas the RAS through ACE-AngII-AT_1 receptor axis promotes adverse remodeling, the ACE2/Ang-(1–7) system through ACE2-Ang-(1–7)-Mas receptor axis is counter-regulatory ([96, 102, 103] for review) and prevents adverse remodeling. The increase in ACE2/Ang-(1–7) mediated by ACE inhibitors and ARBs may contribute to the anti-remodeling and other beneficial effects in HF ([102, 103] for review). However, ACE2/Ang-(1–7) is upregulated in human HF [104] and overexpression of ACE2 attenuates LV remodeling post-MI in young rats [105].

In human HF, plasma ACE2 activity is elevated and correlates with poor outcome [106, 107], suggesting a compensatory response to LV dysfunction. ACE2 expression in rat lung decreases with aging [108]. Responses to Ang-(1–7) differ in young, aged, and diabetic rabbit corpus cavernosum [109]. Whether a loss of ACE2 function with aging might lead to amplified activation of RAS and more adverse remodeling and explain the worse clinical outcome in the elderly with HF [6, 8, 14] needs study. Preliminary data from our laboratory showed that more severe age-related LV remodeling and dysfunction after acute reperfused ST-segment elevation MI was associated with downregulation of myocardial AT_2 receptors, ACE2, Ang-(1–7), Ac-SDKP, and smad-2 in the dog model [110].

Since Ang-(1–7) is a substrate for inactivation by ACE, it competes with AngI and bradykinin for degradation, thereby inhibiting AngII formation and augmenting bradykinin activity and its vasodilatory effects [111]. Increased Ang-(1–7) with ACE inhibition may further augment bradykinin activity. Later, AT_1 blockade was shown to increase bradykinin levels in hypertensive humans, probably due to decreased metabolism by ACE and neutral endopeptidase [112]. The authors warned that the increased bradykinin with ARBs may augment their therapeutic actions but may also lead to angioedema. Collectively, these findings indicated that ACE inhibitors and ARBs increase both Ang-(1–7) and bradykinin. Whether these effects are amplified in the elderly needs study. An alternative strategy needing study for slowing progression of HF with aging would be to increase levels of Ang-(1–7) as opposed to reducing levels of AngII with ACE inhibitors and ARBs, thereby avoiding side effects related to increased bradykinin such as coughing, dizziness, and angioedema.

Role of the Chymase/Ang-(1–12) Axis in Renin-Independent Generation of AngII

Recent evidence since 2006 suggests that Ang-(1–12), a propeptide cleaved from angiotensinogen, may represent an alternate substrate for the formation of angiotensins including AngII [113, 114]. Ang-(1–12) was shown to be increased in cardiomyocytes of adult spontaneously hypertensive rats [115]. Cardiac Ang-(1–12) as well as AngI and AngII was increased in myocardium of rats with bilateral nephrectomy and absence of circulating renin while plasma levels decreased [116]. In a rat model of ischemia–reperfusion injury, pro-angiotensin 12 (PA12) was suggested to act as a circulating substrate for a chymase-mediated AngII production [117]. Recently, this renin-independent mechanism of AngII generation was demonstrated in human left atrial tissue from patients undergoing the MAZE surgical procedure for chronic atrial fibrillation [118].

This pathway has also been demonstrated in the normal and diseased human LV tissue [119, 120].

Whether this system is augmented in the elderly needs study.

RAS Inhibition for Heart Failure: ACE Inhibitors and ARBs

The introduction of RAS inhibition with ACE inhibitors and ARBs for the treatment of chronic HF represents one of the most significant advances in CV medicine during the latter half of the twentieth century. When the role of the RAS in CV disease was first recognized in the 1950s, the focus was on HTN and the neurohumoral paradigm. Several major large-scale, multicenter randomized clinical trials (RCTs) of ACE inhibitors since the mid-1980s helped to establish its use for improving the survival of patients with HF and acute MI [121–126] (Table 18.1). The rationale for using ACE inhibitors was to inhibit ACE and thereby decrease the formation of AngII and its adverse effects. Subsequently, RCTs since the mid-1990s investigated the benefits of using ARBs in patients with HF and MI [127–136] (Table 18.2). The main rationale for ARBs was to achieve specific and selective blockade of the effects of AngII via the AT_1 receptor [137].

Three points about those and subsequent RCTs need emphasis. First, most of the early RCTs recruited patients aged ≤65 or 18–65 years as reflected in the mean ages in Tables 18.1 and 18.2. Elderly patients were excluded. Second, since the benefits of ACE inhibitors in hypertension, HF, and MI were already established when ARBs were introduced, it became necessary to demonstrate that ARBs were superior to them or equally effective in patients intolerant to them and receiving other background therapies in RCTs rather than relative to a true placebo group. Third, ACE inhibitors and ARBs were used on top of background contemporary therapy that often included β-blockers in patients with LV systolic dysfunction and HF, and β-blockers were known to reduce renin [138] and AngII [139] and produce effects additive to that of ACE inhibitors [140].

Additionally, three reasons were proposed as justification for using ARBs as an add-on or alternative to already established ACE inhibitors. First, compared to ACE inhibitors, ARBs were expected to provide more complete inhibition of AngII derived from all sources, including non-ACE and non-renin pathways, especially as the latter is increased during ACE inhibition [43, 55]; however, ARBs were subsequently found to increase renin, AngI, and AngII as well as Ang-(1–7) levels [94, 96]. Second, since ARBs do not inhibit kininase II, or via this mechanism increase systemic peptides of the inflammatory response such as bradykinin, substance P, and other tachykinins known to produce cough and angioedema side effects associated with ACE inhibitors [141, 142], these side effects would be avoided; however, as discussed before, ARBs can also increase release of kinins and stimulation of kinin B_1 or B_2

Table 18.1 Major trials of ACE inhibitors in heart failure

Year—trial [reference]	*N*	Drug	Comparator	Age (years)	Outcome
1987 CONSENSUS [121]	253	Enalapril	Placebo	70	↓ Mortality/morbidity
1989 Lisinopril [122]	189	Lisinopril	Captopril	60	↑ EF, function, and QOL
1991 SOLVD (symptomatic) [123]	2,569	Enalapril	Placebo	61	↓ Mortality/morbidity
1992 SOLVD (asymptomatic) [124]	4,228	Enalapril	Placebo	59	↓ Mortality (NS); ↓ morbidity
2000 ATLAS [125]	3,164	Lisinopril (high dose)	Lisinopril (low dose)	64	↓ Mortality/morbidity with high dose
2006 PEP-CHF [126]	850	Perindopril	Placebo	76	Short-term symptoms improvement; ↓ hospitalization

Abbreviations: ↓ decrease in, *EF* ejection fraction, *HF* heart failure, *N* number of patients, *NS* nonsignificant, *QOL* quality of life

Table 18.2 Major trials of ARBs in heart failure

Year—trial [reference]	*N*	Drug	Comparator	Age (years)	Outcome
1997 ELITE [127]	722	Losartan	Captopril	73	Unexpected 46 % ↑ in mortality (2° end-point)
1999 RESOLVD [128]	768	Candesartan	Enalapril	63	Early trend in ↑ mortality and HF (2° end-point)
2000 ELITE II [129]	3,152	Losartan	Captopril	71.5	Not superior
2001 Val-HeFT [130]	5,010	Valsartan	ACE-Is	62.5	Not superior; ↓ composite end-point
2003 CHARM-Overall [131]	7,601	Candesartan	ACE-Is	66	Improved 1° outcome (mortality and morbidity)
2003 CHARM-Added [132]	2,548	Candesartan	ACE-Is	64	Improved 1° outcome (clinical, morbidity)
2003 CHARM-Alternative [133]	2,028	Candesartan	ACE-Is	66.5	Improved 1° outcome (mortality and morbidity)
2003 CHARM-Preserved [134]	3,023	Candesartan	ACE-Is	67	Similar 1° outcome (improved 2° outcome)
2005 VALIANT (MI + HF) [135]	14,703	Valsartan	Captopril	55, 70, 79, 88	Not superior; ↑ risk adverse events with combination
2008 I-PRESERVE [136]	4,128	Irbesartan	Placebo	72	Not superior

Abbreviations: ↑ increase in, ↓ decrease in, *ACE-I* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *HF*, heart failure, *MI* myocardial infarction, *N* number of patients

receptors [46–49]. Third, ARBs might produce unopposed AT_2 receptor stimulation resulting in added benefits, including long-term CV structural changes over that seen with ACE inhibitors [43]. These arguments led to RCTs on the effects of valsartan in post-MI LV systolic dysfunction and/or HF [130] and chronic HF [144], respectively. However, in that study (VALIANT), there was no upper age limit and valsartan was shown to be not superior to the ACE inhibitor captopril and the combination increased the risk of adverse events in elderly patients [135]. Importantly with increasing age (<65, 65–74, 75–84, and ≥85 years), the 3-year mortality increased fourfold (13 %, 26 %,36 %, and 52 %, respectively), the composite end-point events increased more than twofold (25 %, 41 %, 52 %, and 67 %, respectively), and HF admissions increased threefold (12 %, 23 %, 31 %, and 35 %, respectively) in VALIANT [135]. These findings further underscore the fact that the elderly represent a high-risk group for acute MI and HF/low EF with disproportionately high mortality and morbidity in need of improved therapies.

RAS Inhibitors for Hypertension: ACE Inhibitors and ARBs

The central role of RAS in the regulation of BP, fluid and electrolyte balance, and pathophysiology of CV disease is well recognized (Fig. 18.1) [24, 144–147]. AngII not only increases BP but also promotes vascular inflammation leading to endothelial dysfunction and atherosclerosis, stimulates vascular smooth muscle hypertrophy and vascular remodeling, and stimulates myocardial fibrosis and hypertrophy leading to cardiac remodeling [144–147]. Importantly, it also increases aldosterone which stimulates fibrosis and CV remodeling (Fig. 18.1). The fact that most of the effects of AngII are mediated via AT_1 receptors provides the rationale for ACE inhibition and AT_1 receptor blockade (Fig. 18.1). Since aging is associated with increased AngII and other RAS components which in turn contribute to increased CV remodeling and CV risk in the elderly [6], RAS inhibition with ACE inhibitors and ARBs is recommended in that group [24].

ACE inhibitors have also been studied for reducing CV risk. Indeed, they effectively control BP in patients with hypertension and have additional benefits on CHD, stroke, MI, HF, diabetes, or chronic kidney disease. Several RCTs have established that ACE inhibitors reduce rates of death, MI, and stroke in patients with HF [123], LV dysfunction [148], vascular disease [149–152], or high-risk diabetes [153]. The HOPE trial with the ACE inhibitor ramipril showed improved prognosis; decreased rate of death, MI, and stroke in high-risk patients for CV events and without low EF or HF; and decreased new-onset diabetes and complications of diabetes [154]. The EUROPA trial, which included lower risk patients than HOPE, showed improvement in the composite end-point of CV mortality, MI, and resuscitation [149]. However, QUIET which included low-risk patients showed no significant benefit [150]. The PEACE trial, which also included low-risk patients and used the ACE inhibitor trandolapril, showed no benefit [151].

Although the dose of ACE inhibitors in QUIET and PEACE may not have been optimal, a meta-analysis of the trials, with pooled data in 31,600 patients, showed that ACE inhibitors are effective in preventing CV events, with 26 % reduction in the risk of HF or stroke and 13–18 % reduction in total and CV mortality, and MI compared to placebo [152]. Other studies suggested that ACE inhibitors not only control BP and reduce stroke but also prevent renal complications of diabetes [155]. In the HOPE/The Ongoing Outcomes (TOO) study, development of diabetes in the follow-up phase decreased, suggesting an added benefit of long-term ramipril [156]. In the MICRO-HOPE substudy [153], ramipril was beneficial for CV events and overt nephropathy in patients with diabetes. In the ADVANCE trial, the ACE inhibitor perindopril together with the diuretic indapamide reduced the risks of major vascular events and death in type 2 diabetes [157].

As discussed before, the ability of ARBs to selectively block AngII at the AT_1 receptor resulting in more complete inhibition was considered advantageous (Fig. 18.4). ARBs also do not increase bradykinin by suppressing its degradation as ACE inhibitors do, thereby enhancing vasodilation but also increasing cough and angioneurotic edema that troubles ~20 % of patients, especially women and Asians [29, 153, 154]. ARBs may result in unopposed AT_2 receptor activation and enhance vasodilation via downstream AT_2-mediated signaling (Fig. 18.4). Apart from blocking deleterious effects of AngII and controlling BP, ARBs might have similar protective effects as ACE inhibitors. RCTs showed that ARBs effectively control BP in HTN and are well tolerated [158]. However, despite well-known arguments for using ARBs [29], whether ARBs are as effective as ACE inhibitors in reducing events such as stroke and MI has been questioned [159]. Moreover, ARBs can also release kinins and increase bradykinin levels in hypertensive patients [112, 158] and thereby mediate CV protection. Such ARB-induced increase in bradykinin can augment therapeutic actions but also lead to cough and angioedema [112, 158]. As discussed before, both ACE inhibitors and ARBs can increase Ang-(1–7) in the counter-regulatory arm of the RAS.

A complicating factor with the chronic use of ACE inhibitors in HF patients is that AngII levels increase and symptoms worsen [128]. However, studies in HTN have shown that ARBs such as losartan and valsartan are as effective as ACE-Is in lowering BP [160, 161]. In hypertensive patients with ACE-I-induced cough, this complication is less frequent with ARBs [162]. In patients with HF/low EF, an ARB was shown to reduce the rate of death or hospitalization relative to placebo in those patients who could not tolerate an ACE inhibitor [133] or were already receiving it [130, 132]. In the LIFE study, compared to β-blockers, ARBs reduced vascular events in high-risk patients with hypertension and LV hypertrophy (LVH) [163]. Taken together, these studies suggest that an ARB is an effective and well-tolerated alternative to an ACE inhibitor for CV protection.

Since ACE inhibitors preceded ARBs for treating HTN and HF, it has become necessary in clinical trials to demonstrate non-inferiority or superiority of an ARB over an ACE inhibitor as comparator. In patients with MI, two studies comparing an ARB with an ACE inhibitor produced different results. OPTIMAAL [164] and

VALIANT [143] compared the ARBs losartan and valsartan, respectively, to the captopril in patients with signs of HF within 10 days of MI. In OPTIMAAL, the ARB was not superior and the non-inferiority criteria were not met; in fact, there was an increase in CV mortality after a 2.7-year mean follow-up [164]. In VALIANT, the ARB was non-superior and non-inferior for mortality and the composite end-point of fatal and nonfatal events; the study established that valsartan was as effective as an ACE inhibitor in reducing mortality in high-risk survivors of MI [143]. A meta-analysis of 54,254 patients from 11 trials showed a potential 18 % increase in MI with ARBs compared to placebo and a possible increase compared with other active therapy [165]. In a separate meta-analysis of 55,050 patients from 11 trials that compared ARBs with either placebo or an active comparator, ARBs were found to reduce event rates for stroke, not to reduce event rates for global death, and to increase rates of MI by 8 % [159]. The cloud of doubt cast by these reports has been partly dispelled by studies with the ARB telmisartan [166–169].

Aging, RAS Dysregulation, and AngII Inhibition with ACE Inhibitors and ARBs

The contribution of the RAS to CV changes during aging has been confirmed in experimental studies. As mentioned previously, aging alters all RAS components and results in increased angiotensinogen, AngII, AT_1 and AT_2 receptors, and ACE in rat hearts [30, 31]. Increased AngII and other RAS components with aging may explain increased cytosolic and mitochondrial oxidant production, mitochondrial dysfunction, and increased ECM deposition associated with aging [32]. Short-term AngII was shown to downregulate AT_1 receptor mRNA in fibroblasts from aged rat myocardium [170]. A study with long-term AngII inhibition with the ACE inhibitor enalapril or the ARB losartan protected against CV effects of aging and prolonged life in rats [171], implying a harmful effect of increased RAS and AngII effects during aging. Furthermore, disruption of the AT_1 receptor in aging mice was shown to protect from CV morbidity and mortality and promote longevity [33].

As discussed above, clinical studies of RAS inhibition with using ACE inhibitors and ARBs in predominantly non-elderly patients with HF/low EF produce undeniable benefits. However, evidence from some of these clinical studies has established that elderly patients with post-MI HF are at higher risk despite therapy and a dominant mechanism is persistent adverse LV remodeling [6, 8, 10]. While reperfusion is widely used in acute MI, data on healing and remodeling post-reperfused MI in the elderly is lacking [6]. Post-MI survivors who develop HF on therapy have a 10-fold greater risk of dying [172], and the risk is even greater in the elderly [28, 173, 174]. The survivors with persistent post-ischemic LV dysfunction after reperfused MI remain at risk for remodeling and its consequences including HF despite receiving optimal therapy [135, 175–182]. Evidence suggests that aging-related impaired or defective healing/repair may be a major culprit resulting in adverse remodeling and poor outcome [6, 181].

Recent evidence from our laboratory suggests that the RAS may become dysregulated with aging [6, 9]. Physiological, cellular, and molecular changes that occur with CV aging appear to negatively impact the healing/repair response to injury including reperfused MI [6]. Timed release of several factors after injury modulate healing/repair [6, 26, 38, 176, 177]; the factors include AngII, ROS, chemokines, inflammatory cytokines, growth factors, MMPs, and other matrix proteins such as healing-specific matrix and matricellular proteins (HSMPs) including secretory leukocyte protease inhibitor (SLPI), secreted protein acidic and rich in cysteine (SPARC), and osteopontin (OPN) [6]. Together, they orchestrate inflammation, ECM remodeling and fibrosis, and adverse LV remodeling [6, 175–177]. In 2008, Bujak et al. first reported defective infarct healing and increased adverse remodeling after reperfused MI in old versus young mice [7, 8]. Since therapy for optimizing healing is lacking [6, 8], our laboratory considered the hypothesis that in aging hearts, increased myocardial AngII,

through its pro-inflammatory, pro-oxidant, and pro-remodeling effects, may amplify increases in pro-inflammatory cytokines, MMPs, and oxidative markers and contribute to impaired healing/repair and adverse LV remodeling [6]. We postulated that aging results in a dysregulation of matrix, inflammation, and fibrosis pathways, leading to impaired healing and adverse LV remodeling post-reperfused MI (Fig. 18.3). In this construct, aging-related impaired or defective healing post-MI may be the major culprit leading to defective infarct fibrosis that in turn might result in amplified adverse maladaptive LV remodeling, increased progressive LV enlargement, and increased disability and/or death in older patients. Evidence from our laboratory supports the idea that aging-related adverse remodeling may be due in part to impaired healing/repair mechanisms after reperfused MI [6, 9, 182], but further research is needed.

Our preliminary data in dog, rat, and mouse models of post-reperfused MI suggest that concurrent upregulation of the three HSMPs (SLPI, SPARC, and OPN) may interact with concurrently upregulated ECM-proteolytic, inflammation, and fibrosis pathways and contribute to remodeling in young animals [9, 182] and upregulation of the HSMPs and proteolytic, inflammation, and fibrosis pathways is amplified in old animals that develop more severe LV remodeling and dysfunction [9, 182, 183]. Importantly, the ARB candesartan attenuated these changes across the old groups albeit with a trend towards lesser benefit in the oldest [9], implicating AngII and dysregulation of inflammatory and ECM-proteolytic pathways in the augmented remodeling.

Taken together, our data suggest that the HSMPs SLPI, SPARC, and OPN that are increased post-reperfused MI may interact with inflammation and fibrosis pathways and improve healing and LV remodeling in the young, but the pathways become dysregulated in the old [9]. Thus, aging amplifies responses in the critical cellular signaling and ECM-proteolytic pathways, and interaction with the AngII/AT_1 receptor pathway after reperfused MI in the clinically relevant dog model [182]. Our preliminary data during healing after reperfused MI in rats [183] confirm that aging amplifies the increased expression of HSMPs, MMPs, and inflammatory and fibrogenic cytokines in infarct zones during healing after reperfused MI. In that study [183], SLPI, SPARC, and OPN were colocalized in macrophages and monocytes. Importantly, candesartan during healing suppressed these changes in the HSMPs and remodeling in young and old rats, implying regulation by AngII with aging. Candesartan also attenuated increases in MMPs, inflammatory and fibrogenic cytokines, and iNOS in the young and old rats, implying regulation by AngII during healing. The data also showed age-related increase in tissue myeloperoxidase (MPO, oxidant activity marker), and MPO-positive granulocytes and CD68 and MAC387-positive macrophages at day 25, implying persistent inflammation and granulation tissue with impaired healing in the late phase after reperfused MI.

In summary, our data suggest that aging upregulates two critical pathways: (1) increased AngII/ROS → increased iNOS-NO → peroxynitrite → MMP and HSMP activation → adverse remodeling and dysfunction and (2) increased AngII/ROS → increased inflammatory cytokines → MMP and HSMP activation → adverse remodeling and dysfunction.

Dysregulation of AT_2 Pathway with Aging and Effect of ACE Inhibitors and ARBs

Evidence also suggests that other components of the RAS are altered with aging. Normally in adults, most actions of AngII are mediated through AT_1 and AT_2 receptor expression is low. However, AT_2 is reexpressed in CV disease, and during AT_1 blockade, AngII induces AT_2-mediated vasodilation through the bradykinin/NO/cGMP pathway [184]. Paradoxically with aging, AT_2 activation leads to vasoconstriction via ROS rather than vasodilation in old rats [185], which explains the aging-induced AT_2R paradox in resistance arteries. This may also explain the so-called ARB-MI paradox suggesting that increased AT_2 receptor signaling during ARB therapy may prove harmful in elderly patients [159].

In the study by Pinaud et al. [185], the resistance arteries of the old rats had impaired flow- and NO-mediated vasodilation and reduced expression of endothelial NO synthase compared to young rats. Importantly, aging increased AT_2 expression in vascular smooth muscle rather than endothelial cells, and AT_2 receptor blockade improved flow-mediated dilation, implying AT_2-receptor-mediated vasoconstriction [185]. In addition, treatment with the vasodilator hydralazine attenuated AT_2 receptor induction of ROS and direct vasoconstriction, thereby enhancing flow-mediated vasodilation [185]. In a study of microvascular AT_2 receptor expression in hypertensive patients with type 2 diabetes receiving therapy with an ARB, AT_2 appears to mediate vasodilation [186]. Whether aging in humans leads to (1) a similar molecular switch from AT_2-receptor-mediated vasodilation to vasoconstriction, (2) impaired responsiveness of the bradykinin/NO/cGMP vasodilator cascade to AT_2 receptor activation, and a cell signaling switch that converts AT_2 receptor inhibition of phosphorylation of mitogen-activated protein kinase (extracellular signal-related kinase 1/2) into stimulation needs verification [184]. Whether AT_2 receptor blockers and hydralazine might be beneficial in the elderly HF patient needs study.

Aging and Remodeling of ACE-2/Ang-(1–7) and Other Pathways

Interestingly, besides AngII receptor remodeling with aging [184], in the counter-regulatory arm of the RAS, decrease of ACE-2 in null mice is associated with decreased cardiac function [93] and ACE-2 also decreases with aging [108–110]. Whether increasing the ACE2/Ang-(1–7) pathway might be beneficial in the elderly HF patient needs study. Our studies with ACE inhibition and AT_1 blockade in aging hearts with HF post-reperfused MI suggest that beneficial effect of RAS inhibition may be blunted in elderly [6, 8–10]. Remodeling of other RAS-related pathways with aging has also been described, including the inflammation and Kallikrein–kinin pathways [187], the β-adrenergic pathway [188], and the AngII-aldosterone pathway [189]. It should be noted that precautions in using both ACE inhibitors and ARBs are needed in the elderly with MI and hypertension [24, 28, 159, 190–193].

Taken together, remodeling of RAS with aging may account for the reported poor outcome post-MI despite optimal use of evidence-based therapy in the elderly [6, 27, 28]. As discussed before, clinical studies indicate that elderly post-MI patients are at higher risk for adverse events despite contemporary therapy including RAS inhibitors. Since AngII is the primary effector molecule of the RAS and AngII inhibitors form the basis of therapy for both elderly and non-elderly HF patients, this aging-induced remodeling of the RAS may have important implications for therapy based on AngII inhibitors for the elderly with post-MI HF.

RAS, Aldosterone, and the Mineralocorticoid Receptor Antagonists

The RAS was expanded to RAAS in order to emphasize the importance of the AngII-/AT_1-receptor-mediated activation of aldosterone which promotes sodium retention, loss of magnesium and potassium, sympathetic activation, parasympathetic inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction, vascular damage, and impaired arterial compliance. The rationale for using mineralocorticoid receptor (MR) antagonists (MRAs) is that AngII stimulates the release of aldosterone from the adrenal cortex, thereby activating MRs whose activation persists despite treatment with ACE inhibitors, ARBs, and β-adrenergic blockers. Several trials with MRAs have shown that MRAs effectively reduce total mortality in patients with HF/low EF [194–199] (Table 18.3). Based on evidence from two of the first two RCTs [194, 196], the addition of an MRA is reasonable in patients with moderate to severe HF/low EF provided renal function (serum creatinine ≤2.5 mg/dL in men and ≤2.0 mg/dL in women) and serum potassium (≤5.0 mEq/L) are carefully

Table 18.3 Some major trials of mineralocorticoid receptor antagonists (MRAs) in heart failure

Year—trial [reference]	*N*	Drug	Comparator	Age (years)	Outcome
1999 RALES [194]	1,663	Spironolactone	Placebo	65	↓ Mortality/morbidity
2000 RALES substudy [195]	261	Spironolactone	Placebo	69	↓ Mortality/morbidity; benefit highest in patients with high baseline collagen synthesis marker (PIIINP)
2003 EPHESUS (MI + HF) [196]	6,632	Eplerenone	Placebo	64	↓ Mortality/morbidity
2005 EPHESUS substudy [197]	6,632	Eplerenone	Placebo	64	↓ All-cause mortality at 30 days
2009 Diastolic HF [198]	44	Eplerenone	Control	80	↓ Collagen turnover marker (PIIINP); no clinical benefit
2011 Systolic HF [199]	2,737	Eplerenone	Placebo	69	↓ Mortality; ↓ hospitalization

Abbreviations: ↓ decrease in, *HF* heart failure, *MI* myocardial infarction, *N* number of patients

monitored. In RALES [194], the MRA spironolactone as an add-on to background therapy with ACE inhibitor, β-adrenergic blocker, diuretic, and digoxin in patients with moderate to severe HF (EF < 35 %) was prematurely terminated due to an early finding of a 30 % reduction in all-cause mortality and reduced morbidity and hospitalization. However, gynecomastia occurred in 10 % and hyperkalemia in 2 % of treated patients. In EPHESUS [196], the MRA eplerenone that selectively blocks the MR but not glucocorticoid, progesterone, or androgen receptors was assessed as an add-on to optimal medical therapy in post-MI HF patients with EF ≤ 40%. EPHESUS [196] reported a 14 % reduction in all-cause mortality, 17 % in CV mortality, and 15 % in risk of hospitalization. However, serious hyperkalemia occurred in 5.5 % and increased to 10 % in patients with baseline renal dysfunction defined as creatinine clearance <50 mL/min [196]. In a recent trial in patients with systolic HF and mild symptoms, eplerenone reduced both the risk of CV death and HF hospitalization but the trial was terminated prematurely according to prespecified rules [199]. In that study [199], serum potassium was >5.5 mmol/L in 11.8 % of patients receiving eplerenone compared to 7.2 % receiving placebo ($P < 0.001$).

In a substudy of RALES [195], the MRA spironolactone increased levels of markers of collagen synthesis, suggesting that limitation of excessive extracellular matrix (ECM) turnover contributed to the benefits. In a substudy of EPHESUS [197], early initiation of eplerenone was reported to reduce the 30-day all-cause mortality after acute MI. In a study of HF/PEF patients, eplerenone prevented progressive increase in procollagen type-III aminopeptide but had no impact on other markers of collagen turnover or diastolic function [198]. A recent meta-analysis of RCTs with MRAs spironolactone, canrenoate, and eplerenone demonstrated that MRAs exert beneficial effects on reversal of LV remodeling and dysfunction [200].

Close monitoring of renal function and serum potassium should be done when using MRAs, especially in the elderly. Both RALES and EPHESUS excluded patients with serum creatinine >2.5 mg/dL. Since use of aldosterone antagonists in patients with renal dysfunction (creatinine clearance <50 mL/min) increases the risk of hyperkalemia and this risk is greater in elderly patients and those receiving an ACE inhibitor or ARB concurrently, spironolactone or eplerenone should be used at a low dose under those circumstances and avoided in those with creatinine clearance <30 mL/min. In patients already receiving a long-term diuretic and potassium supplements, the latter should be reduced or discontinued.

Aging, RAAS, and Mineralocorticoid Receptor Antagonists

Whereas AngII is increased AngII [30, 31] with aging and AngII stimulates aldosterone secretion, aging in healthy humans results in decreased

plasma aldosterone levels [201]. While this finding implies a dysregulated response in the AngII–aldosterone axis with aging and would suggest a reduced need for MRAs in elderly patients with HF, several lines of evidence suggest that aging may in fact result in enhanced activation of the MR. First, in a study of steroid hormone metabolites in hypertensive patients aged 18–84 years, aging was associated with decreased 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) activity [202]. This might explain the rising prevalence of HTN in the elderly. Importantly, the enzyme 11βHSD2 has been shown to convert cortisol and corticosterone to cortisone and 11-dehydrocorticosterone which are MR-inactive 11-keto derivatives [203, 204]. More importantly, cortisol not only activates MR but has greater affinity for MRs than aldosterone [205]. Since 11βHSD2 in renal tubular epithelium converts most of the cortisol into cortisone, aldosterone is the main endogenous agonist and activator of MRs in renal tubules normally and in the young [205]. Normally, cortisol seems to occupy epithelial and nonepithelial cells in tonic inhibitory fashion but, in the presence of tissue damage, becomes an MR agonist; this may explain both vascular and myocardial MR activation in HTN and HF and efficacy of MRAs despite low aldosterone levels [206]. Moreover, in the elderly with HTN [202] and non-elderly patients with essential HTN aged 40–60 years [207] with low aldosterone levels, decreased renal 11βHSD2 activity and increased cortisol may explain enhanced MR activation and justify use of MRAs. While data from mostly non-elderly patients show that the gene encoding aldosterone synthase (CYP11B2) is associated with high aldosterone and HTN and the adjacent gene (CYP11B1) encoding 11β-hydroxylase is associated with altered adrenal 11-hydroxylation efficiency (deoxycortisol to cortisol), more research is needed to determine their relative roles in the elderly and very old with HTN.

Second, while MRs are also present in myocardium, most cardiac aldosterone seems to come from the adrenals via the circulation, and glucocorticoids and aldosterone may serve as endogenous cardiac MR agonists [208]. As discussed before, low myocardial 11βHSD2 and increased cortisol in the elderly may lead to enhanced myocardial MR activation. In addition, increased AngII, ROS, and oxidative stress in the elderly and HF may act in synergy and contribute to increased MR activation, inflammation, fibrosis, myocardial hypertrophy and apoptosis, and thence HF progression [6, 189].

Third, a study in rats showed that aging is also associated with increased MR activity in vascular smooth muscle cells which promotes inflammation via extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase and epidermal growth factor receptor-dependent pathways [209]. Fourth, since enhanced MR activation in the elderly leads to increased expression of tissue ACE and upregulation of AT_1 receptors [210], combined AngII and aldosterone blockade or inhibition has been proposed for increasing benefits [211]. Both these studies [210, 211] used telomere length in white blood cells (WBCs), an index of CV aging and the burden of oxidative stress. Fifth, the three early clinical trials of MRAs in HF/low EF included the elderly and showed efficacy in both young and old patients with [194–196]. The mean age was 65 years in RALES with spironolactone [194] and 64 and 69 years, respectively, in EPHESUS [196] and EMPHASIS-HF [199] with eplerenone. Importantly, the decrease in total mortality and HF hospitalizations was similar in the elderly and non-elderly groups.

Sixth, MRAs may be especially effective in elderly patients with HF/PEF, where the dominant pathology is HTN associated with LV hypertrophy and myocardial fibrosis. Therapy with ACE inhibitors, ARBs, and β-adrenergic blockers fail to reduce mortality in that group. Specific therapy for diastolic dysfunction is lacking in all age groups and myocardial fibrosis is a major cause of diastolic dysfunction in the elderly even in the absence of HTN. Since RAAS inhibitors are powerful antifibrotic agents, it is reasonable to hypothesize that elderly patients might benefit from them unless the pathways are dysregulated [6].

As discussed before, the emerging paradigm is that aldosterone-induced MR activation leads to myocardial and vascular fibrosis in the non-elderly,

while amplified cortisol-induced MR activation leads to amplified stimulation of fibrosis in the elderly and patients with essential HTN. In a substudy of RALES in patients with HF/low EF, spironolactone limited fibrosis and reduced procollagen I and III levels [195] and the mortality benefit was mainly in patients with continuing collagen turnover [189]. In the 4E trial of older adult patients with essential HTN, LV hypertrophy, and mean ages between 59 and 60 years [212], combination therapy with the ACE inhibitor enalapril and the MRA eplerenone was more effective than monotherapy in decreasing LV mass and albuminuria despite normal plasma aldosterone levels, endorsing the hypothesis that the MRA may have blocked cortisol-induced MRA activation in the face of decreased 11β-HSD2. In the small study of elderly patients with HF/PEF ($N=44$; mean age 80 ± 8 years), eplerenone prevented progressive increase in collagen turnover assessed by procollagen III aminoterminal peptide and despite background therapy with ACE inhibitors in 64 %, ARBs in 34 %, and β-adrenergic blockers in 68 % [198]. In a small study of older adult patients with HF/PEF and mean age 62 ± 6 years, spironolactone limited diastolic dysfunction [213]. In another small study of patients with HTN aged between 30 and 70 years, eplerenone reduced vascular stiffness more than the β-adrenergic blocker atenolol [214]. However, the mean ages in the three groups in that study (controls 51, eplerenone 54, atenolol 44 years, respectively) suggested that most patients were non-elderly [214]. In a small study of patients with HTN, regression of LV mass correlated with the decrease in plasma aldosterone, and the ARB losartan reduced LV mass more than the calcium channel blocker amlodipine by reducing plasma aldosterone in addition to BP [215]. In the Aldo-DHF multicenter, prospective, randomized, double-blind, and placebo-controlled 6-year (2007–2012) trial of spironolactone in HF/PEF patients aged ≥50 years (mean 67 ± 8 years), spironolactone improved diastolic function without improving exercise capacity or quality of life [216].

In the ongoing 6-year (2006–2013) phase 3 treatment of preserved cardiac function heart failure with an aldosterone antagonist (TOPCAT) trial of spironolactone on CV mortality and HF hospitalization in 3,445 older adult and elderly patients with HF/PEF (age ≥50 years; mean 69 ± 10 years), 91 % have HTN [217]. This trial is also multicenter, prospective, randomized, double-blind, and placebo controlled. Comorbidities typically include coronary artery disease (57 %), atrial fibrillation (35 %), chronic kidney disease (38 %), and diabetes mellitus (32 %) [217].

MRAs in Very Old Elderly Patients with HF/PEF

Elderly and especially very old (aged ≥80 years) patients with HF/PEF frequently have concomitant comorbidities including obesity, sleep apnea, coronary artery disease, atrial fibrillation, chronic renal disease, and diabetes that may benefit from MRAs [189, 217]. Several lines of evidence provide justification for blockade of effects of aldosterone and MR activation in epithelial and nonepithelial tissues of these patients. First, evidence from studies of telomere length in white blood cells (WBCs) suggests that aldosterone accelerates CV aging through mechanisms that generate ROS and telomere length may serve as an index of the burden of oxidative stress. In a study of normotensive and mild hypertensive males, plasma aldosterone was inversely related to telomere length, suggesting that aldosterone is not only pro-oxidant but increased levels might be linked to accelerated telomere shortening and increased biological aging [211].

Second, other studies suggest that aldosterone and MR activation exert CV and renal pleiotropic effects that extend well beyond the classical renal regulation of sodium balance. Mechanisms include oxidative stress, inflammation, impaired vascular reactivity, and endothelial-mediated vasorelaxation, downregulation of proteins in insulin metabolic pathways, and impaired renal podocyte and mesangial cell integrity. Elevated plasma aldosterone in patients with metabolic syndrome [218], kidney fibrosis [219], sleep apnea [220], and CHD [221, 222] has been implicated in the pathophysiology of these conditions.

Interestingly in the latter study [222], plasma aldosterone was directly related to BMI (body mass index), HTN, and NYHA class besides mortality and ischemic events and inversely to age, creatinine clearance, and use of β-blockers.

Third, adipocytes which protect against urinary protein loss were shown to release Rac-1 and other proteins that stimulate adrenal release of aldosterone [223]. Interestingly, while obese patients with metabolic syndrome often have salt-sensitive HTN and only ~33 % have elevated plasma aldosterone, MRAs prevent salt-induced cardiorenal damage suggesting that high salt and aldosterone contribute to the damage [224]. This is explained by the discovery of an alternative pathway of MR activation through the small GTP-binding protein Rac-1 which is activated by both high salt and hyperglycemia [224]. Fourth, evidence from patients with primary aldosteronism also supports the hypothesis that aldosterone suppresses pancreatic beta-cell function leading to insulin resistance with hyperglycemia and diabetes [225]. Fifth, aldosterone was shown to impair vascular reactivity by reducing glucose-6-phosphate dehydrogenase (G6PD) expression thereby decreasing glutathione, antioxidant reserve, nitric oxide (NO) generation, and NO availability [226].

Sixth, aldosterone was shown to increase signaling via nuclear factor κB (NFκB) and transcription factor activator protein-1 (AP-1) pathways, inflammation, and cytokine expression in vascular smooth muscle cells, thereby contributing to endothelial dysfunction and atherosclerosis [227, 228]. These and other studies of the aldosterone → oxidative stress → inflammation → endothelial dysfunction axis and the aldosterone → oxidative stress → hypertrophic remodeling/fibrosis axis suggest that many of the effects of aldosterone are mediated by genomic and nongenomic pathways in MR-dependent or independent manner [227]. Seventh, macrophages in the vascular wall and atherosclerotic plaques have been shown to express MRs [229]; aldosterone also stimulates vascular NADPH oxidase and p38MAP kinase and release of MMPs that mediate progression of atherosclerosis and plaque rupture [189, 227, 228]. Eighth, other studies in monocyte-derived macrophages from patients with congestive HF suggested that the protective role of MRAs is partly due to increased generation of Ang-(1–7) and ACE2 and decreased AngII formation, and the effects were mediated by NADPH oxidase [230]. Interestingly, aldosterone and/or cortisol-induced of MR is associated with upregulation of the AT_1 receptor as well as downregulation of ACE2 [231].

Ninth, in the EMPHASIS-HF study of elderly patients with systolic HF and mild symptoms, eplerenone not only reduces mortality and hospitalization [199] but also reduces the incidence of new atrial fibrillation/flutter likely via attenuation of atrial remodeling and fibrosis [232]. Tenth, MRAs also block the aldosterone-induced renal podocyte injury associated with decreased NADPH oxidase, increased oxidative stress, and enhanced aldosterone effector kinase Sgk1, thereby decreasing podocyte damage, albuminuria, and mesangial fibrosis [219, 233]. MRAs also inhibit MR-mediated kidney DNA damage in DOCA-salt hypertensive rats [234]. Eleventh, MRAs also attenuate LV hypertrophy and vascular stiffness in chronic kidney disease [223].

Twelfth, although many studies show that MRAs limit remodeling and fibrosis in various models of chronic HF, the mechanisms of benefit are not completely clear. In one study of MI in rats, angiotensin and aldosterone blockade inhibited osteopontin expression, LV remodeling, and fibrosis [235]. Enhanced MR signaling induced by transgenic expression of 11βHSD2 to drive cardiac hypertrophy and HF results in severe cardiomyopathy, fibrosis, and increased mortality that are partially improved by eplerenone treatment [236]. Transgenic overexpression of aldosterone synthase in cardiomyocytes causes coronary dysfunction but prevents harmful effects of diabetes by preserving capillary density [237]. Ablation of MRs in cardiomyocytes but not cardiac fibroblasts preserves cardiac function and limits cardiac dilation in chronic pressure overload [238]. Studies of selective ablation of MR expression in different cardiac cell types may help to clarify mechanisms of cardioprotection by MRAs [238]. More systematic studies of MRAs in the old and very old versus young groups are needed to uncover ancillary pathways.

MRAs and Hyperkalemia in the Elderly and Very Old Elderly Patients with HF

While MRAs are considered beneficial in elderly and very old patients, the risk of hyperkalemia is greater in very old elderly HF patients [189] and those with chronic kidney disease and/or diabetes [239]. It is therefore prudent to closely monitor serum potassium and reduce the dose of MRAs in these patients. In TOPCAT, spironolactone was initiated at a lower dose of 15 mg daily, with escalation to 45 mg daily provided serum potassium is <5 mEq/L [217]. Hyperkalemia can be treated by the new potassium binding polymer RLY5016 [240]. This was evaluated in patients with mean age of 68 years, chronic kidney disease, and a history of hyperkalemia resulting in discontinuation of RAAS therapy in the PEARL-HF trial [240]. The patients received 30 g/day of RLY5016 on top on spironolactone 25–50 mg/day; adverse drug reactions (ADRs) with RLY5016 were seen in 7 % (versus 6 % in placebo) while hypokalemia ($K^+ < 3.5$ mEq/L) occurred in 6 % (versus 0 % in placebo) [240]. More cardioselective MRAs with better Na+/K+ ratio than spironolactone and eplerenone may be safer in elderly and very old patients [189].

Novel RAAS Therapies in Hypertension: Aldosterone Synthase Inhibition

A meta-analysis of RCTs of RAAS inhibitors in hypertensive patients suggested that in patients with HTN, ACE-inhibitor treatment, but not ARB treatment, resulted in further reduction of all-cause mortality [241]. However, the authors did not discuss impact of age. Control of BP and end-organ damage with therapy of HTN with conventional RAAS inhibitors can be challenging but a number of novel approaches hold promise for treatment of resistant HTN [242] and need evaluation in the elderly. Resistant or uncontrolled HTN despite three antihypertensive agents of different classes [243] is considered a trigger of cardiac decompensation in very old patients with HF/PEF and comorbidities such as diabetes and chronic kidney disease [189]. While there are proponents of triple therapy with combined RAAS inhibition using combined ACE inhibitor, ARB, and MRA for resistant HTN, such triple therapy is not recommended for all patients along the cardiorenovascular continuum; rather, in congestive HF patients with incomplete neuroendocrine blockade evidenced by repeated bouts of cardiac decompensation, dual therapy can be tried with close attention to patient safety [244].

The rationale for aldosterone synthase (CYP11B2) inhibitors is to inhibit aldosterone formation and thereby prevent increase in aldosterone levels and their MR-independent effects. Evidence suggested that the aldosterone synthase inhibitor LCI99 was modestly effective in patients with primary aldosteronism (mean age 50 years), decreased BP, corrected hypokalemia, and produced latent inhibition of cortisol synthesis [245]. Its development was stopped in favor of the search for more specific inhibitors [242]. The aldosterone synthase inhibitor FAD286 was shown to reduce mortality, cardiac hypertrophy, albuminuria, cell infiltration, and matrix deposition in the heart and kidney of double transgenic renin and angiotensinogen (dTGR) rats without profound effect on BP [246]; reduce cardiac and renal fibrosis induced by AngII and high salt in uninephrectomized rats [247]; and improve LV hemodynamics, remodeling, function, and redox status in rats with HF [248]. Data on the aldosterone synthase inhibitors in older groups is lacking.

Novel RAAS Therapies in Hypertension: Renin Inhibition

Renin as a target has been debated at least since the 1990s, since it catalyzes the key rate limiting step in the RAAS cascade. The selective renin inhibitor aliskiren has been shown to reduce AngI and AngII levels [249] and attenuate BP comparable to β-blockers [250], diuretics [251], ACE inhibitors [252, 253], and ARBs [254]. It attenuates plasma renin activity that is increased by ACE inhibitors and ARBs [255]. However, high renin levels due to escape during aliskiren therapy is a concern [256] as aliskiren does not prevent binding of renin to pro(renin) and

activation of pro(renin) receptors [257]. Aliskiren, in a dose that did not reduce BP, improved LV dysfunction and remodeling after MI in mice and decreased apoptosis [258]. In patients with symptomatic HF, HYHA class II–IV, a history of HTN, elevated BNP, and mean age of 68 years, aliskiren on top of an ACE inhibitor or ARB and β-blocker had favorable neurohumoral effects [259]. The ASTRONAUT study will test whether aliskiren on top of standard therapy will reduce post-discharge mortality and rehospitalization in patients with worsening HF/low EF [260]. The ATMOSPHERE study will determine whether aliskiren added to or as an alternative to ACE inhibition in patients with chronic systolic HF improves outcomes [261]. In the ASPIRE study, adding aliskiren to standard therapy including a RAAS inhibitor in high-risk post-MI patients with LV systolic dysfunction did not result in further attenuation of LV remodeling and was associated with more adverse effects [262]. The ASPIRE HIGHER program should provide data on protection from target organ damage and CV morbidity/mortality in a range of cardiorenal conditions including HF, post-MI, and diabetic nephropathy [263]. The AVOID study showed that aliskiren may be renoprotective and reduced albuminuria in patients with type 2 diabetes, kidney disease, and HTN [264]. Several of those studies included the elderly. The ALTITUDE study which aimed to determine whether aliskiren on top of an ACE inhibitor or ARB therapy delays cardiorenal complications in patients with type 2 diabetes at high risk for cardiorenal events was stopped in 2012 because of no apparent benefit and an increase in adverse events including hyperkalemia (aliskiren 11 % versus placebo 7 %) and hypotension (12 % versus 8 %) [265]. Whether aliskiren might benefit the elderly with HTN and HF/PEF remains to be addressed.

Dual-Action Molecules in Elderly Patients with HF/PEF

Dual inhibition of ACE and neutral endopeptidase (NEP) pathways in a single molecule such as omapatrilat (OMA) was studied in patients with HTN, but despite superior antihypertensive efficacy over ACE inhibition and equal anti-remodeling efficacy in HF patients [266], the Federal Drug Administration (FDA) bureau did not approve OMA for patients with HTN because of troubling angioedema. The concept of dual-action molecules was recently revisited with LCZ696, which combines neprilysin (NEP) and the ARB valsartan in a phase 2 trial and was shown to be beneficial in patients with HF/PEF [267] and is being evaluated in patients with HF/low EF [267, 268]. Whether dual pathway inhibition may be more effective in elderly HF patients needs study.

Conclusion

The RAS/RAAS has critical functions in CV physiology and CV pathophysiology. Evidence over three decades since the 1980s indicates that RAS/RAAS upregulation plays a major role in CV pathophysiology. Thus, the RAS/RAAS play critical roles in both post-MI dilative remodeling associated with HF/low EF and hypertrophic remodeling and fibrosis associated with hypertensive disease and HF/PEF. Aging is associated with enhanced dysregulation of the RAS evidenced by increased AngII and several components of the RAS. Evidence suggests that dysregulation of the RAS may contribute to CVD and the RAS dysregulation may be further amplified with aging. This enhanced remodeling of the RAS may account for the poor outcome in elderly post-MI patients. Emerging evidence suggests aging-related dysregulation in the RAAS with reduced plasma aldosterone and enhanced MR activation related to cortisol and other pathways that may benefit from MRAs. Enhanced RAS/RAAS remodeling may have important implications for therapy based on AngII inhibitors and MRAs in elderly patients with post-MI HF. It is important to remember that these therapies were tested in mostly non-elderly patients. More research into the biology of aging-induced remodeling of the RAS/RAAS and related pathways may lead to discovery and development of improved therapies for post-MI HF and post-HTN HF in different age groups and tailored for the young, adult, and elderly patient.

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19 Aging and Right Ventricular Failure from Pulmonary Hypertension: Effect of Right Ventricular and Pulmonary Artery Remodeling

Joseph Szeman Wong and Bodh I. Jugdutt

Introduction

Pulmonary hypertension (PHTN) is defined as a mean pulmonary arterial pressure at rest ≥25 mmHg. There are five types of PHTN according to the most recently published world health organization (WHO) classification (see Table 19.1) [1]. Pulmonary arterial hypertension (WHO type I) is rare, with prevalence of 15 cases per million [2], but other types (WHO types II–V) of PHTN are common, affecting 10–20 % of the population [3]. For comparison, the prevalence of systemic hypertension in the USA is 29–31 % [4]. Increasing age, left ventricular (LV) end-diastolic pressure (LVEDP) >25 mmHg, obesity, dyspnea on exertion, atrial arrhythmia, and chronic obstructive pulmonary disease (COPD) are associated with development of PHTN [3].

Previous diagnostic criteria [5] also define PHTN as a mean pulmonary arterial pressure of ≥35 mmHg with exercise; however, studies showed that mean pulmonary arterial pressure can be elevated above 35 mmHg in apparently normal individuals [6, 7]. PHTN was also classified as primary and secondary, implying that secondary causes may be present. However, it is becoming clear that some types of secondary PHTN resemble primary pulmonary arterial hypertension in clinical manifestations and responses to therapy; it was therefore reclassified into five types as shown in Table 19.1 [8].

This chapter presents known information on the effects of aging on the structures of the pulmonary vasculature and right ventricle. It draws attention to the more common types of PHTN and their prognosis and treatment. The relevant pathobiology is presented briefly and updated references provided as there is increasing interest in the effect of PHTN on right ventricular structure and function.

Pathophysiology

Sustained PHTN exerts hemodynamic stresses on the pulmonary vasculature and right ventricle, leading to biochemical and structural changes. Aging [9], through various mechanisms, results in structural changes in the pulmonary vasculature, right ventricle [10, 11], and pulmonary hemodynamics [12]. Aging also determines the timing of the manifestation of the disease.

J.S. Wong, MBBS, MRCP, FHKCP, FRCPC (✉)
Division of Cardiology, Department of Medicine, University of Alberta Hospital, 2C2, WMC, 8440 112 Street, Edmonton, AB, Canada T6G 2B7
e-mail: josephswong@gmail.com

B.I. Jugdutt, MD, MSc, DM, FRCPC
2C2 W.C. Mackenzie Health Sciences Centre, Division of Cardiology, Department of Medicine, Mazankowski Alberta Heart Institute, University of Alberta and Hospitals, 727, Todd Landing NW, Edmonton, AB, Canada T6G 2B7
e-mail: bjugdutt@ualberta.ca

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Table 19.1 WHO Classification of Pulmonary Hypertension (Modified from Dana Point 2008)

Type 1. Pulmonary arterial hypertension
Idiopathic PAH; heritable such as in familial PAH associated with BMPR2 Persistent pulmonary hypertension of the newborn; congenital heart disease
Drug and toxin induced; pulmonary veno-occlusive disease
Connective tissue disease; chronic liver disorder with portal hypertension
HIV infection, schistosomiasis
Chronic hemolytic anemia
Pulmonary capillary hemangiosis
Type 2. Pulmonary hypertension due to left heart disorders
Systolic or diastolic heart failure; valvular heart disease
Type 3. Pulmonary hypertension due to lung disease and/or hypoxia
Chronic obstructive pulmonary diseases
Sleep-disordered breathing; alveolar hypoventilation disorders
Interstitial lung disease; chronic exposure to high altitude
Developmental abnormalities
Other pulmonary disease with mixed restrictive and obstructive pattern
Type 4. Chronic thromboembolic pulmonary hypertension
Type 5. Pulmonary hypertension with unclear multifactorial mechanisms

Aging-related changes in the right ventricle and pulmonary vasculature should be distinguished from adaptive and pathological responses to PHTN.

One example of how aging affects the manifestation of the disease is with arrhythmogenic right ventricular dysplasia (ARVD), which commonly presents at ages between 10 and 50 years, the mean age of presentation being 30 years. It seldom presents before the age of 10 years or during infancy [13]. The exact mechanism is unknown. Interaction with aging-related changes in the right heart and pulmonary vasculature may play a role in the late presentation.

Right ventricular remodeling refers to the adaptive changes in right ventricular cavitary geometry and wall thickness in response to increased load such as pressure afterload and volume overload [14]. Failure of this adaptive response carries important prognostic information in primary PHTN, left-sided heart failure, as well as in congenital heart diseases. Right ventricular remodeling and failure are important indicators in terms of understanding of the pathogenesis and prognosis in PHTN [15]. It is best studied in primary PHTN, and we are beginning to recognize the importance of right ventricular failure and PHTN in association with other subsets of PHTN [16]. Right ventricular function is very important in the pathogenesis and prognosis, and a landmark report has been published in recognition of this [17].

Historically, the right ventricle is "silent" and has been considered as a mere conduit for the left ventricle. As a result, clinical knowledge and pathophysiological understanding of right ventricular dysfunction have lagged behind those of the left ventricle. Because of the poor survival in patients with primary PHTN, with a mortality rate of 20–40 % 3 years after initial diagnosis [18, 19], no long-term human data on the impact of aging on the remodeling pathways are available. However, the effect of aging on survival can be gleaned from registry data. In 2009, the first longitudinal follow-up data for the effect of PHTN on survival was reported from Olmsted County. Pulmonary arterial blood pressure was found to be the independent predictor of survival when adjusted for aging, pulse pressure, left ventricular ejection fraction (LVEF), LVEDP, and spirometry [10].

Aging and Normal Right Ventricular Function

The right ventricle is different from the left ventricle, both in embryonic origin [20] and mechanics. In contrast to the left ventricle, the right ventricle is triangularly shaped and wraps around the left ventricle. Its particular morphology precludes simplistic geometrical assumption both in normal and disease state. It has two major components: the inflow (sinus) portion and an outflow (conus or infundibular) portion separated by the crista supraventricularis, which serves as a contractile strut to transmit septal contraction to the right ventricular free wall.

In the absence of a shunt, the right ventricular cardiac output is the same as the LV cardiac output since the two systems are connected in series. However, the pulmonary vasculature is normally a low-pressure system with mean arterial pressure that is about 1/5–1/6 of the systemic circulation and vascular resistance of 1/10 of the systemic circulation; the right ventricular cavity is also slightly larger than on the left side, and the resulting normal ejection fraction is less on the right than on the left (45–70 %) [21].

In the healthy state, the transpulmonary gradient is 5 mmHg, and this drives continuous flow of blood into the low-resistance pulmonary arterial system throughout systole. An often overlooked point is that the right coronary artery supplies the majority of the right ventricle both during diastole and systole. However, in the presence of PHTN and right ventricular hypertrophy, the coronary flow becomes predominantly diastolic [22] and less tolerant to ischemia [23]. In the normal right ventricle, longitudinal shortening contributes to the systolic ejection more than the transverse contraction, and therefore longitudinal shortening correlates more to the ejection fraction; however, in the hypertrophied right ventricle, circumferential contraction and free wall translation contribute more to the systolic function [24].

The right ventricle and the left ventricle share the same interventricular septum and coronary supply; they are both encased in the same pericardial cavity and interconnected to the same pulmonary vasculature. The endothelial overlay of the pulmonary vasculature is the largest of all the organ endothelium systems [25–27] and plays a significant role in both the initiation of pathological changes and in communications of signals at cellular and molecular levels.

During the normal process of aging, the pulmonary artery becomes slightly stiffer as histologically there are more elastic materials in the arterial wall; the right ventricular size and systolic function remain unchanged, but right ventricular diastolic function is altered, typically with reduced early diastolic flow and increased late diastolic flow as well as reduced diastolic flow velocities.

Right Ventricular Remodeling and Right-Sided Heart Failure: Definitions and Causes

Right ventricular remodeling defines the adaptive process involving right ventricular wall thickness, chamber geometry, and with time, progressive dilatation. Right ventricular remodeling can result from pressure overload, volume overload, ischemia, primary myocardial disease, or a combination of several causes. The mechanism of human right ventricular remodeling is less well characterized, but it has received much attention in animal models. Understanding of the adaptive mechanism, either physiological or pathological, in various types of PHTN will help develop interventions to arrest the disease process early and prevent its progression.

Right ventricular dysfunction results in abnormal diastolic filling and systolic contraction. Right ventricular failure refers to the inability of the right ventricle to fulfill its functional role, resulting in constellations of clinical manifestations which most of them are nonspecific. Therefore, it is more difficult to make a specific clinical diagnosis of right ventricular failure [28].

Causes of right ventricular failure include primary right ventricular myopathies such as ARVD, right ventricular infarction, massive pulmonary embolism, PHTN, valvular heart disease such as tricuspid stenosis or regurgitation, pulmonic stenosis and congenital conditions such as Tetralogy of Fallot, pulmonary stenosis, Ebstein's anomaly, and congenitally corrected transposition of great arteries. The most common cause resulting in right ventricular failure is left-sided heart failure, both systolic and diastolic LV dysfunction. Uncoupling of the right ventricle to the pulmonary circulation can result in acute right ventricular failure, such as perioperative acute right heart failure in heart transplant patients who have a preexisting high pulmonary vascular resistance (PVR). Acute right heart failure in the intensive care setting predicts early mortality [29].

Symptoms associated with aging often mask the presentation of PHTN. Others are nonspecific and include dyspnea on exertion, fatigue, chest pain, or near-syncope or actual syncope. Clinical suspicion with early investigation is indicated.

Physical examination will reveal the underlying disorders and might be associated with a heart murmur and increased pulmonary component of second heart sound (P2). Normal aging can give rise to a slightly higher pulmonary arterial pressure at rest and also after exercise [30].

Epidemiology

The classic form of PHTN is characterized by changes in the small pulmonary arteries with intimal fibrosis, vascular smooth muscle hypertrophy, and remodeling of the adventitia (Fig. 19.1). Aging confounds the pathogenesis by associated structural changes in pulmonary arteries and right ventricle [31–33]. In primary PHTN, males aged >60 years was one of the indicators of poor prognosis in the REVEAL Registry predictive model [34].

All forms of PHTN share the common pathway (Figs. 19.2 and 19.3) of increased stress on the right ventricle. This leads to secondary changes in the right ventricle, including right ventricular hypertrophy and with time, dilatation, and failure [28, 35–37]. Epidemiological study demonstrated that right ventricular dysfunction is associated with high risk of cardiovascular mortality and morbidity [38]. The best characterized entity is primary PHTN.

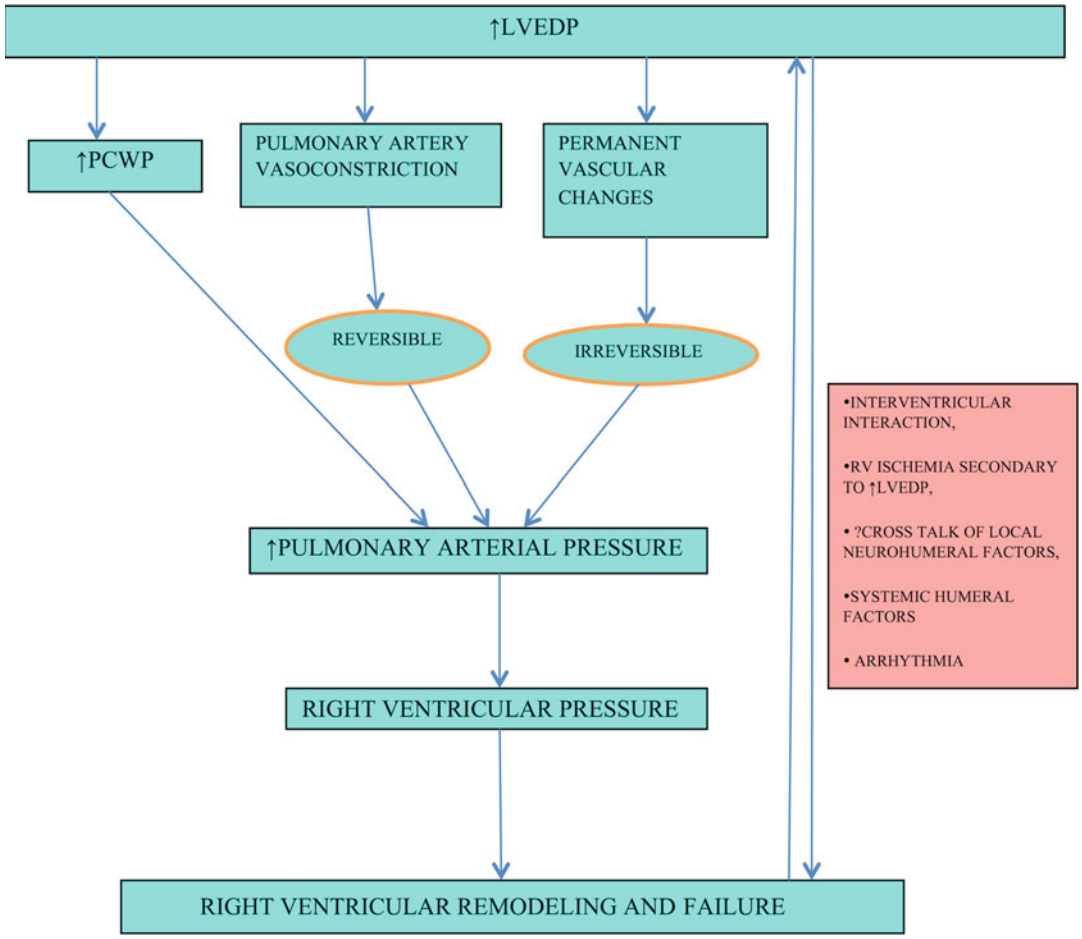

Fig. 19.1 Pathogenesis of pulmonary hypertension in left-sided heart failure. Progressive increase in the left ventricular end-diastolic pressure leads to a progressive worsening of right ventricular remodeling and failure. *LVEDP* left ventricular end-diastolic pressure, *PCWP* pulmonary capillary wedge pressure, *RVSP* right ventricular systolic pressure

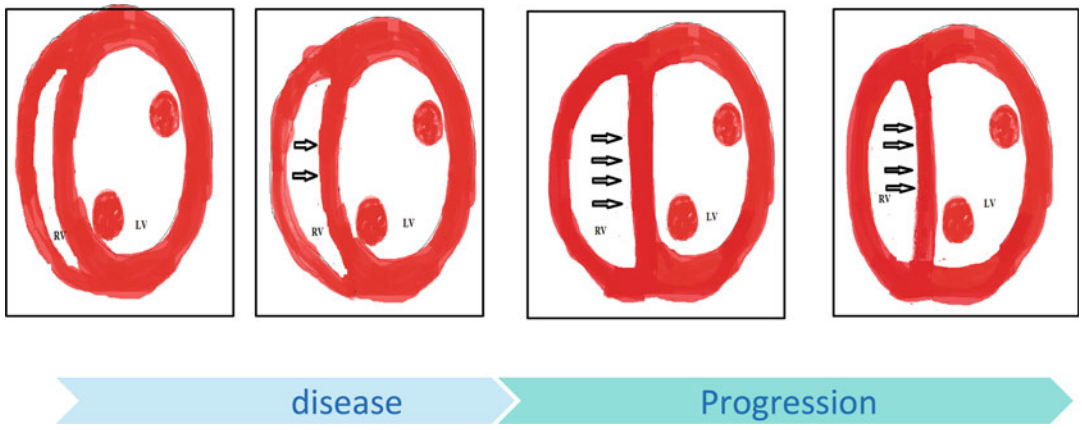

Fig. 19.2 Progressive right ventricular remodeling and failure. Progressive changes in the size of right ventricle and position of septum during diastole. Transverse section of the ventricles in end-diastole with progressive right ventricular remodeling and failure. Note that the normal right ventricle is only 1/3 of the left ventricle in size; as the right ventricle dilates and right-sided pressure increases, there is flattening of the interventricular septum and ultimately reversed bowing of the interventricular septum so that the curvature is away from right ventricle. *LV* left ventricle, *RV* right ventricle, *LVEDP* left ventricular end-diastolic pressure, *TPG* transpulmonary pressure gradient, *PCWP* pulmonary capillary wedge pressure, *RVSP* right ventricular systolic pressure, *Ees* right ventricular end-systolic elastance, *Ea* effective arterial elastance, *IVS* interventricular septum

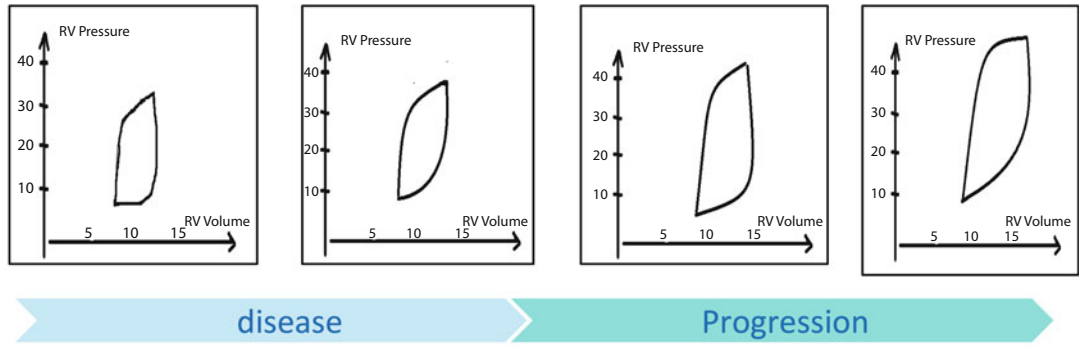

Fig. 19.3 Pressure–volume loop for the right ventricle as remodeling progresses. Pressure–volume *loop curve* depicts the progression of right ventricular failure. The *vertical axis* is the right ventricular pressure/pulmonary artery pressure; the *horizontal axis* is the right ventricular volume. There is progressive reduction of the slope of the *curve* at peak systolic pressure representing reduced right ventricular contractility; the peak right ventricular pressure increases as pulmonary hypertension increases; also the pulmonary vascular resistance increases and effective arterial elastance increases; these changes result in a worsening of right ventricular contractility and pulmonary vascular uncoupling (↓Ees/Ea)

Right Ventricular Failure Secondary to Primary Arterial Hypertension

Primary PHTN is a rare disease with incidence of 2.4 per million and prevalence of 15 per million [2]. It is defined by resting mean pulmonary arterial pressure ≥25 mmHg, PVR > 3 Woods units, and pulmonary capillary wedge pressure <15 mmHg. Historically, it is called pulmonary arterial hypertension (PAH) [39].

Primary PHTN typically affects young women, but several registry data have shown that the mean age of presentation has moved from 36 years to 45

years in recent years. The exact reason for this change in age of presentation is unknown and might be related to more widespread use of echocardiography in screening.

The precise etiology of PAH is unknown [40]; it might represent a common pathway resulting in abnormal function of the pulmonary vascular tree predominantly the endothelial system and pulmonary arterial smooth muscle cells [41]. Evolving new paradigms are being developed as a result of extensive research [42]. Genetic influence has been implicated, as more than 80 % of familial PAH have loss of function mutation in bone morphogenetic protein receptor 2 (BMPR2); this mutation promotes cellular proliferation in pulmonary artery endothelium and vascular smooth muscle cells [43]. It is also associated with a panvasculopathy involving circulating blood [44], endothelial cells [45], pulmonary artery smooth muscle cells [46–48], as well as adventitia [49]. Varying degrees of thrombosis, vasoconstriction, vascular proliferation, and chronic inflammation underlie chronic PHTN and perpetuate the disease progression. The resulting effect is progressive increase in pulmonary vascular resistance and PHTN.

The right ventricular adaptation to PHTN is characterized by increase in wall thickness, and the right ventricle assumes a more rounded shape. This is achieved through an increase in cell size and the number of sarcomeres per cell [50], as well as a concomitant increase in the extracellular matrix (ECM) and supporting vasculature [51]. The right ventricle in primary PHTN has the feature of ischemic, hibernating myocardium. Functionally, there is progressive decline in both the longitudinal and transverse contraction of the right ventricle, and the septum tends to bulge towards the left side. As the disease progresses, several maladaptive mechanisms including switching in contractile protein isoforms [52], mitochondrial membrane hyperpolarization [53, 54], and switch in energy metabolism [55] as well as in ion channels involved in myocyte excitation and contraction coupling. There is also neurohumoral and cytokine activation and supporting matrix remodeling.

Right Ventricular Failure Secondary to Left-Sided Heart Failure

This is a much more common form of PHTN and began to receive more attention recently (Fig. 19.1). In patients with heart failure and preserved left ventricular function defined by LVEF>50 %, its prevalence is 83 % in comparison to 8 % in hypertensive patients [56]. In remodeling of the pulmonary artery and right ventricle associated with left-sided heart failure, the initial phase involves passive increase in the hydrostatic pressure in the pulmonary capillaries as a result of increased LVEDP (>15 mmHg). This leads to loss of pulmonary capillary integrity, interstitial and alveolar edema, pulmonary vein dilatation, and extravasation of red blood cells into the pulmonary interstitium. In the canine model, this leads to thickening of the basement membrane with deposition of type IV collagen [57]. The transpulmonary gradient remained same (mean pulmonary arterial pressure minus pulmonary capillary wedge pressure <12 mmHg). Further microvascular remodeling might be triggered by local disturbance in nitric oxide (NO) signaling, the tissue angiotensin pathway, and endothelin-1 activation [58]. This might result in vasoconstriction and reversible increase in the PVR. With disease progression, prolonged vasoconstriction and smooth muscle proliferations may be involved secondary to endothelial dysfunction with local endothelin secretion [59] and dysfunctional NO signaling [60]. In the rat model of PHTN secondary to left heart failure caused by ligation of the left anterior descending coronary artery, there is decrease in the expression of PTEN (phosphatase and tensin homolog on chromosome 10) and increased level of peroxynitrite in the pulmonary vascular cells which is correlated with pulmonary smooth muscle proliferation; application of the scavenger of peroxynitrite inhibited the cell proliferation and normalized the pulmonary arterial pressure [61].

For the small- to medium-sized pulmonary arteries, chronic pressure overload results in disruption of the endothelial barrier with activation of endogenous serine protease and matrix

metalloproteinase and release of local growth factors such as tenascin-C and fibronectin [62]. In patients with advanced heart failure, there is intimal disruption and significant medial hypertrophy of small- to medium-sized pulmonary arteries. Some pulmonary veins show dilatation and intimal fibrosis and "arterialization" characterized by extra external lamina developed away from internal elastic lamina separated by a layer of smooth muscle cells characteristic of chronic pulmonary venous hypertension [63].

In right ventricular remodeling associated with left heart failure, the right ventricle responds to PHTN in a similar way as in PAH. The main difference is in ventricular interdependence and myocardial ischemia. Dilatation of the right ventricle and atrium limits blood flow to the right side, and since both right and left ventricles are within the pericardial space, the leftward septal shift ("D-shaped left ventricle") limits the left ventricular inflow further, and these effects lead to further reduction in cardiac output. Careful diuresis with reduction of the right ventricular volume can improve left ventricular filling. However, overdiuresis can lower right ventricular preload and reduce LV filling, leading to paradoxically low pulmonary wedge pressure and reduced cardiac output. Coronary perfusion is dependent on the pressure difference between the aorta and left ventricle during diastole. Elevation of LVEDP and shifting of right coronary flow to diastole reduce right ventricular perfusion, and this compounds the effect of right ventricular hypertrophy, making the right ventricle more prone to ischemia and acute dysfunction.

Other changes involve disturbances in the catecholaminergic receptor populations in the right ventricle associated with left-sided heart failure. This is characterized by downregulation of α-1 adrenergic receptors, β-1 adrenergic receptors, and dopaminergic D1 receptor dysfunction [64]. Phosphodiesterase-5 (PDE-5) expression is markedly increased in the pulmonary arteries and in the hypertrophied right ventricle [65]. It is also increased in the failing left ventricle as well as the renal circulation; the latter explains renal tubular resistance to natriuretic peptide. In patients with heart failure and reduced LV function, there is an abundance of immunoreactivity in the pulmonary artery endothelial cells [66]. All these findings imply that further exploration with endothelin antagonists and PDE5 inhibitors in appropriate patients with PHTN might be helpful. The RELAX Trial is a multicenter randomized, double-blind, prospective study on the effect of sildenafil in patients with diastolic heart failure [67].

During exercise in patients with diastolic heart failure, the LVEDP increases significantly with only limited increase in diastolic volume. The normal response to exercise is an increase in the mean pulmonary arterial pressure, but this is more marked in patients with diastolic dysfunction [68]. In some patients, the difference between the diastolic pulmonary arterial pressure and pulmonary capillary wedge pressure may approach zero, indicating the absence of a forward driving force during diastole [69]. This dynamic change in pulmonary pressures may explain the disproportionate exercise intolerance in patients with diastolic heart failure.

Chronic right heart failure with elevated right atrial pressure results in elevated pressure in the superior vena cava, and this compromises the systemic lymphatic drainage through the thoracic duct from the lungs and abdominal organs. Congestion in the splanchnic circulation contributes to abnormal liver function, development of ascites, impaired clearance of toxins, as well as absorption of nutrients and medications. This also contributes to translocation of enteric microbes. Increased renal vein pressure reduces glomerular blood flow and contributes to the cardiorenal syndrome [70].

Right-Sided Heart Failure Secondary to Pulmonary Emboli

In the thromboembolic PHTN, the thrombus travels up the inferior vena cava and enters the right ventricle. A thrombus lodged in the main pulmonary artery or its bifurcations may result in hemodynamic compromise, while smaller thrombi disperse more distally and cause microinfarction and release inflammatory mediators resulting in pleuritic chest pain. In acute pulmonary embolism,

when the obstruction is greater than 75 %, the right ventricle has to generate a systolic pressure of 50 mmHg to preserve pulmonary perfusion which the normal right ventricle cannot do and therefore fails [71]. If the thrombus does not resolve, the increase in PVR results in right ventricular pressure overload leading to subsequent right ventricular remodeling [72].

Therefore, acute right ventricular failure can occur in the setting of massive pulmonary emboli with sudden increase in the PVR even if the baseline right ventricular function is normal. The right ventricle cannot generate enough pressure to match the sudden increase in resistance against forward blood flow in the pulmonary artery; this represents an instance of uncoupling of the right ventricle and pulmonary artery elastance [73]. The right ventricle can fail within 90 min and likely secondary to the activation of endogenous protease such as calpain [74] or cellular apoptosis [75].

Pulmonary Hypertension in Patients with Chronic Obstructive Lung Disease

The prevalence of PHTN in patients with COPD was estimated to be 31 %, with an additional 17 % who have pulmonary venous hypertension [76]. In patients scheduled for lung reduction surgery, the prevalence is 50.1 % by right-sided cardiac catheterization [77]. Presence of PHTN predicts 50 % reduction in 5-year survival [78] and is the strongest independent predictor of survival irrespective of age and lung function test results [79].

Pathogenesis is likely more complicated and involves chronic hypoxemia that results in vasoconstriction. Cardiac comorbidities result in increased left heart filling pressure, pulmonary vascular remodeling, and parenchymal lung destruction with loss of capillary surface area. Pathological findings include prominent pulmonary arterial vascular intimal thickening and muscularization of the small arterioles [80, 81]. Cigarette smoking can also result in pulmonary artery vasculature changes and remodeling [82]. Genetic polymorphism involving the serotonin transporter, but not the 2a receptor or NO synthase, was also implicated in PHTN with COPD [83].

Diagnosis

Clinical manifestations of PHTN are nonspecific, and the most common complaints are shortness of breath and fatigue, complaints that are easily attributed to aging. Other complaints include chest pain, dizziness, syncope, and ankle swelling. However, it can also be completely asymptomatic.

Signs of right-sided heart failure are nonspecific by themselves and are difficult to differentiate from those of left-sided heart failure. They include elevated jugular venous pressure, loud pulmonary component of the second heart sound (P2), ascites, peripheral edema, and right upper quadrant abdominal discomfort secondary to liver distension. The 6-min walk test is commonly used for exercise tolerance assessment and has been a common endpoint for clinical trials. For the WHO type II to type V PHTN, presentation of the primary disease may be the initial manifestation and PHTN is unmasked during the subsequent work-up.

No biomarkers are diagnostic of right ventricular failure. Osteopontin, which is a pleiotropic cytokine, predicts survival in patients with primary pulmonary hypertension [84] and right ventricular remodeling [85].

A noninvasive diagnostic approach is the most commonly used modality for studying right ventricular function. An ideal modality should be easily available, independent on the afterload and preload, and sensitive to changes in inotropy [86]. Cardiac computed tomography (CT), nuclear imaging, and cardiac magnetic resonance imaging (MRI) are additional options. In fact, MRI is considered to be the gold standard for noninvasive right heart assessment [87, 88]. MRI can determine the systolic and diastolic dimensions without assumption about its geometry. MRI can also give a better quantitative estimation of flow through the tricuspid valve and pulmonic valve and therefore can accurately estimate the

Table 19.2 Echocardiographic difference between right ventricular volume versus pressure overload

Measurements	Volume loading	Pressure loading
Dilatation	Markedly increased	Increased
Hypertrophy	Increased	More increased
Contractility	Slightly reduced or unchanged	Reduced
Left ventricle shape "D"	Diastolic D shape	Systolic D shape

ejection fraction, regurgitation fraction, and shunt ratio [89–91].

Echocardiography remains the method of choice among clinicians [92]. Its portability and easy availability make it widely used for evaluation of right ventricular remodeling in response to PHTN [93]. Wall thickness, size of the right ventricle, and septal shift during cardiac cycles are particularly useful for following the progression of the remodeling process. In advanced right-sided heart failure, the interventricular septum can be flat or even convex towards the left ventricle (Fig. 19.2). The shape of the septum is a good measure of the pressure difference between the left and right ventricle [94]. It helps to differentiate volume overload versus pressure overload by observing the septal movement during the cardiac cycle (Table 19.2). The results of 3D echocardiographic studies are comparable to those of cardiac MRI [95].

Hemodynamic data based on right-sided heart catheterization remains the gold standard for the diagnosis of PHTN and right ventricular failure. Right ventricular ejection fraction and other measurements are subjected to the confounding effect of preload. However, right ventricular function measured by studying the pressure-volume relationship (Ees) is not dependent on preload and reflects intrinsic right ventricular contractility. In addition, the pressure-volume loop provides better assessment for right ventricular-pulmonary artery coupling and progression of disease (Fig. 19.3).

Right-sided cardiac catheterizations are required prior to initiation of specific vasodilator therapy and also help to differentiate WHO type II PHTN from WHO type I PHTN. During right-sided catheterization, vasodilator challenge can be performed. An acute vasoreactivity test is considered positive if mean pulmonary artery pressure decreases by at least 10 mmHg and to a value <40 mmHg, with an increased or unchanged cardiac output. Of note, Doppler pressure measurement is not accurate and tends to underestimate the right-sided pressure [96–98].

Prognosis and Treatment

Primary PHTN and right ventricular failure portend a poor prognosis [99]. Intensive laboratory investigations and clinical trials have studied its mechanisms and therapeutic options [100, 101]. Primary PHTN is the most well-studied disease entity. Its management comprises supportive management plus PAH-specific therapy [102]. Ideally the disease should be approached by a multidisciplinary team in tertiary centers. Modern therapies can improve outcome; median survival can be improved from 2.8 years [103] to greater than 7 years [104]. PAH-specific therapies generally involve different classes of agents from prostanoids [105], endothelin receptor antagonists, and PDE-5 inhibitors which are summarized in Table 19.3. Combination therapies are used in patients with severe PHTN. Heart-lung transplant may be the last resort.

New therapeutic entities under development or undergoing clinical trials include selexipag [106], imatinib [107], macitentan [108], and riociguat [109, 110]. Given the fact that more and more treatment modalities are available, a systematic approach is needed [111].

PHTN in patients with both systolic and diastolic dysfunction is associated with poor prognosis [112]. The mortality doubles once right ventricular dysfunction develops. PAH specific therapy might help in selected groups of patients; for example, for patients with impaired left ventricular function and clinical heart failure, 1-year use of PDE-5 inhibitor improves functional capacity and left ventricular diastolic function and geometry [113].

PHTN associated with advanced COPD has no specific vasodilator treatment. Treatment of

Table 19.3 Primary pulmonary hypertension: disease-specific treatment [102, 105]

Prostanoids	Epoprostenol	Intravenous prostaglandin I agonist, improve 5 years survival
	Treprostinil	Tricyclic benzene prostacyclin analog available in iv and subcut form
	Iloprost	Inhaled prostanoid, improved 6-min walk distance in functional class III and IV pulmonary hypertension patients
Endothelin receptor antagonist	Bosentan	Nonselective ERA, improves 6-min walk distance
	Ambrisentan	Selective ERA, improves 6-min walk distance
PDE-5 inhibitors	Sildenafil	Improves functional class
	Tadalafil	Improves 6-min walk distance
	Vardenafil	Improves 6-min walk distance

the underlying lung disease and exclusion of other causes of PHTN is the mainstay management [114]. A trial of sildenafil in 20 COPD patients resulted in reduction of mean pulmonary arterial pressure at the expense of worsening hypoxemia due to increased ventilation-perfusion mismatch [115]. A trial involving bosentan found those treated with bosentan suffered a decrease in quality of life, worsening of arterial oxygen saturation, and no change in exercise capacity [116]. A second study with bosentan involving 16 patients with matched control showed significant improvement in mean pulmonary arterial pressure, PVR, and 6-min walk without a significant decline in arterial oxygen saturation [117].

Chronic thromboembolic PHTN results from incomplete resolution of the obstructing thrombus which gives rise to right ventricular pressure overload, remodeling, and right heart failure [118]. If untreated, prognosis is poor [119]. However, successful pulmonary endarterectomy results in immediate improvement in global myocardial performance index and gradual recovery of both diastolic and systolic right ventricular function [120].

Conclusion

In the past decade, we saw an explosion of information on the right-sided heart failure and PHTN. Aging affects normal pulmonary vasculature and right ventricular diastolic function. Aging also adds other co-variables that affect the disease progression. We know that aging is one of the poor prognostic indicators in primary PHTN. Indeed, as we started paying more attention to the right ventricle in different disease entities, we found that the prevalence of PHTN is higher than suspected and PHTN plays an important role in the progression of various diseases.

Primary PHTN has received intensive laboratory and clinical investigation, and based on the knowledge of its pathogenesis, new therapeutic options have been added to the previously existing armamentaria, and we have begun to see encouraging outcomes in registry survival data. We are not sure at this point whether the same therapeutic options for PAH can be extrapolated to other subtypes of PHTN, so that further dedicated studies of their respective pathobiologies and the impacts of aging are warranted.

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Biomarkers of Cardiovascular Aging

20

Nirankar S. Neki, Paramjit S. Tappia, and Naranjan S. Dhalla

Introduction

Aging is a universal complex biological process in which various adverse changes are associated with increased risk of morbidity and mortality. The biological changes occurring with aging are not uniform due to the genetic heterogeneity and the impact of environmental factors. Thus, the aging state is different in every individual and is generally characterized as the decline of functional capacity and stress resistance and has been termed as the disablement process [1]. A scheme depicting these factors in addition to changes in sex hormones and neurohormones as well as reduction in cognitive function in aging is shown in Fig. 20.1. It is known that the chronological age does not represent the "real" age or biological age of an individual. In fact, the health change in aging occurs in an orderly fashion beginning with the development of risk factors through the onset of different diseases and pathophysiological conditions, leading to the loss of function and/or loss of ability to perform certain physiological functions. Several attempts have been made to analyze the biological age in comparison to chronological age as these have led to the identification of various biomarkers of aging. Although there is no accepted definition of aging, the World Health Organization has defined senility at the age of >60 years, while in the USA, it is defined as 65 years of age. Furthermore, most of the gerontologists have distinguished three subsets of senility: younger old people (60–75 years of age), older people (75–85 years of age), and very old people (>85 years of age) [2]. It is noteworthy that cardiovascular disease (CVD) is the leading cause of mortality (approximately 80 %) in old people over 65 years of age [3–7] and more than 70 % men and women over 75 years of age show some clinical evidence of CVD [2].

Various biomarkers of aging are mainly based on age-related changes in body function or composition and are considered to assess biological age in the absence of disease and predict the age-related diseases at a later stage [8]. The Biomarker Definitions Working Group [9] has defined biomarkers as characteristics that are objectively measured and evaluated in terms of biological processes or pharmacological responses to therapeutic interventions. In a recent strategic plan of the National Heart, Lung, and Blood Institute, the word genotype has been added to this definition [10]. On the

N.S. Neki, MD, FRCP, FACP (USA), FAMS
Department of Internal Medicine, Government Medical College and Guru Nanak Dev Hospital, House No. 88, Street 4 Gopal Nagar, Majitha Road, Amritsar 143001, Punjab, India

P.S. Tappia, PhD
Office of Clinical Research, Asper Clinical Research Institute, St. Boniface Hospital Research, Winnipeg, MB, Canada

N.S. Dhalla, PhD, MD (Hon), DSc (Hon) (✉)
Department of Physiology, Faculty of Medicine, Institute of Cardiovascular Sciences, University of Manitoba, St. Boniface Hospital Research, 351 Tache Avenue, Winnipeg, MB, Canada R2H 2A6
e-mail: nsdhalla@sbrc.ca

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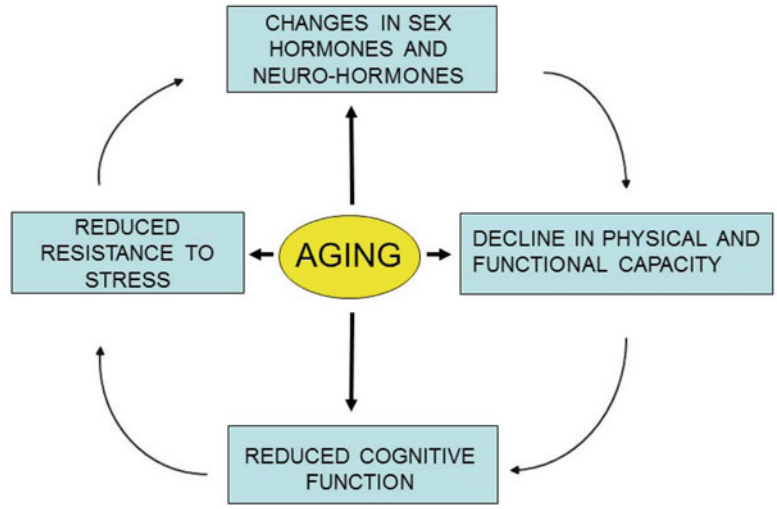

Fig. 20.1 Functional impact of aging. Scheme depicting a cycle of interrelated events that occur in the aging process which increase the predisposition of the aging individual to morbidity

other hand, the American Federation for Aging Research has described biomarkers of aging in a comprehensive manner [11] indicating that a biomarker should be (1) predictive of the state of aging as well as indicative of the stage of an individual's life span, (2) able to monitor a basic process that underlies the aging process and not the effects of a disease state, (3) detectable through a simple blood test or an imaging technique, and (4) detectable in both animals and humans to allow for validation and further testing. It has also been suggested that a biomarker must be measurable during a short interval of life span and should vary with the age of an individual, but not strictly chronological [12]. However, the level of biomarker should correlate with the remaining life span and with predisposition to acquiring multiple age-related conditions. While an understanding of the processes involved in aging is required to identify biomarkers of aging, consideration of the primary mechanisms of aging can be seen to result in the development of different biomarkers that can determine the biological age.

The concepts of aging are categorized into three major groups: (a) the central "use it or lose it" dogma assumes a greater significance in the fact that with aging, we use less of our physical and mental abilities over a period of time [13–15]; (b) gene mutations that lead to irreversible changes in the organ function, accumulation of metabolites, as well as development of cancer and other abnormalities [16, 17]; and (c) mitochondrial dysfunction characterized by irreversible mitochondrial DNA mutations over time that cause elevated production of reactive oxygen species (ROS), altered oxidative respiration, and changes in adenosine triphosphate (ATP) uncoupling and cell senescence [18, 19]. However, current consensus is that aging occurs as a result of progressive molecular defects over the life span of an individual [20]. Although a specific biomarker of aging has not been identified, Crimmins et al. [21] have suggested that biomarkers of CVD and diabetes are useful predictors of healthy aging. Kannel [22] has indicated that biomarkers may be useful for assessing the benefits of therapy and for stratifying individuals at intermediate risk for CVD. Some studies [23, 24] have revealed that several biomarkers including high-sensitivity C-reactive protein (hs-CRP), N-terminal pro-B type natriuretic peptide, as well as cardiac troponin T and I can be used to predict heart failure, adverse remodeling, and cardiovascular mortality in older adults. This review is focused on a discussion on biomarkers of oxidative stress, inflammatory responses, and immunosenescence as well as genetic factors and their applicability to linking the aging process to increased risk for cardiovascular morbidity and mortality.

Oxidative Stress and Aging

The free radical theory of aging provides an extensive explanation on the aging process [25], and different events related to the role of oxidative stress in aging are shown in Fig. 20.2. It has been suggested that ROS are key players in the aging process. Intracellular ROS are mainly generated by the mitochondrial respiratory chain, primarily due to electron leakage occurring at complexes I and II [26, 27]. In addition, mitochondrial NADPH oxidase also plays a major role in intracellular ROS production. The most studied oxidative DNA lesion is 8-hydroxyl-2-deoxyguanosine (8-OH dG) which is formed when ROS, particularly, the hydroxyl radical, acts on deoxyguanine in DNA [28]. 8-OH dG inhibits methylation and is mutagenic because it can be paired with adenosine during DNA replication [29]. The level of 8-OH dG is inversely related to the life span in mammals and is increased in mitochondrial DNA with age [30]. However, such an alteration in 8-OH dG levels is not specific for aging because its levels are also increased in Parkinson's disease, diabetes, cystic fibrosis, and muscular dystrophy [31]. The formation of 8-OH dG in leukocyte DNA and urinary excretion of 8-OH are measurable by high performance liquid chromatography or mass spectrometry and can be used to evaluate oxidative stress and oxidative DNA damage in humans. Furthermore, the measurement of urinary levels of 8-OH dG is highly reproducible [32]. It should be noted that smoking has also been shown to result in an increase in urinary excretion of 8-OH dG and 50 % increase in oxidative DNA damage [33].

Proteins are known to scavenge 50–75 % of generated ROS [34] leading to the formation of carbonyl groups and changes in protein structure and function. Carbonyls have been shown to accumulate during aging, chronic inflammation, ischemia-reperfusion injury, and other age-related diseases [35, 36]. However, an age-dependent increase in protein carbonyls was not seen in a study by Gil et al. [37]. On the other hand, Grune et al. [38] have reported that oxidized proteins, which are resistant to proteolysis,

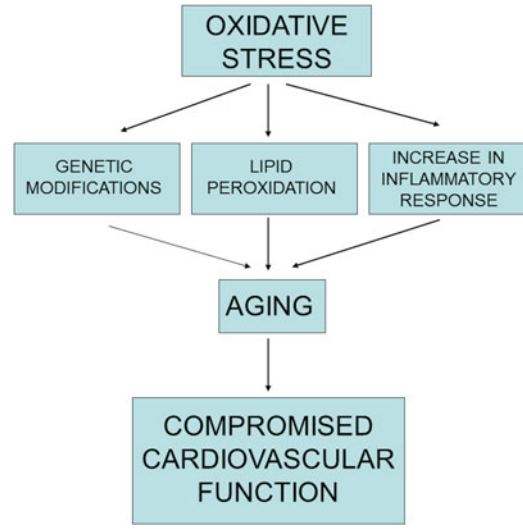

Fig. 20.2 Role of oxidative stress in the aging-induced changes in cardiovascular function. The figure shows the contribution of oxidative stress to genetic modifications, lipid peroxidation, and the inflammatory response that are considered as part of the aging process leading to a functional compromise of the cardiovascular system

may contribute to disease and the aging process. Oxidative stress is associated with aging-related conditions such as CVD, diabetes, cancer, and Alzheimer's disease [39, 40]. Products of membrane lipid peroxidation play a significant role as biomarkers of oxidative stress. F2-isoprostanes are chemically stable isomers of prostaglandin F2 and are considered as useful biomarkers for CVD, pulmonary, renal, neurological, and hepatic diseases [41]. Other important harmful end products of lipid peroxidation are malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE). The levels of MDA are increased in diabetes and in atherosclerotic plaques from diabetic patients [42]. HNE reacts with nucleic acids, proteins, and phospholipids, thus inducing mutagenic, cytotoxic, and genotoxic effects as well as alterations in signal transduction cascades [43]. In a study by Gil et al. [37] with 194 healthy men and women between 18 and 84 years of age, it was found that plasma MDA and HNE levels increased with age, indicating accelerated oxidation during aging. Another set of biomarkers relate to metabolic processes and cardiovascular outcomes. In middle-aged populations, total

cholesterol is directly associated with CHD and all-cause mortality [44, 45]. Increased levels of oxidized LDL correlate directly with CHD [46], coronary atherosclerosis, and increased risk of mortality [47]. LDL oxidation is a prelude to atherogenesis [48], and like LDL, levels of VLDL increase with age [49]. Whyanye et al. [50] reported that VLDL was a more effective predictor of CHD among persons >50 years of age, whereas LDL levels were more significant in individuals <50 years of age. High triglycerides (>150 mg/dL) are also associated with CAD [51] and heart attack [52].

Endogenous antioxidant defense mechanisms include glutathione (GSH), superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSH-Px). In addition, the recently discovered SOD isozyme, extracellular SOD (EC-SOD), scavenges superoxide anion in the extracellular space [53]. The BELFAST Study [54] has shown a decline in GSH-Px in free-living elderly subjects. Other groups have reported that cognitive decline is associated with lower selenium-dependent GSH-Px activity and a higher Cu/Zn SOD activity [55]. GSH deficiency leads to oxidative stress. GSH levels and GSH to oxidized GSH (GSSG) ratio are decreased in models of aging, and longevity is increased with normalization of low tissue GSH [56]. Thus, GSH status can be proposed as an indicator of health and functional age, whereas low GSH levels correlate with aging [57]. However, the BELFAST Study revealed an increase in plasma levels of GSH in nonagenarians, unlike in septo-/octogenarians [54].

Recently, total plasma carotenoid levels have been suggested as a possible health indicator in elderly populations. In this regard, the Epidemiology of Vascular Aging (EVA) study found that low plasma levels of total carotenoids had a significant correlation to all-cause mortality in men, but not in women [58]. Others have suggested that carotenoids may have protective effects against both CVD and cancer [59, 60]. In response to stress, eukaryotic cells are able to induce heat shock proteins (HSPs), a highly conserved class of proteins also referred to as stress proteins, and exert cellular protection against ROS as well as other insults including heat, ischemia, hypoxia, glucose deprivation, and aging [61–63]. HSP 70 has been proposed as a potential biomarker for healthy aging [64, 65], and in fact, low serum levels of HSP 70 have been correlated to aging [62, 66].

Cyclophilin A (Cyp A), an oxidative stress-induced factor, is a 20 kDa chaperone protein secreted by VSMCs, endothelial cells, and macrophages in response to ROS and is considered as a biomarker for necrotic cell death [67, 68]. Cyp A stimulates ERK 1/2, Akt, and JAK; increases DNA synthesis; inhibits nitric oxide-induced apoptosis in VSMCs [67]; and plays an important role in ROS production [69]. ROS-induced Cyp A secretion increases ROS production synergistically leading to inflammatory cell migration and abdominal aorta aneurysm (AAA) [70]. Cyp A (both extracellular and intracellular) leads to atherosclerosis by promoting endothelial cell (EC) apoptosis and EC expression of leukocyte adhesion molecules, stimulating inflammatory cell migration, enhancing ROS production, and increasing macrophages, VSMC, as well as proinflammatory signal transduction in VSMCs. Thus, Cyp A can be regarded as a proinflammatory and pro-atherogenic molecule [71, 72]. A close relationship between Cyp A and angiotensin II with increased ROS production has been suggested [73]. This is borne out from the fact that ROS stimulates myocardial hypertrophy, matrix remodeling, and cell dysfunction and that Cyp A enhances angiotensin II-induced cardiac hypertrophy [74]. Furthermore, Cyp A activates Rho-kinase in patients with pulmonary artery hypertension [73, 75]; Rho-kinase is an important therapeutic target in CVD [76], the inhibition of which reduces angiotensin II-induced AAA formation [77] as well as atherosclerosis and cardiac hypertrophy [78].

Inflammation and Aging

Aging is accompanied by chronic low-grade inflammatory state, characterized by a two- to fourfold increase in the serum levels of inflammatory mediators. These mediators act as

predictors of mortality independent of morbidity. Aging is associated with the activation of both innate and adaptive immune systems. The innate immune system induces a chronic low-grade inflammatory response, while the adaptive immune system induces decreases in T cells [79, 80]. The age-related changes in inflammatory markers include a wide range of potential indicators: (a) C-reactive protein (CRP), an acute-phase protein produced in the liver, which increases as part of the immune response to infection and tissue damage. It is increased in many chronic conditions including heart disease [81, 82]. High levels of hs-CRP (between 3 and 10 mg/dL) have been linked to the development of CVD [83, 84]; (b) interleukin-6 (IL-6), high levels of which have been correlated to CVD and heart attack [85, 86], functional disabilities and decline [87, 88], as well as mortality [89]. The association of IL-6 with CVD is related to its central role in promoting the production of CRP [90]; (c) fibrinogen has also been shown to be associated with CVD [91] and mortality [92]; (d) tumor necrosis factor-α (TNF-α), a polypeptide that plays an important role in the inflammatory response and immune function. High levels of TNF-α are associated with Alzheimer's disease [93, 94], atherosclerosis [95], obesity and diabetes [96], as well as stroke [97]; (e) albumin is the major plasma protein and low levels have been reported to be linked to heart attack, functional decline, and mortality among older individuals [98, 99]; (f) serum amyloid A (SAA) is another acute-phase protein known to increase in response to inflammation and injury [100]. SAA has also been linked to atherosclerosis and CHD [101, 102]; (g) cytomegalovirus (CMV), a herpes virus that has been associated with the inflammatory response, CVD, endothelial dysfunction, frailty, as well as cognitive decline [103–105]; and (h) T helper cells are also known as CD4 or T4 cells. CD4 counts are used to assess immune system status; the CD8 count has also been associated with age-related conditions. A constant CD4:CD8 ratio indicates healthy aging, while a decrease in this ratio reflects an increased immunological risk in the elderly [106].

Some studies have suggested a positive correlation between in vitro T cell function and individual longevity [107–109], whereas others have reported a lack of circulating B cell response to new extracellular pathogens with advancing age. In addition, decreases in B cell levels are associated with poor health status in older people. The decreased IgM and IgD levels in the elderly suggest a shift from the naïve (CD27) compartment of the B cell toward the memory (CD27+) compartment [110]. Circulating B cells can be divided into different functional subsets depending on the expression of IgD and CD27. There is a significant increase in IgD-CD27-B cell subset in aging. As B naïve lymphocytes are increased in offspring of healthy centenarians, it has been suggested that a loss in B naïve lymphocytes may represent a hallmark of immunosenescence and thus may provide a biomarker possibly related to the human life span [111]. With respect to natural killer (NK) cells, low cell activity is associated with infections and death due to infection in immunologically normal elderly subjects with functional impairment. NK cells also secrete chemokines or interferon-γ in response to IL-2 which are also decreased in the aged. Thus, high NK cytotoxicity represents biomarkers of healthy aging and longevity, while low NK cytotoxicity is predictive of morbidity and mortality due to infections [112, 113].

Genetic Markers

Genetic markers are usually employed in population studies with an aim to identify genetic variants associated with different diseases [17]. Although very limited information on genes related to healthy aging is available, some studies have been directed toward longevity [114, 115], which does not necessarily correspond to healthy aging. The most commonly examined genetic indicator for CHD is apolipoprotein E (APOE), which has three alleles: E2, E3, and E4. Studies have shown that APOE 4 is associated with CVD and stroke [116] as well as with Alzheimer's disease [117]. Lunetta et al. [118] have reported a markedly higher frequency of APOE E2 allele in

men between the ages of 60 and 90 years as compared to individuals less than 60 years of age, suggesting that APOE genotype may correlate to prolonged survival. The genotype reflecting the overall genetic makeup of an individual has also been correlated to a healthy aging phenotype. In this regard, an individual can be genotyped with or without disease for a high number of single nucleotide polymorphisms (SNPs) of which 10^3–10^6 are located throughout the genome [118]. Polymorphism for the gene coding for angiotensin-converting enzyme (ACE) has been shown to be correlated to CVD and renal disease [119], Alzheimer's disease [120], and human longevity [121]. However, others have not found a positive correlation of ACE [122, 123]. HTR 2A genotype has also been associated with memory change and is likely to be included with APOE as genetic markers for cognitive loss due to aging [124].

Telomeres are regions at the end of chromosomes containing 5–15 kb of $(TTAGGG)_n$ repeats, and the telomere length is considered to be another biological marker of aging. These so-called capping regions protect the DNA against degradation and recombination and thus render stability to the chromosome [125]. Telomere shortening is closely associated with increased age [126] and oxidative stress [127]. Although some investigators have reported no association of telomere length and longevity [128], telomeres lose their protective capping function when they become too short or when telomere-binding proteins such as TRF 2 are disrupted [129]. Dysfunctional telomeres trigger senescence through the p53 pathway [130], a response known as telomere-initiated cellular senescence. Peripheral blood mononuclear cells (PBMCs) are frequently used to measure telomere length in humans. PBMC telomere length decreases on average by 20–60 bp/year increase in age [131]. While telomere length may be considered as a marker of aging, telomere length in white blood cells has been shown not to be linked to morbidity and mortality [132]. Another important biomarker of aging is a mitochondrial transcript 6S rRNA. A study by Calleja et al. [133] showed that decreased levels of 16S rRNA are associated with aging. Others have found that 16S rRNA degradation is associated with oxidative stress [134]. This would seem to suggest that mitochondria of higher biological age should exhibit lower expression levels of 16S rRNA. Interestingly, 16S rRNA expression is 700 % higher in females than in males [134].

Hormones and Aging

It has been suggested that a number of different hormones including estrogen, testosterone, growth hormone (GH), dehydroepiandrosterone (DHEA), and insulin are involved in the aging process. A decrease in estrogen in postmenopausal women results in a rapid loss of skeletal mass, vasomotoric instability, psychological symptoms, as well as increased risk of CVD [135]. Indeed, the risk for CVD in premenopausal women is lower than in men, but the risk increases to that of males of equivalent age during the postmenopausal period [136]. It is well known that alterations in the lipid profile characterized by increases in LDL and total cholesterol and a decrease in HDL increase the risk of CHD and stroke in postmenopausal women [137]. Paganini-Hill have reported increased longevity in older women receiving estrogen replacement therapy [138]; however, hormone replacement therapy is associated with increased risk of CVD and thus individual risk-benefit has to be considered before initiating this therapy. Aging is associated with a lower production of gonadal steroids in both men and women. A gradual, but progressive age-dependent decrease in testosterone has also been reported [139]. In the Massachusetts Male Aging Study [140] in 1,709 men aged between 40 and 70 years, it was found that free testosterone levels were significantly associated with ischemic heart disease and respiratory mortality. On the other hand, total testosterone had no association with mortality [141]. Testosterone replacement therapy may be of value in elderly men to restore muscle strength and virility [142], but may evoke adverse cardiovascular effects in the form of increased blood pressure and reduced HDL levels [143].

After the age of 20–25 years, an approximate 14 % decline per decade in GH secretion has been reported leading to age-related adiposity, loss of muscular mass, and decreased bone mineral density [144]. Some studies have shown that the increased levels of GH in premature aging mice lead to decreases in antioxidant activities including catalase, Cu/Zn SOD, and GSH-Px [145, 146]. In contrast, the absence or low level of GH has been reported to reduce antioxidant capacity [147]. GH replacement therapy in both men and women lowers LDL and the LDL:HDL ratio as well as reduces body fat and increases lean mass; however, it causes a low-grade inflammatory response [148, 149]. GH has been reported to reduce insulin sensitivity [150]. Although mutations of the insulin-like receptor in *Drosophila melanogaster* can extend the median life span by up to 85 % [151], insulin receptor knockout mice die in early neonatal life [152]. Insulin-like growth factor-1 (IGF-1) modulates cell growth and survival. IGF-1 throughout the life span exerts its effects on GH [153]. Although low IGF-1 is related to coronary artery disease [154] and increased mortality [155], no correlation between low IGF-1 and all-cause mortality or mortality from CVD or cancer has been reported [156].

Elevated levels of cortisol, produced by the adrenal gland in response to stress, are associated with increased CVD risk [157], poor cognition [158], and increased risk for fractures [159]. Dehydroepiandrosterone (DHEA) is a steroid hormone also produced by the adrenal gland and is a precursor to estrogen and testosterone, and the levels of DHEA are age dependent [160, 161]. Peak levels of DHEA are seen at 25–30 years of age after which decline occurs until the age of 80 years where the level remains at about 10–20 % of the peak [161]. Functional decline was associated with lower levels of DHEA-sulfate mainly in women [162]. DHEA-sulfate concentration is independently and inversely associated with mortality from any cause and mortality due to CVD in men over the age of 50 years [163, 164]. Cappola et al. [165] have shown that disabled older women with either low or high levels of DHEA-sulfate have a higher risk of fatality than those with an intermediate level. Some studies have shown that DHEA-sulfate is a marker for bone turnover and for predicting bone mineral density [166]; low levels have been linked to Alzheimer's disease [167]. On the other hand, Nair et al. [168] in a double-blind placebo-controlled study compared elderly men and women on DHEA for 2 years and found no benefit or adverse effects on bone mineral density, muscle fat composition, physical performance, insulin resistance, or quality of life.

Age-related changes in leptin levels are controversial [169]. While circulating levels of leptin have been shown to decline with aging [170], other investigators have reported that independent of adiposity, age has a minor contribution to the variance in leptin levels [169]. On the other hand, aging has also been linked to hyperleptinemia [171], whereas adipokine dysregulation in centenarians has been reported to be associated with very low leptin levels [172]. Furthermore, animal and human studies have shown that the aging process may be associated with impaired leptin signal transduction as well as resistance to the actions of leptin [171, 173]. Nonetheless, various studies have shown that the increased leptin levels may be linked to atherosclerosis, metabolic syndrome, diabetes, malnutrition, dyslipidemia, hypertension osteoarthritis, and osteoporosis [174, 175]. The markers of sympathetic nervous system activity include norepinephrine and epinephrine. High plasma epinephrine has been linked to poor survival in patients with previous myocardial infarction [176]. However, high plasma norepinephrine levels have been correlated to increased overall mortality in the elderly [177] and reduced survival in healthy old people, in patients with previous myocardial infarction [178], as well as in congestive heart failure [179]. In addition, both urinary epinephrine and norepinephrine levels are high in smokers [180]. Although elevated homocysteine has also been associated with increased risk of CVD, peripheral vascular disease, and cognitive decline [181–183], its prevalence has declined with the introduction of dietary fortification with folate [184].

Aging-Induced Changes in Vital Signs

Systolic blood pressure (SBP) is more predictive of coronary artery disease and life expectancy at advanced ages [185, 186]. The Framingham Heart Study has shown that SBP is directly related to CHD risk, whereas diastolic blood pressure (DBP) is inversely related to CHD risk in old people [187]. The rise in SBP and pulse pressure in middle-aged and elderly subjects is closely associated with increased arterial thickness and increased wave reflection amplitude [188]. In fact, increases in pulse pressure are predictive of CHD in middle and old ages [6, 189]. A pulse rate of 90 or higher is also considered as an increase in risk of CHD and all-cause mortality [190]. Although the body mass index (BMI) is linked to weight and adiposity, the waist-to-hip ratio (WHR) and waist circumference are often preferred to BMI as indicators of risk for CVD [191]. Individuals with higher values for BMI, waist and hip circumference, and WHR are more susceptible to development of heart disease, hypertension, atherosclerosis [192, 193], diabetes [194], osteoarthritis [195], and disability [196, 197]. Others have shown that WHR is a strong predictor of cardiovascular events and that a 1 % increase in WHR is associated with a 5 % increase in CVD risk [198]. It is emphasized that most of the elderly individuals die due to the development of heart failure and thus it is rather difficult to distinguish between the biomarkers and signs and symptoms for aging and heart failure.

Conclusion

Aging is an inevitable process which exerts negative effects on different organ systems and functional capacity of the body. Since age is a major risk factor for many degenerative diseases, some of the markers described in this review could be used to identify individuals at high risk of developing age-related diseases and disabilities. There is no specific biomarker of aging because most of the biomarkers discussed here are also related to CVD. Furthermore, these biomarkers do not account for why certain older adults age with or without any disease. However, it should be noted that cardiac dysfunction due to aging is invariably associated with activated sympathetic nervous system, activated renin–angiotensin system, hypertension, cardiac hypertrophy, and myocardial infarction, cardiac remodeling, and congestive heart failure. Accordingly, the identification of biomarkers of aging independent of comorbidities is warranted. Multiple biomarkers which mostly indicate physiological responses to challenge should be included in screening the elderly population. The availability of specific biomarkers may allow for the assessment of the efficacy of pharmacological interventions particularly with regard to antiaging therapies to ameliorate the aging process, to improve the quality of life, and to postpone death by delaying the onset of age-related disease including CVD.

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21 Changes in the Heart That Accompany Advancing Age: Humans to Molecules

Edward G. Lakatta, Harold A. Spurgeon, and Andrzej M. Janczewski

Introduction

Hypertension, atherosclerosis, and resultant chronic heart failure (HF) reach epidemic proportions among older persons, and the clinical manifestations and the prognoses of these maladies worsen with increasing age (Fig. 21.1).

A steady stream of incremental knowledge, derived from both animal and human studies, has established that several of the aging-associated changes in the heart and in the walls of the central arteries are, themselves, potent and independent risk factors for cardiovascular diseases. This suggests that these age-associated alterations in arterial and cardiac structure and function may link aging to the risk for these disease states. Thus, one way to conceptualize why the clinical manifestations and the prognosis of CV diseases worsen with age is that in older individuals, the specific pathophysiologic mechanisms that cause clinical disorders are superimposed on heart and vascular substrates that are modified by aging (Fig. 21.2).

Imagine that age increases as one moves from the lower to the upper part of Fig. 21.2 and that the line bisecting the top and bottom parts represents the clinical practice "threshold" for disease recognition. Entities above the line are presently classified as "diseases," and lead to heart and brain failure.

Arterial and cardiac changes presently thought to occur as a result of the "normal aging process" are depicted below the line. These age-associated changes in cardiac and vascular properties alter the substrate on which cardiovascular disease becomes superimposed in several ways. First, they lower the extent of disease severity required to cross the threshold that results in clinically significant signs and symptoms. Aging should no longer be viewed as an immutable risk factor. In one sense, those processes below the line in Fig. 21.2 ought not to be considered to reflect normal aging, because these are specific risk factors for the diseases that they relate to, and thus might be targets of interventions designed to decrease the occurrence or manifestations of cardiovascular disease at later ages.

Because many of the age-associated alterations in cardiovascular structure and function, at both the cellular and molecular levels, have already been identified as specific risk factors for cardiovascular diseases, there is an urgency to incorporate cardiovascular aging into clinical medicine. Such a strategy would be aimed at treatment (preventative measures) to retard what is now considered to be normal aging.

E.G. Lakatta, MD (✉)
National Institute on Aging/NIH,
251 Bayview Boulevard, Baltimore, MD 21224, USA
e-mail: lakattae@grc.nia.nih.gov

H.A. Spurgeon, PhD
Laboratory of Cardiovascular Science, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA

A.M. Janczewski, MD, PhD
Department of Internal Medicine, PCK Marine Hospital, Gdynia, Poland

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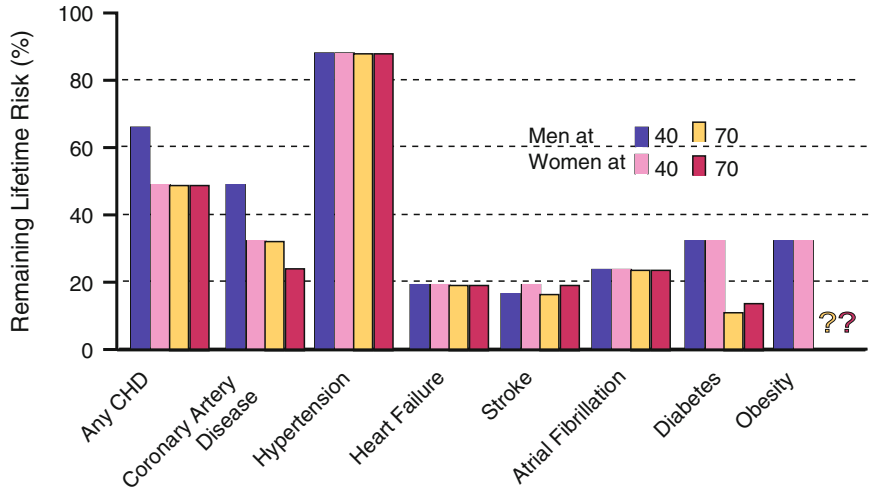

Fig. 21.1 Remaining lifetime risk for CVD and other diseases among men and women free of disease at 40 and 70 years of age (Based on data from Lloyd-Jones D. et al. Heart Disease and Stroke Statistics–2010 Update. A Report From the American Heart Association. *Circulation*. 2010;121:e1–e170)

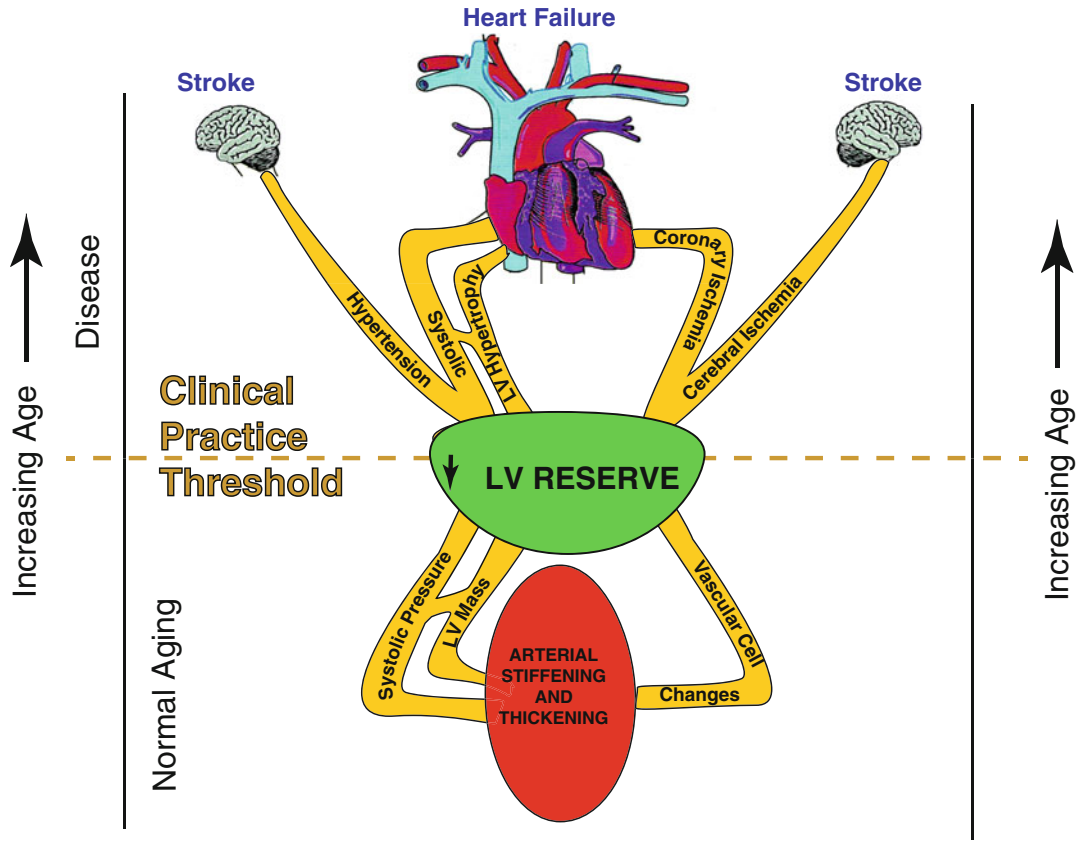

Fig. 21.2 Schematic of cardiovascular factors as they relate to clinical practice threshold [Adapted from Najjar SS, Lakatta EG, Gerstenblith G. Cardiovascular Aging: The Next Frontier in Cardiovascular Prevention. In Blumenthal R, Foody J, Wong NA (editors), *Prevention of Cardiovascular Disease: Companion to Braunwald's Heart Disease*. Philadelphia: Saunders, 2011:415–432]

Cardiac Aging in Humans

A unified interpretation of identified cardiac changes that accompany advancing age in otherwise healthy persons suggests that at least in part, these are adaptive, occurring to some extent in response to arterial changes that occur with aging (Fig. 21.3) [1].

With advancing age, the walls of the left ventricle (LV) increase in thickness, in part, resulting from an increase in arterial impedance in ventricular myocyte size and increase in size and increase in LV wall thickness; this helps to moderate the increase in LV wall tension. Modest increases in collagen levels also occur with aging.

Prolonged contraction of myocytes within the thickened LV wall maintains a normal ejection time in the presence of the late augmentation of aortic impedance. This preserves the systolic cardiac pumping function at rest. One disadvantage of prolonged contraction is that, at the time of the mitral valve opening, myocardial relaxation is relatively more incomplete in older than in younger individuals, and this causes the early LV filling rate to be reduced in older individuals.

Structural changes and functional heterogeneity occurring within the left ventricle with aging may also contribute to this reduction in peak LV filling rate. However, concomitant adaptations—left atrial enlargement and an enhanced atrial contribution to ventricular filling—compensate for the reduced early filling and prevent a reduction of the end-diastolic volume. Age-associated changes in the tissue levels of or responses to growth factors (catecholamines, angiotensin II, endothelin, TGF-β, or fibroblast growth factor) and cytokines that influence myocardial or vascular cells or their extracellular matrices (see below) likely have a role in the schema depicted in Fig. 21.3.

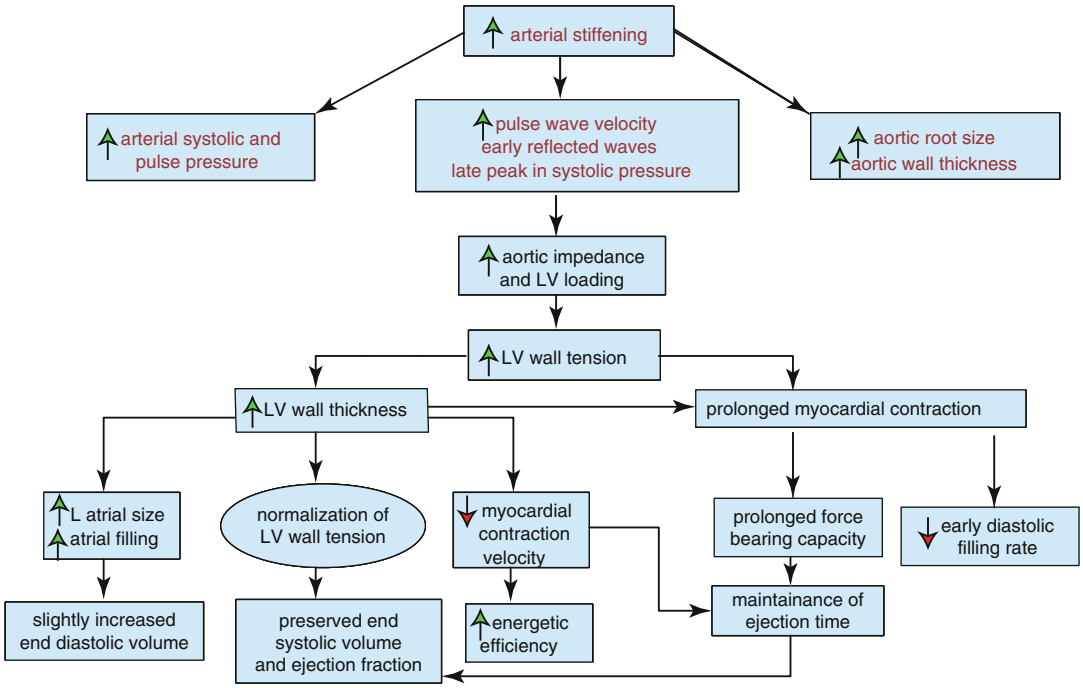

Fig. 21.3 Arterial and cardiac changes that occur with aging in normotensives and at any age in hypertensives are shown. One interpretation of the constellation (flow of *arrows*) is that vascular changes lead to cardiac structural and functional alterations that maintain cardiac function. *LV* left ventricular (Modified from Lakatta EG. Normal Changes of Aging. In: Abrams WB, Berkow R (Eds), *Merck Manual of Geriatrics*, Rahway, N.J.: Merck Sharp & Dohme Research Laboratories, 1990, pp. 310–325)

Biologic sex is a well-recognized factor in the physiology and pathophysiology of the cardiovascular system, including the aging heart (reviewed in [2, 3]). Postmortem morphometric assessments in non-failing human hearts have shown extensive age-related myocyte loss and hypertrophy of the surviving myocytes in male hearts but preserved ventricular myocardial mass and average cell diameter and volume in aging female hearts. These sex differences may stem, in part, from differences in the replicative potential of cardiac myocytes. Analysis of gene expression differences by sex and age in samples of the left ventricle from patients with dilated cardiomyopathy has identified more than 1,800 genes displaying sexual dimorphism in the heart. A significant number of these genes were highly represented in gene ontology pathways involved in ion transport and G protein-coupled receptor signaling [4].

Cardiovascular Reserve in Humans

Impaired heart rate acceleration and impaired augmentation of blood ejection from the left ventricle, accompanied by an acute modest increase in LV end-diastolic volume in males, are the most dramatic changes in cardiac reserve capacity that occur during aging in healthy, community-dwelling persons (Table 21.1).

Mechanisms that underlie the age-associated reduction in maximum ejection fraction are multifactorial and include a reduction in intrinsic myocardial contractility, an increase in vascular afterload, and an arterial–ventricular load mismatch.

Ventricular load is the opposition to myocardial contraction and the ejection of blood; afterload is the component of load that pertains to the time after excitation, as opposed to preload, before excitation. Although these age-associated changes in cardiovascular reserve are insufficient to produce clinical heart failure, they do affect its clinical presentation, that is, the threshold for symptoms and signs or the severity and prognosis of heart failure secondary to any level of disease burden (e.g., chronic hypertension that causes either systolic or diastolic heart failure).

Table 21.1 Exhaustive upright exercise: changes in aerobic capacity and cardiac regulation between ages of 20 and 80 years in healthy men and women

Oxygen consumption	↑ (50 %)
$(A\text{-}V)O_2$	↑ (25 %)
Cardiac index	↑ (25 %)
Heart rate	↑ (25 %)
Stroke volume	No change
EDV	← (30 %)
Vascular afterload (PVR)	← (30 %)
ESV	← (275 %)
Contractility	↑ (60 %)
Ejection fraction	↑ (15 %)
Plasma catecholamines	←
Cardiac and vascular responses to β-adrenergic stimulation	↑

Adapted from Lakatta E, Sollott S. The "Heartbreak" of Older Age. Mol Interventions 2002; 2:431–446
EDV end diastolic volume, *ESV* end systolic volume, *PVR* peripheral vascular resistance, *AV* arteriovenous

A sizeable component of the age-associated deficit in cardiovascular reserve is composed of diminished effectiveness of the autonomic modulation of heart rate, LV contractility, and arterial afterload. The essence of sympathetic modulation of the cardiovascular system is to ensure that the heart beats faster; to ensure that it retains a small size, by reducing the diastolic filling period, reducing LV afterload; to augment myocardial contractility and relaxation; and to redistribute blood to working muscles and to skin to dissipate heat. Each of the deficient components of cardiovascular regulation with aging, that is, heart rate (and thus filling time), afterload (both cardiac and vascular), myocardial contractility, and redistribution of blood flow, exhibits a deficient sympathetic modulation [1].

Multiple lines of evidence support the idea that the efficiency of postsynaptic β-adrenergic signaling declines with aging [1]. One line of evidence stems from the observation that cardiovascular responses to β-adrenergic agonist infusions at rest decrease with age [1]. A second type of evidence for a diminished efficacy of postsynaptic β-adrenergic receptor (β-AR)

signaling is that acute β-adrenergic receptor blockade changes the exercise hemodynamic profile of younger persons to make it resemble that of older individuals. Significant beta blockade-induced LV dilation occurs only in younger subjects [5]. The heart rate reduction during exercise in the presence of acute β-adrenergic blockade is greater in younger vs. older subjects [5], as are the age-associated deficits in LV early diastolic filling rate, both at rest and during exercise [5]. It has also been observed in older dogs that the age-associated increase in aortic impedance during exercise is abolished by acute β-adrenergic blockade [6].

Apparent deficits in sympathetic modulation of cardiac and arterial functions with aging occur in the presence of exaggerated neurotransmitter levels. Plasma levels of norepinephrine and epinephrine, during any perturbation from the supine basal state, increase to a greater extent in older compared with younger healthy humans. The age-associated increase in plasma levels of norepinephrine results from an increased spillover into the circulation and, to a lesser extent, reduced plasma clearance. The degree of norepinephrine spillover into the circulation differs among body organs; increased spillover occurs within the heart. Deficient norepinephrine reuptake at nerve endings is a primary mechanism for increased spillover during acute graded exercise. During prolonged exercise, however, diminished neurotransmitter reuptake might also be associated with depletion and reduced release and spillover. Cardiac muscarinic receptor density and function are also diminished with increasing age and might contribute to the decrease in baroreflex activity observed in aged subjects [7].

Age-Associated Cell and Molecular Changes in Heart Cells

Cellular and molecular mechanisms implicated in age-associated changes in myocardial structure and function in humans have been studied largely in rodents (Table 21.2).

The altered cardiac structural phenotype that evolves with aging in rodents includes an increase in LV mass due to an enlargement of myocyte size [8] and focal proliferation of the matrix in which the myocytes reside, which may be linked to an altered cardiac fibroblast number or function. The number of cardiac myocytes becomes reduced because of necrosis and apoptosis, with the former predominating [9]. Putative stimuli for cardiac cell enlargement with aging in rodents include an age-associated increase in vascular load due to arterial stiffening and stretching of cells caused by dropout of neighboring myocytes [10]. Stretch of cardiac myocytes and fibroblasts initiates growth factor signaling (e.g., angiotensin II/TGF-β) that, in addition to modulating cell growth and matrix production, leads to apoptosis [11]. The expression of atrial natriuretic [12] and opioid [13] peptides, molecules that are usually produced in response to chronic stress, is increased in the senescent rodent heart.

Excitation–Contraction Coupling in the Aging Heart

Ca^{2+} influx via L-type calcium channels (LCC) has a dual role in cardiac EC coupling: peak L-type Ca^{2+} current (I_{CaL}) provides the primary "trigger" for sarcoplasmic reticulum (SR) Ca^{2+} release, while the integrated Ca^{2+} entry replenishes the SR Ca^{2+} content available for release. The SR Ca^{2+} release and uptake play key roles in the regulation of cardiac contraction and relaxation. The SR Ca^{2+}-transporting proteins include the sarcoplasmic reticular Ca^{2+}-ATPase (SERCA2), its inhibitory protein phospholamban (PLB), the Ca^{2+}-storage protein calsequestrin (CSQ), and the SR Ca^{2+} release channel (ryanodine receptor; RyR). The SR Ca^{2+} cycling is further modulated by Ca^{2+} influx through LCC and by Ca^{2+} transport via Na^{+}–Ca^{2+} exchanger (NCX) (Fig. 21.4).

Coordinated changes in the expression and function of proteins that regulate several key steps of the cardiac EC coupling process (Fig. 21.4) occur in the rodent heart with aging.

Table 21.2 Myocardial changes with adult aging in rodents

Structural change	Functional change	Ionic, biophysical/biochemical mechanisms	Molecular mechanisms
↑ Myocyte size	Prolonged contraction	Prolonged cytosolic Ca^{2+} transient	–
↓ Myocyte number		↓ SR Ca^{2+} pumping rate	↓ SERCA mRNA
		↓ Pump site density	No change in calsequestrin mRNA
	Prolonged action potential	↓ I_{Ca} inactivation	↑ Na^{+}–Ca^{2+} exchanger mRNA
		↓ I_{To} density	
	Diminished β-adrenergic contractile response	↓ Coupling βAR-AC	β_1AR mRNA
		No change in G_i activation	No change in βARK mRNA
		No change in βARK activity	–
		↓ TNI, phospholamban	–
		↓ Phospholamban phosphorylation	–
		↓ I_{Ca} augmentation	–
		↓ Ca_i transient augmentation	–
		↑ Enkephalin peptides	–
		↑ Proenkephalin mRNA	–
	Diminished contraction velocity	↓ α MHC protein	↓ α MHC mRNA
		↑ β MHC protein	↑ β MHC mRNA
		↓ Myosin ATPase activity	No change in actin mRNA
		↓ RXRβ1 and γ mRNA	↓ RXRβ1 and γ mRNA
		↓ RXRβ1 and γ protein	
		↓ Thyroid receptor protein	
↑ Matrix connective tissue	↑ Myocardial stiffness	↑ Hydroxyproline content	↑ Collagen mRNA
		↑ Activity of myocardial RAS	↑ Fibronectin mRNA
			↑ AT1R mRNA
		↑ Atrial natriuretic peptide	↑ Atrial natriuretic peptide mRNA
	↓ Growth response	–	↓ Induction of immediate early genes
	↓ Heat shock response	–	↓ Activation of HSF

Modified from Lakatta EG. Cardiovascular regulatory mechanisms in advanced age. Physiol Rev 1993; 73:413–67. With permission from American Physiological Society
SR sarcoplasmic reticulum, *SERCA* sarco/endoplasmic reticulum calcium ATPase, *MHC* myosin heavy chain, *RXR* Retinoid X receptor, *AR* adrenergic receptor, *HSF* heat shock factor, *RYR2* cardiac ryanodine receptor, *AT1R* angiotensin II type 1 receptor, *RAS* renin–angiotensin system

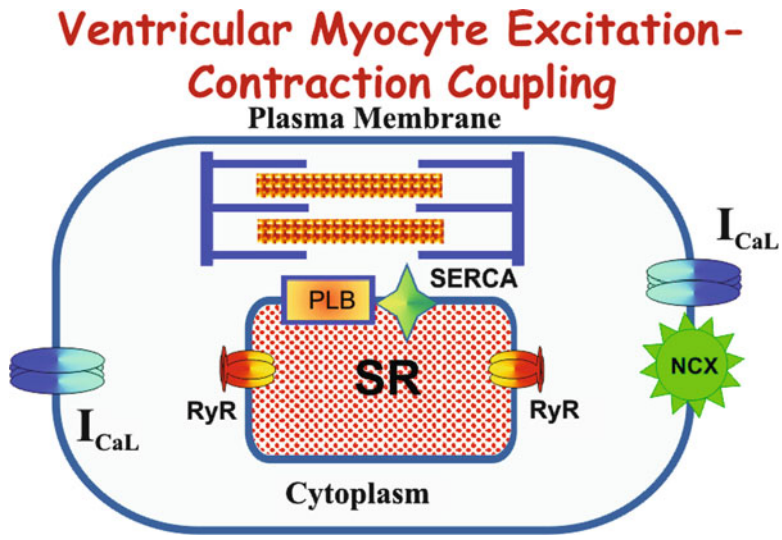

Fig. 21.4 Key events in ventricular excitation–contraction coupling

Prolonged time to peak and slower relaxation of contraction (Fig. 21.5), typical for aged myocardium [14–19], are attributable to changes in both the αMHC and βMHC protein ratio (Table 21.2) [1] and in the configuration of the Ca^{2+} transient. A slower decay of the Ca_i^{2+} transient is a hallmark of the aged cardiac myocyte (Fig. 21.4 and Table 21.1) (Fig. 21.5).

Action Potential Prolongation

L-Type Ca^{2+} Channel

Age-associated prolongation of the action potential (AP) (Fig. 21.5) [20–23] is thought to stem, in part at least, from changes in L-type Ca^{2+} channel characteristics [20, 22, 24]. Perspectives on how age affects I_{CaL} characteristics differ among studies, depending upon species, stress, and age range studied. Peak density of I_{CaL} in ventricular myocytes from senescent (21–25 months) does not differ from that of young (2–3 months) male Wistar rats [22, 25] and does not differ between 20–22 and 10- to 12-month-old male FVB mice [26]. I_{CaL} inactivates more slowly in myocytes from older vs. younger Wistar rats [22, 24], and this might partially account for prolongation of the AP reported in senescent Wistar and Fisher 344 rat hearts [22, 23]. In contrast, in ventricular myocytes isolated from young adult (6 months) and aged (27 months) Fischer 344 or Long–Evans rats, however, an age-associated decrease in peak density of I_{CaL} was observed and was accompanied by a slower inactivation and a greater amplitude of transient outward current (IT_O) [27]. Compared to young myocytes, AP duration in these myocytes from aged rats was longer at 90 % of repolarization but shorter at 20 and 75 % of repolarization [27].

In ventricular myocytes isolated from young (2 months) and senescent (20–27 months) C57/BL6 mice (sex unspecified), peak I_{CaL} density was similar at stimulation rates of 2–8 Hz but higher in myocytes of the older group at 0.4 and 1 Hz [28]. The I_{CaL} time integral (a function of peak amplitude and inactivation rate) normalized to cell capacitance did not differ with age during 6 Hz stimulation. Compared to young cells, I_{CaL} time integral in aged myocytes was significantly smaller at 8 Hz and larger at 0.4 Hz [28]. In ventricular myocytes isolated from young adult (~7 months) and aged (~24 months) male and female B6SJLF1/J mice [14] stimulated at 2 Hz, a significant reduction in peak I_{CaL} density, accompanied by a significantly slower inactivation, occurred in aged vs. young adult myocytes from males. No age-associated changes in I_{CaL} characteristics were identified in the females. In myocytes isolated

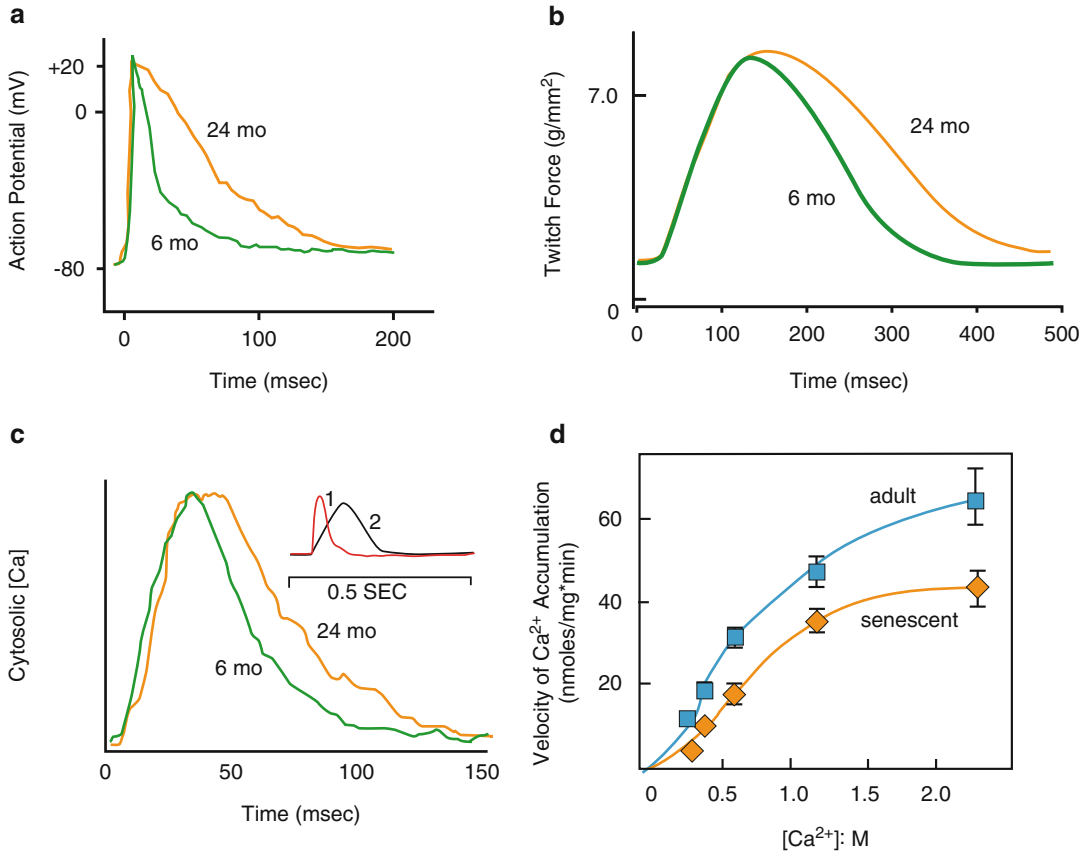

Fig. 21.5 Action potential (**a**), isometric contraction (**b**), and cytosolic Ca^{2+} (Ca_i) transient (**c**), measured via aequorin luminescence, in isometric right ventricular papillar muscles isolated from the hearts of young adult and senescent Wistar rats, are shown. (Inset) Time course of the Ca_i transient (1) relative to that of contraction (2). (**d**) Effect of age on Ca^{2+} accumulation velocity by sarcoplasmic reticulum (SR) isolated from senescent and adult Wistar rat hearts. (**a**) and (**b**): Reprinted from Spurgeon HA, Steinbach MF, Lakatta EG. Chronic exercise prevents characteristic age-related changes in rat cardiac contraction. Am J Physiol 1983; 244:H513–H518. With permission from American Physiological Society. (**c**): Reprinted from Orchard CH, Lakatta EG. Intracellular calcium transients and developed tensions in rat heart muscle. A mechanism for the negative interval–strength relationship. J Gen Physiol 1985; 86: 637–651. With permission Rockefeller University Press. (**d**): Reprinted from Froehlich JP, Lakatta EG, Beard E, Spurgeon HA, Weisfeldt ML, Gerstenblith G. Studies of sarcoplasmic reticulum function and contraction duration in young adult and aged rat myocardium. J Mol Cell Cardiol 1978; 10:427–438. With permission from Elsevier

from the hearts of young (18 months) and aged (8 years) female sheep, the AP duration and both the peak I_{CaL} and integrated Ca^{2+} entry were significantly greater in aged cells [20].

Ca^{2+} influx via LCC is a complex function of several interdependent mechanisms: voltage-dependent modulation; Ca^{2+}-dependent modulation via direct binding to LCC of Ca^{2+}–calmodulin and via calmodulin-dependent protein kinase II (CaMKII); and β-adrenergic modulation via protein kinase A (PKA) signaling. Voltage-dependent changes may be consequent to prolongation of the AP duration that accompanies advancing age and manifested by reduced peak amplitude accompanied by slower inactivation/larger time integral of I_{CaL} (e.g., [29]). Ca^{2+}-mediated effects may contribute to frequency-dependent reduction in the amplitude and time integral of I_{CaL} [28] due to rate-dependent diastolic Ca^{2+} accumulation, which slows the rate

of LCC recovery from inactivation in both normal and failing cardiac myocytes (reviewed in [30]). In addition, Ca^{2+}-dependent cross talk between LCC and RyR [30] may facilitate Ca^{2+} influx via LCC in the presence of slower and/or smaller SR Ca^{2+} release in aging myocardium. For instance, buffering of Ca_i^{2+} with EGTA eliminated age-related differences in the AP configuration and the time course of I_{CaL} inactivation in myocytes from senescent and young rats [22].

Reductions in outward K^+ currents [22] also contribute to the prolonged AP in cardiocytes of the aged heart. Of particular interest is the role of IT_O as an indirect modulator of EC coupling in cardiac cells (reviewed in [31]). Specifically, recent studies have provided evidence that the early repolarization phase may considerably influence the entire AP waveform and that IT_O is the main current responsible for this phase. Decreased IT_O density is observed in immature and aging myocardium, as well as during several types of cardiomyopathy and HF, i.e., under conditions in which SR function is depressed.

The AP prolongation that evolves during aging and accompanies heart failure favors Ca^{2+} influx during the depolarization and limits voltage-dependent Ca^{2+} efflux via NCX and thus may be adaptive since it provides partial compensation for SR deficiency, although possibly at the cost of asynchronous SR Ca^{2+} release and greater propensity to triggered arrhythmias [31].

SR Ca^{2+} Pump

The development of the Ca_i^{2+} transient is dependent primarily on the amount and the rate of Ca^{2+} release from the SR, and the decline of the Ca_i^{2+} transient and the amount of Ca^{2+} available for subsequent release are dependent primarily on Ca^{2+} sequestration by the SR. Sequestration of Ca^{2+} by the SERCA2 pump serves a dual function: (1) to cause muscle relaxation by lowering the cytosolic Ca^{2+} and (2) to restore SR Ca^{2+} content necessary for subsequent muscle contraction.

An age-associated reduction in the rate of rise and the amplitude of the Ca_i^{2+} transient (systolic dysfunction), as well as the rate of decline of the Ca_i^{2+} transient (diastolic dysfunction), appears to result, in large part, from impaired Ca^{2+} pumping by SERCA2. These changes have been extensively documented in biochemical and functional studies [32–36]. At the molecular level, they are attributable to a reduced protein expression of SERCA2 or its ratio to PLB and/or reduced phosphorylation of the SERCA2–PLB complex by PKA and CaMK [36–38]. A shift of SERCA2b distribution to the subsarcolemmal space has also been suggested [28].

The age-associated reduction in SERCA2 mRNA levels is well documented (Table 21.2). The majority of studies in aging vs. younger rats have shown a significant reduction in protein levels of SERCA2 [19, 34, 35, 39]. In contrast, most studies in aging mice have shown unchanged levels of SERCA2 [16, 28, 40]. Apart from the phosphorylation status of SERCA2–PLB complex, discussed later, SR Ca^{2+} uptake is dependent on the relative levels of both proteins, i.e., reduced at lower SERCA2/PLB ratio [41].

The majority of studies reporting expression levels of both SERCA2 and PLB showed reduced SERCA2/PLB ratios in aging rodent hearts. Increasing SERCA/PLB ratio through in vivo gene transfer of SERCA2a markedly improved rate-dependent contractility and diastolic function in 26-month-old rat hearts [34]. Functional improvement consequent to increasing SERCA/PLB ratio by PLB suppression was also reported in human failing myocytes [42]. On the other hand, PLB ablation in transgenic mouse models of HF was beneficial only in some models (reviewed in [41, 43]).

Age-associated decline in the Ca^{2+}-sequestering activity of SERCA2 in rodent myocardium has been well documented both by biochemical studies in isolated SR vesicles and by biophysical studies in cardiac preparations [32–36].

In addition to a reduced content of SERCA2 or SERCA2/PLB ratio, discussed earlier, lower pumping activity of SERCA2 in aging myocardium may result from reduced phosphorylation of the SERCA2–PLB complex. Specifically, in its unphosphorylated state, PLB interacts with SERCA2 exerting an inhibitory effect manifested largely through a decrease in the enzyme's affinity for Ca^{2+}.

Phosphorylation of PLB by PKA and/or Ca^{2+}/CaMK is thought to disrupt this interaction resulting in enhanced affinity of the ATPase for Ca^{2+} and stimulation of Ca^{2+} pump activity [41]. In addition to PLB, CaMK has been suggested to modulate the SR Ca^{2+} uptake and release through direct phosphorylation of SERCA2 [38]. Recent studies have also shown that significant age-associated decrements occur in (1) the amount of CaMK (δ-isoform) in the rat heart, (2) the endogenous CaMK-mediated phosphorylation of SERCA and PLB, and (3) the phosphorylation-dependent stimulation of SR Ca^{2+} sequestration [36]. Increased activity of the SR-associated phosphatase PP1, which dephosphorylates PLB, had already been reported, and overexpression of PP1 in transgenic mice resulted in HF. PP1 activity was further shown to be regulated by the inhibitor I-1, and I-1 was found to be reduced in human HF (reviewed in [44]). However, potential age-related changes in the activity of cardiac phosphatases have yet to be examined.

Age-related alterations in the gating properties of RyR [19, 45], resulting in an increased SR Ca^{2+} leak, may also contribute to both diastolic and systolic dysfunction of the aging myocardium by limiting the net rate of SR Ca^{2+} sequestration and SR Ca^{2+} loading, respectively. Finally, a slower rate of development/longer time to peak of the Ca_i^{2+} transient in aging myocytes is likely to result from reduced SR Ca^{2+} loading but may be also consequent to a longer time to peak I_{CaL} [22], which synchronizes SR Ca^{2+} release.

SR Ca^{2+} Release Channel

In addition to Ca^{2+} pumping by SERCA2, RyR characteristics are regulated by its protein expression and gating properties, a major determinant of the SR Ca^{2+} release, triggered by Ca^{2+} influx through LCC, as well as during cardiac relaxation and diastole. Accordingly, alterations in the expression or function of RyR have been implicated in both systolic and diastolic dysfunction of the aging heart. Reduced protein expression of cardiac RyR has been reported in aging Wistar rats [39], but not Fisher 344 rats [19, 34, 36]. The RYR is phosphorylated by PKA and CaMK, and a significant reduction in the CaMK-mediated phosphorylation of the RyR has been shown to occur in the aged compared with adult Fisher 344 rats [36].

Single-channel properties of RyR and unitary SR Ca^{2+} release events (Ca^{2+} sparks) in ventricular cardiomyocytes were recently examined in hearts from 6- to 24-month-old Fisher 344 rats [19]. Senescent myocytes displayed a decreased Ca_i^{2+} transient amplitude and an increased time constant of the Ca_i^{2+} transient decay, both of which correlated with a reduced Ca^{2+} content of the SR. Senescent cardiomyocytes also had an increased frequency of spontaneous Ca^{2+} sparks and a slight but statistically significant decrease in their average amplitude, full-width-at half-maximum and full-duration-at-half-maximum.

Single-channel recordings of RyR demonstrated that in aging hearts, the open probability of RYR was increased but the mean open time was shorter, providing a molecular correlate for the increased frequency of Ca^{2+} sparks and decreased size of sparks, respectively [19]. These results suggest modifications of normal RyR gating properties associated with increased sensitivity of RyR to resting and activating Ca^{2+} that may play a role in the altered Ca^{2+} homeostasis observed in senescent myocytes. Another recent study [45] examined the effects of aging on whole cell electrically stimulated Ca^{2+} transients and Ca^{2+} sparks at 37 °C in ventricular myocytes isolated from young adult (~5 months) and aged (~24 months) B6SJLF1/J mice of both sexes. A reduced amplitude and abbreviated rise time of the Ca_i^{2+} transient in aged cells stimulated at 8 Hz and a markedly higher incidence and frequency of spontaneous Ca^{2+} sparks were observed in aged vs. young adult cells. Spark amplitudes and spatial widths were similar in both age groups. However, spark half-rise times and half-decay times were abbreviated in aged cells compared with younger cells. Neither resting Ca_i^{2+} levels nor SR Ca^{2+} content differed between young adult and aged cells, indicating that increased spark frequency in aging cells was not attributable to increased SR Ca^{2+} stores and that a decrease in the Ca_i^{2+} transient amplitude was not due to a decrease in SR Ca^{2+} load. These results suggest that alterations in SR Ca^{2+} release units occur in aging ventricular myocytes and raise the possibility that alterations in Ca^{2+} release may

reflect age-related changes in fundamental release events rather than changes in SR Ca^{2+} stores and/or diastolic Ca_i^{2+} levels. Differences in the characteristics of Ca^{2+} sparks (and the SR Ca^{2+} content) reported in these experiments [19, 45] might be partly related to differences in species and experimental conditions (e.g., temperature) employed.

Consistent with previous findings [45], both studies discussed above [19, 45] have shown increased frequency of spontaneous Ca^{2+} sparks in aging ventricular myocytes. The resulting increased Ca^{2+} leak from the SR may reduce the net rate of SR Ca^{2+} sequestration. Functional consequences of the latter include a slower decline of the Ca_i^{2+} transient and increased diastolic Ca_i^{2+} (diastolic dysfunction), a reduced SR Ca^{2+} load available for release (systolic dysfunction), and a reduced threshold for myocardial cell Ca^{2+} intolerance [46, 47]. PKA-dependent hyperphosphorylation of RYR, resulting in abnormal SR Ca^{2+} leak through the RyR, has been implicated in both diastolic and systolic dysfunction of the failing heart [48]. However, more recent evidence points to CaMKII site phosphorylation of RYR in normal cardiac tissue [49, 50], and a potential role and mechanism for PKA modulation of this process in the pathophysiology of HF associated with aging remains lacking.

Calsequestrin

Reports have consistently shown that aging does not alter CSQ expression at either the transcriptional (Table 21.1) or protein level [19, 34–36].

Na^+–Ca^{2+} Exchanger

The NCX serves as the main transsarcolemmal Ca^{2+} extrusion mechanism and is centrally involved in the beat-to-beat regulation of cellular Ca^{2+} content and cardiac contractile force, including regulation of the AP configuration in the late repolarization phase and the later Ca^{2+} clearance phase of the Ca_i^{2+} transient. Thus, alterations in NCX activity may contribute to the prolongation of both the AP duration and relaxation in aging myocardium [1]. An age-associated increase in the NCX expression has been demonstrated at the transcriptional level, but protein levels of NCX reported in aging rodent hearts were unchanged [21, 34, 51] or reduced compared to younger adults [16, 39, 52].

Results of experiments using enriched sarcolemmal vesicles or muscle strips isolated from rats were also inconsistent, i.e., the NCX activity in aged myocardium was observed to be decreased [52, 53], increased [54], or unchanged [55]. More recent functional assessments of NCX activity in cardiac myocytes isolated from young (14–15 months) and aged (27–31 months) male Fischer Brown Norway rats [21] showed that under conditions where membrane potential and intracellular $[Na^+]$ and $[Ca^{2+}]$ could be controlled, "forward" NCX activity was increased in aged vs. young cells. The increased "forward" NCX activity was interpreted as a factor contributing to the late AP prolongation in aging myocardium [21]. An increased Ca^{2+} efflux via NCX would compensate for increased Ca^{2+} influx via LCC [20, 22, 24]. Prolongation of the AP consequent to reduced I_{TO} [22] may temporarily limit "forward" NCX during relaxation, allowing better SR Ca^{2+} reuptake by SERCA2 [29].

The imposition of a shorter AP to myocytes from the old rat heart reduces the amplitude and the rate of decline of the steady-state Ca^{2+} transient and Ca_i^{2+} transient [29]. This is attributable to a reduction in the SR Ca^{2+} uptake and loading, which, in the presence of a reduced rate of Ca^{2+} sequestration by SERCA2, is presumably due to a reduced I_{CaL} time integral and likely also to an increased net Ca^{2+} extrusion via NCX [29].

Response to Action Potentials of an Increased Frequency

Reduction in the amplitude of the Ca_i^{2+} transient in myocytes from aged hearts, compared to younger counterparts, has been reported in some studies already at low (<2 Hz) stimulation rates [14, 19]. Studies that have employed a range of stimulation rates [15, 28] typically showed blunted force and relaxation-frequency responses in myocytes from old vs. young hearts (Fig. 21.6).

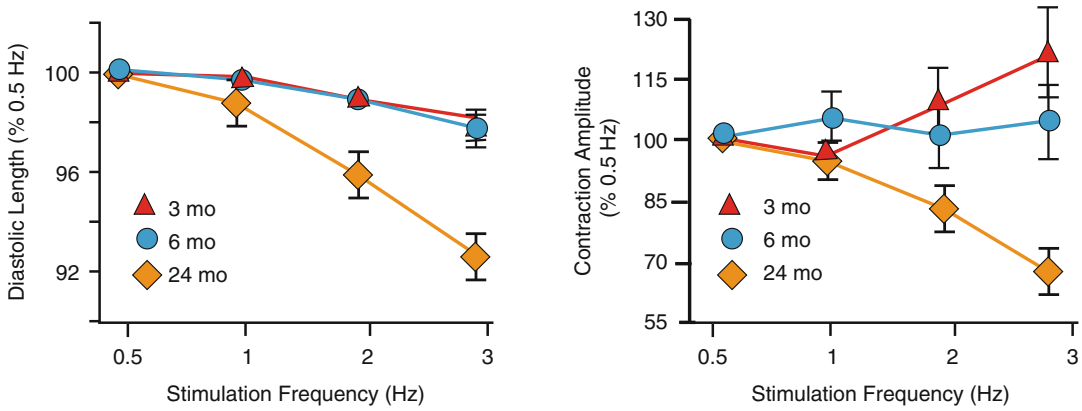

Fig. 21.6 Response to an increase in stimulation frequency in single ventricular myocytes isolated from rats of three ages

Thus, while the age-related differences in the amplitude and the rate of decay of the Ca_i^{2+} transients (and diastolic Ca_i^{2+} levels) were small or absent at low stimulation rates, they became apparent and progressively larger at pacing rates approximating those in vivo [15, 28].

Likewise, abrupt changes in the stimulation rate reveal an impaired SR Ca^{2+} release in ventricular myocytes isolated from senescent vs. young rats (Fig. 21.6). Specifically, in the presence of similar kinetics of I_{CaL} recovery, reduction in the amplitude of the Ca_i^{2+} transients and the gain of I_{CaL}-dependent Ca^{2+} release during premature depolarizations is attributable to a slower rate of SR Ca^{2+} reuptake in older myocytes (Fig. 21.7).

Consistent with the major role of SERCA2 in these effects, studies in rat-isolated cardiac muscle preparations have shown that exercise training reverses age-associated slowing of contraction and relaxation [17, 18]. This was associated with increased Ca^{2+} transport by SERCA2 but not myosin ATPase activity in cardiac homogenates [18]. Likewise, overexpression of SERCA2 markedly improved rate-dependent contractility and contractile function in senescent rat hearts [34]. Clearly, the latter underlies impaired frequency-dependent inotropic and lusitropic responses [14–16, 34] that largely contribute to the systolic and diastolic dysfunction of the aging heart.

Reduced Acute Response of Myocardial Cells from Older Hearts to Acute β-Adrenergic Receptor Stimulation

Age-associated deficits in the myocardial β-AR signaling cascade also occur with aging in rats. The richly documented age-associated reduction in the postsynaptic response of myocardial cells to β-adrenergic stimulation seems to be due to multiple changes in the molecular and biochemical steps that couple the receptor to postreceptor effectors. However, the major limiting modification of this signaling pathway that occurs with advancing age in rodents seems to be the coupling of the β-AR to adenylyl cyclase via the G_s protein and changes in adenylyl cyclase protein, which lead to a reduction in the ability to sufficiently augment cell cAMP and to activate PKA to drive the phosphorylation of key proteins that are required to augment cardiac contractility [37, 56]. In contrast, the apparent desensitization of β-adrenergic signaling that occurs with aging does not seem to be mediated via increased β-AR kinase or increased G_i activity [57]. A blunted response to β-adrenergic stimulation of the cells within older myocardium can, in one sense, be viewed as adaptive with respect to its effect to limit the risk of Ca^{2+} overload and cell death in these cells in response to stress (Table 21.3),

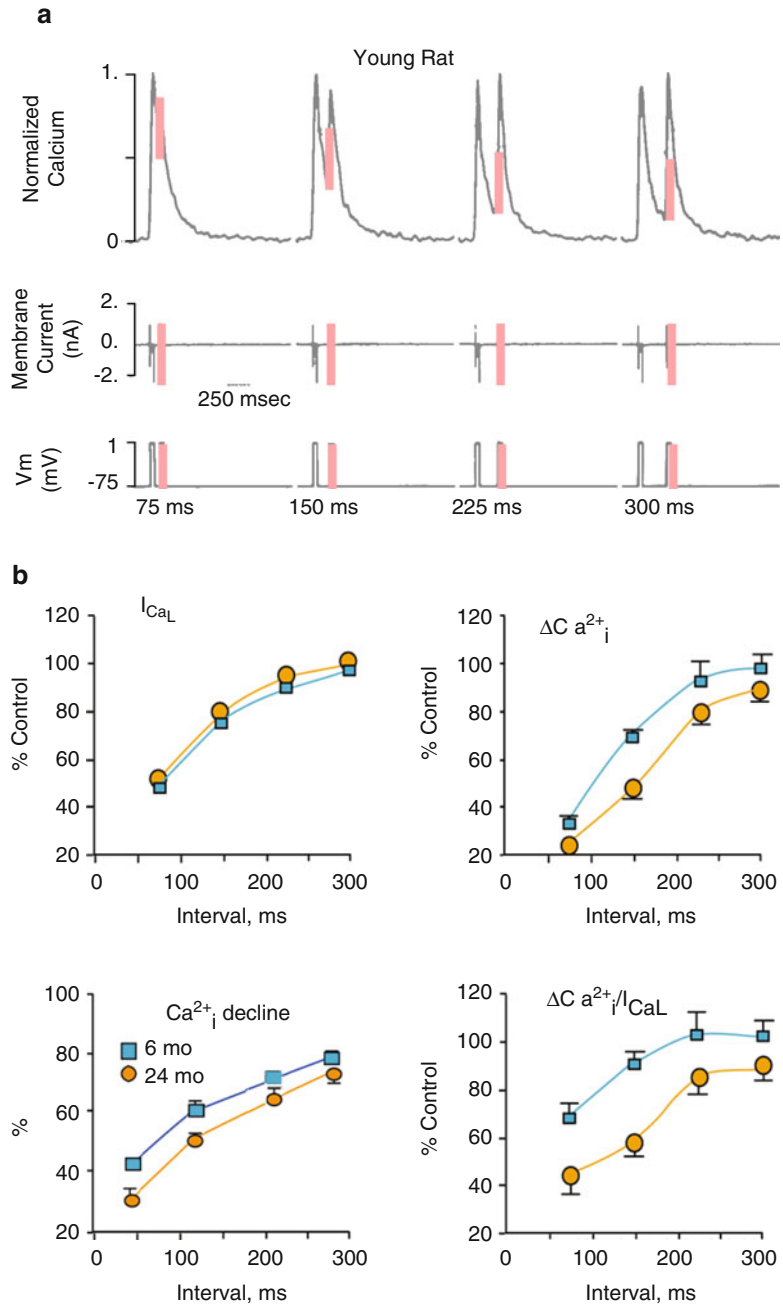

Fig. 21.7 Recovery of the L-type Ca^{2+} current (I_{CaL}) and the intracellular Ca^{2+} (Ca_i^{2+}) transient following a prior depolarization. (**a**) Recordings of Ca_i^{2+} transients (*top*) and I_{CaL} (*middle*), induced by voltage clamp depolarizations (*bottom*) from −75 to 0 mV (with Na^+ current, K^+ currents, and "reverse" Na^+–Ca^{2+} exchange blocked) in a representative ventricular myocyte isolated from young adult (6 months) Wistar rat. Test pulse intervals of 75–300 ms duration were applied following a train of nine conditioning voltage pulses (50 ms, from −75 to 0 mV at 0.5 Hz). (**b**) Averaged data from these experiments in myocytes from young ($n=5$) and old (24 months; $n=7$) rats show slower rate of Ca_i^{2+} decline during the last conditioning pulse and similar kinetics of I_{CaL} recovery but prolonged recovery time of the Ca_i^{2+} transient and "gain" of I_{CaL}-dependent Ca^{2+} release (Ca_i^{2+}/I_{CaL}) during premature depolarizations in old vs. young myocytes (courtesy of Andzej M. Janczewski and Edward G. Lakatta)

Table 21.3 Ventricular cells within the old heart operate "on the edge"

Myocyte enlargement
Altered gene expression
Altered levels and functions of proteins that regulate Ca^{2+} homeostasis
Reduced response to acute stress
Increased markers of chronic stress
Altered membrane lipid composition
Increased threat of reactive O_2 species
Increased cell death in the context of reduced cell replacement

including reduced augmentation of the I_{CaL} (Fig. 21.8) [25] through PKA-mediated changes in the availability and gating properties of LCC. The well-established deficits in β-AR signaling that occur in aging humans and animals [1] include significantly lower PKA-dependent phosphorylation of PLB in aged vs. adult rat ventricular myocardium [37]. A reduced myocardial contractile response to either β_1AR or β_2AR stimulation is observed with aging [25, 57, 58]. This is due to failure of β-adrenergic stimulation to augment Ca_i^{2+} to the same extent in cells of senescent hearts that it does in those from younger adult hearts (Fig. 21.8), an effect attributable to a deficient increase of L-type sarcolemmal Ca^{2+} channel availability (Fig. 21.8), which leads to a lesser increase in Ca^{2+} influx [25].

Markers of Chronic Stress in the Aged Heart Suggest That It "Operates on the Edge of Disease"

Acute excess myocardial Ca^{2+} loading leads to dysregulation of Ca^{2+} homeostasis, impaired diastolic and systolic function, arrhythmias, and cell death [47]. The cell Ca^{2+} load is determined by membrane structure and permeability characteristics, the intensity of stimuli that modulate Ca^{2+} influx or efflux via their impact on regulatory function of proteins within membranes, and ROS, which affect both membrane structure and function. Excessive cytosolic Ca^{2+} loading occurs during physiological and pharmacological scenarios that increase Ca^{2+} influx (e.g., neurotransmitters, postischemic reperfusion, or oxidative stress) [46, 59]. In hearts or myocytes from the older heart, enhanced Ca^{2+} influx, impaired relaxation, and increased diastolic tone occur during pacing at an increased frequency [15, 18, 60, 61]. This is a "downside" of the age-associated adaptations that occur within the cells of senescent heart and also of young animals chronically exposed to arterial pressure overload (Table 21.4). Causes of reduced Ca^{2+} tolerance of the older heart include changes in the amounts of proteins that regulate Ca^{2+} handling, caused in part by altered gene expression (Tables 21.3 and 21.4), and an age-associated alteration in the composition of membranes in which Ca^{2+} regulatory proteins reside, which includes an increase in membrane ω_6:ω_3 polyunsaturated fatty acids (PUFAs) [62]. ω_3 PUFAs are protective of cardiac Ca^{2+} regulation. An additional potential cause of the reduced threshold of senescent myocytes for Ca^{2+} overload is an enhanced likelihood for intracellular generation of ROS [59, 63] in cells from the senescent vs. the younger adult heart during stress. In this regard, the older cardiac myocyte and endothelial cells [64] share common "risks" with aging.

Myocyte Progenitors in the Aging Heart

There are two opposing views regarding cardiomyocyte renewal within the heart: One proposes that the number of myocytes is fixed around birth and remains static; the other purports that the heart is a self-renewing organ containing a pool of progenitor cells (PCs) that dictate cell turnover, organ homeostasis, and myocardial aging. Observations in both humans and animals suggest that myocyte maturation and aging are characterized by loss of replicative potential, telomeric shortening, and the expression of the senescence-associated protein/cell cycle inhibitor $p16^{INK4a}$ [65–69]. Telomeric shortening in PCs leads to generation of progeny that rapidly acquire the senescent phenotype involving a progressive increase in the size of the cell (up to a critical volume

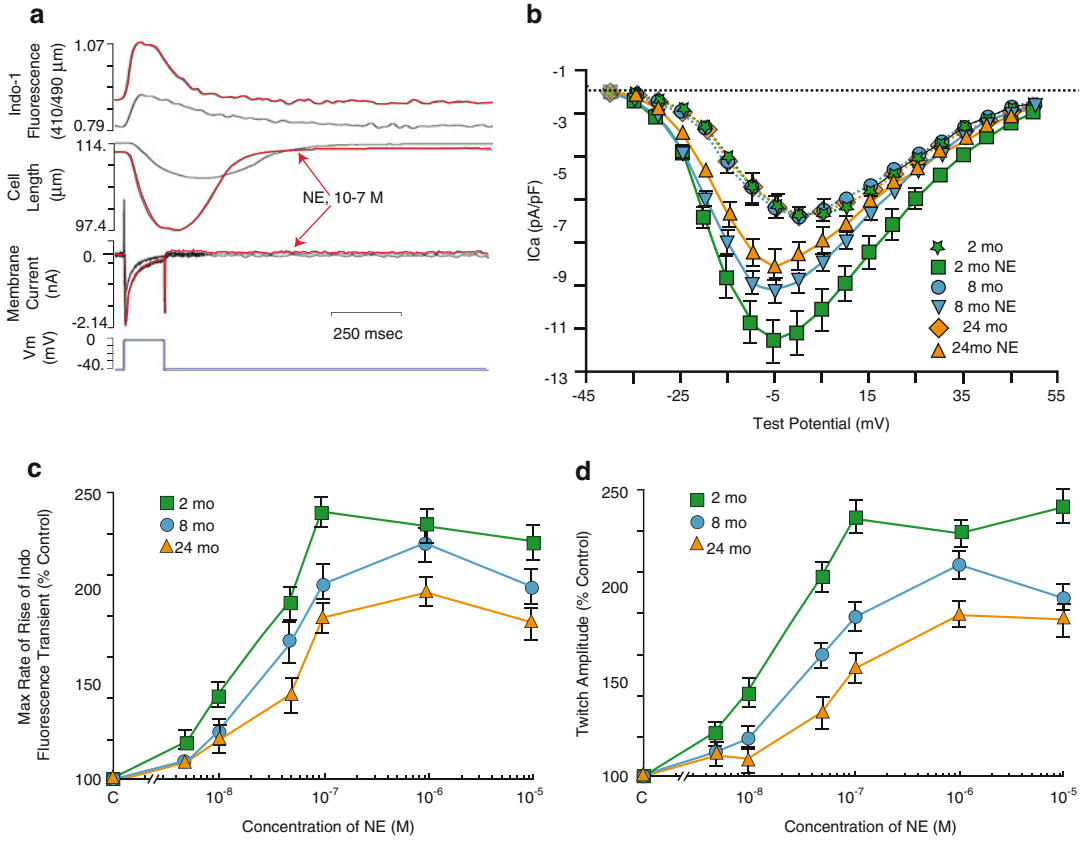

Fig. 21.8 Effects of norepinephrine (10^{-7} M) on contraction and Ca^{2+} transient amplitudes and kinetics. (**a**) Tracings obtained in the presence and absence of NE in the same myocyte are superimposed. (**b**) Peak current–voltage relationship of L-type Ca^{2+} channel activation for young (2 months), adult (8 months), and senescent (24 months) ventricular myocytes from Wistar rats, before and after NE 10^{-7} M. (**c**) Maximum rate of rise of calcium transient indexed by INDO-1 fluorescence in presence of increasing dose of NE in three ages of rat. (**d**) Average contractile amplitude responses to norepinephrine in 3 age groups. (Adapted from Xiao R-P, Tomhave ED, Wang DJ, Ji X, Boluyt MO, Cheng H, Lakatta EG, Koch WJ. Age-associated reductions in cardiac β1- and β2-adrenoceptor responses without changes in inhibitory G proteins or receptor kinases. *J Clin Invest* 1998; 101:1273–1282)

beyond which myocyte hypertrophy is no longer possible), deficits in the electrical, Ca^{2+} cycling, and mechanical properties, and cell death. Cardiac myocytes with senescent and non-senescent phenotypes already coexist at young age [69]. However, aging limits the growth and differentiation potential of PCs, thus interfering not only with their ability to sustain physiological cell turnover but also with their capacity to adapt to increases in pressure and volume loads [65, 68].

A loss of PC function can result in an imbalance between factors enhancing oxidative stress, telomere attrition, and death and factors promoting growth, migration, and survival. Recent findings suggest a preeminent position of insulin-like growth factor-1 (IGF-1) among factors that can partly overcome cardiac cellular senescence. Specifically, cardiac-restricted overexpression of IGF-1 in transgenic mice has been shown to delay the aging myopathy and the manifestations of HF [26] and to restore SERCA2a expression

Table 21.4 Alterations in experimental cardiac myocyte hypertrophy and normal aging

Gene expression	Hypertrophy	Aging
SR Ca^{++} ATPase	↓	↓
Na–Ca^{++} exchanger	↑	↑
Calsequestrin	◁▷	◁▷
Phospholamban	↓	↑
α-Myosin heavy chain	↓	↓
β-Myosin heavy chain	↑	↑
β-Tropomyosin	↓	↑[a]
Skeletal α-actin	↓	↑[a]
Atrial natriuretic factor	↑	↑
Proenkephalin	↑	↓[a]
β_1 receptor	↓	↓
Fibronectin	↑	↑
Type I collagen	↑	↑
Type III collagen	↑	↑
Angiotensinogen	↑	↑
Angiotensin converting enzyme	↑	↑

SR sarcoplasmic reticulum
[a]Transient changes only

and rescue age-associated impairment of cardiac myocyte contractile function [51]. The latter effect was also partly mimicked by short-term in vitro treatment with recombinant IGF-1 [51]. Furthermore, intramyocardial delivery of IGF-1 improved senescent heart phenotype in male Fisher 344 rats [67], including increased proliferation of functionally competent PCs and diminished angiotensin II-induced apoptosis. Myocardial regeneration mediated by PC activation attenuated ventricular dilation and the decrease in ventricular mass-to-chamber volume ratio, resulting in improvement of in vivo cardiac function in animals at 28–29 months of age [67].

More recent studies employing the ^{14}C retrospective dating of myocytes in the human heart are controversial and have been interpreted to indicate that the cell renewal rate is very low [70] or, conversely, becomes substantially higher with advancing age [71]. The latter result suggests that factors that cause excessive cell death, and not a reduced stem cell renewal rate, per se, are the predominant cause of a reduced myocyte number in the aged heart.

Summary

In summary, age per se is the major risk factor for cardiovascular disease. Elucidation of the age-associated alterations in cardiac and arterial structure and function at both the cellular and molecular levels provides valuable clues that may assist in the development of effective therapies to prevent, to delay, or to attenuate the cardiovascular changes that accompany aging and contribute to the clinical manifestations of chronic heart failure. Changes in cardiac cell phenotype that occur with normal aging, as well as in HF associated with aging, include deficits in β-adrenergic receptor signaling, increased generation of reactive oxygen species, and altered excitation–contraction (EC) coupling that involves prolongation of the action potential, intracellular Ca^{2+} transient and contraction, and blunted force and relaxation-frequency responses. Evidence suggests that altered sarcoplasmic reticulum Ca^{2+} uptake, storage, and release play central role in these changes, which also involve sarcolemmal L-type Ca^{2+} channel (LCC), Na^+–Ca^{2+} exchanger, and K^+ channels.

In spite of the interest in the physiology of the age-associated changes in cardiovascular structure and function, however, cardiovascular aging has remained, for the most part, outside of mainstream clinical medicine. This is largely because the pathophysiologic implications of these age-associated changes are largely underappreciated and are not well disseminated in the medical community. In fact, age has traditionally been considered a nonmodifiable risk factor. Policy makers, researchers, and clinicians need to intensify their efforts toward identification of novel pathways that could be targeted for interventions aiming at retardation

or attenuation of these age-associated alterations that occur in the heart and arteries, particularly in individuals in whom these alterations are accelerated. Translational studies would then examine whether these strategies (i.e., those targeting cardiovascular aging) can have a salutary impact on the adverse cardiovascular effects of accelerated cardiovascular aging. As such, cardiovascular aging is a promising frontier in preventive cardiology.

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22 Aging-Related Changes in Cell Death and Cell Survival Pathways and Implications for Heart Failure Therapy

Guido R.Y. De Meyer, Dorien M. Schrijvers, and Wim Martinet

Abbreviations

ACE	Angiotensin-converting enzyme
AMPK	AMP-activated protein kinase
AR	Adrenergic receptor
ARC	Apoptosis repressor with caspase recruitment domain
ATG	Autophagy-related genes
ER	Endoplasmic reticulum
FOXO	Forkhead box protein O
MPTP	Mitochondrial permeability transition pore
mTOR	Mammalian target of rapamycin

Underlying the aging process is a lifelong accumulation of molecular damage [1]. The rate of age-related pathology is modulated by stress responses and repair pathways that gradually decline [2]. In this chapter, we will discuss aging-related changes in cell death and cell survival pathways and their implications for heart failure therapy.

G.R.Y. De Meyer, PharmD, PhD (✉)
Department of Physiopharmacology, University of Antwerp, Universiteitsplein 1, Antwerp 2610, Belgium
e-mail: guido.demeyer@uantwerpen.be

D.M. Schrijvers, PhD • W. Martinet, PhD
Department of Physiopharmacology, University of Antwerp, Antwerp, Belgium

Effect of Aging on Apoptosis and Necrosis in the Heart

Aging is associated with increased oxidative damage of proteins, lipids, and nuclear and mitochondrial DNA, as a result of unbalanced pro- and antioxidant activities. Cells from the elderly contain increased DNA damage in both nuclei and mitochondria as compared with younger subjects [3]. When DNA damage is too extensive to be repaired or when the repairing cascades are impaired, e.g., during chronic oxidative stress associated with aging [4], apoptosis occurs [5]. In the normal human myocardium, apoptosis is rare, with a prevalence of one TUNEL-positive cardiomyocyte per 10,000–100,000 (i.e., 0.01–0.001 %) [6]. However, in heart failure, which is predominantly a disorder of the elderly [7], 0.12–0.70 % apoptotic cells are present in hearts from NYHA (New York Heart Association) class III–IV patients [8]. Because of the limited ability of cardiomyocytes to proliferate, low levels of apoptosis may have profound effects. An apoptotic rate of 0.1 % results in a 37 % loss in cardiomyocyte number over a year [9]. Thus, a very low, albeit elevated, rate of apoptosis can be an important factor in the pathogenesis of heart failure [10], making it a potential target for therapy.

Necrosis is characterized by cell and organelle swelling, plasma membrane damage, and loss of ATP [6]. Disruption of cell integrity and release of the cell content trigger a secondary inflammatory response [11]. Necrosis contributes to the progression of heart failure, and Ca^{2+} handling

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and mitochondrial permeability transition pore (MPTP) opening are critically involved [12–16]. Necrosis is more prominent in failing human hearts than apoptosis [17].

Effect of Aging on Autophagy in the Heart

Macroautophagy (further termed autophagy) is a process of delivery of intracellular components, including mitochondria and long-lived macromolecules, via a double-membrane structure (autophagosome) to lysosomes for degradation (Fig. 22.1), controlled by autophagy-related genes (ATG) [18, 19]. It is an essential and protective pathway in the heart. At basal levels, autophagy performs housekeeping functions, maintaining cardiomyocyte function and ventricular mass [20]. Because cardiomyocytes are terminally differentiated postmitotic cells with a life span of several decades, the maintenance of a healthy pool of mitochondria is vital for the preservation of cardiomyocyte homeostasis [21]. Autophagy clears damaged mitochondria, which release proapoptotic factors such as cytochrome c, and avoids activation of apoptosis. In this way, autophagy contributes to the prevention of heart failure [22]. Indeed, it has been demonstrated that the conditional loss of function of the autophagy-related gene Atg5 in adult mice leads to disorganized sarcomere structure, collapsed mitochondria, cardiac hypertrophy, and significant reduction in fractional shortening of the left ventricle, accompanied with decreased survival, indicating that continuous constitutive autophagy has a crucial role in maintaining cardiac structure and function [23, 24]. Furthermore, the heart consumes the most energy per gram of all organs. Autophagy helps to maintain cellular energy homeostasis, preventing a shortage in the availability of energy substrates. This is a second way by which autophagy contributes to preservation of cardiac function and prevention of heart failure.

However, during aging, the rate of protective autophagy declines (Fig. 22.2) [21, 24, 25]. This is in part due to a decrease in the expression of autophagy proteins [26, 27], resulting in diminished autophagosome formation, impaired fusion of lysosomes with autophagosomes, and decreased lysosomal proteolytic activity. Moreover, aging changes the activity of key regulators of autophagy: AMP-activated protein kinase (AMPK) activity decreases, whereas mammalian target of rapamycin (mTOR) activity increases [26]. Both changes reduce autophagic activity (Fig. 22.3) [28]. Also other factors contribute to the decline in the autophagic process in conjunction with aging. Indeed, NF-κB signaling is a potent repressor of autophagy with aging [28] by increasing the expression of autophagy repressors (such as A20, Bcl-2/Xl, and NLRP receptors). Furthermore, the inability to remove damaged structures when autophagy is decreased results in the progressive accumulation of garbage [29], including dysfunctional mitochondria, which are deficient in ATP production and which produce large amounts of reactive oxygen species (ROS) [21], abnormal intracellular proteins

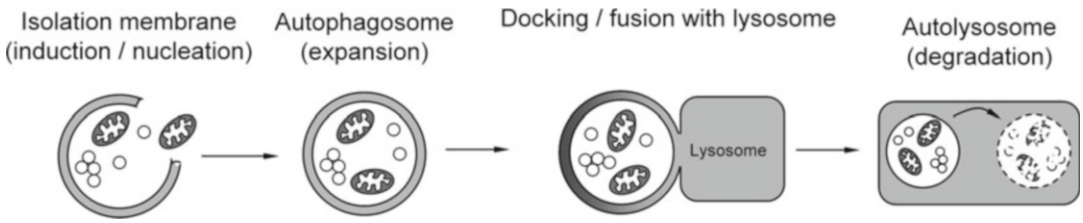

Fig. 22.1 Schematic overview of the autophagic process. Autophagy is initiated by the formation of nascent autophagosomal structures (isolation membranes), which sequestrate small portions of the cytoplasm and organelles for degradation. Expansion of the isolation membrane and enclosure of the cytoplasmic cargo lead to the formation of autophagosomes. Subsequently, autophagosomes dock and fuse with lysosomes to form autolysosomes, in which the cargo is degraded

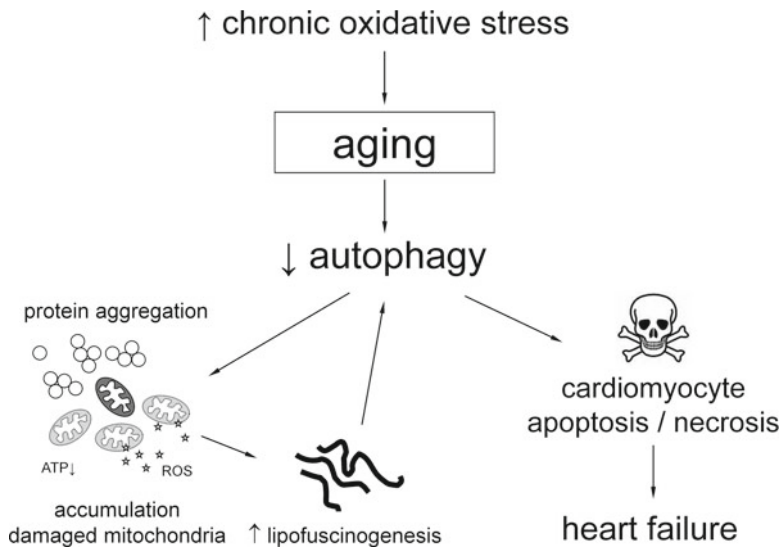

Fig. 22.2 Schematic overview of the modulation of autophagy by aging. Chronic oxidative damage to DNA, proteins, lipids, and cell organelles plays an important role in aging. Autophagy is defective in aged cells due to diminished autophagosome formation, impaired fusion of lysosomes with autophagosomes, and decreased lysosomal proteolytic activity. The progressive inhibition of autophagy in the aging heart is in part attributed to intralysosomal accumulation of lipofuscin. Cross-linked polymeric lipofuscin cannot be degraded by lysosomal hydrolases and leads to preferential allocation of lysosomal enzymes to lipofuscin-loaded lysosomes at the expense of active autolysosomes. Impaired autophagy further stimulates accumulation of damaged mitochondria, which are deficient in ATP production and which produce large amounts of reactive oxygen species (ROS). Moreover, oxidatively modified cytosolic proteins form large indigestible aggregates, enhancing lipofuscinogenesis and sensitizing cardiomyocytes to undergo apoptosis/necrosis, eventually leading to heart failure

aggregates, and undigested materials such as lipofuscin [30]. Cross-linked polymeric lipofuscin cannot be degraded by lysosomal hydrolases and leads to preferential allocation of lysosomal enzymes to lipofuscin-loaded lysosomes at the expense of active autolysosomes. In this environment of decreased autophagy, oxidatively modified cytosolic proteins form large indigestible aggregates, even enhancing lipofuscinogenesis. Eventually, the decrease in autophagic capacity increases the propensity of cardiomyocytes toward apoptosis and necrosis, resulting in heart failure (Fig. 22.2) [31–34].

It is important to note that in contrast to the protective capacities of autophagy, excessive autophagy induction leads to autophagic cell death and loss of cardiomyocytes and may contribute to the worsening of heart failure [30, 35, 36]. Among the factors that determine whether autophagy will be protective or detrimental, the level of autophagy induction is important [30]. Thus, there is an optimal, adaptive zone of autophagic activation: too much or too little autophagy leads to increased hypertrophy and heart dysfunction [6]. These findings have important implications for therapy (*vide infra*). Because in aging protective autophagy progressively declines, as explained above, drugs that stimulate autophagy might be of value in the therapeutic armamentarium of heart failure. However, the dosing should be carefully set in order to avoid (excessive) autophagic cell death.

Sirtuins

Sirtuin activity is linked to aging, DNA repair, and cell survival [37–39]. Sirtuins are deacetylases that mediate posttranslational modification by coupling lysine deacetylation to NAD^+ hydrolysis [40]. Therefore, the biochemical and biological functions of sirtuins are coupled to the

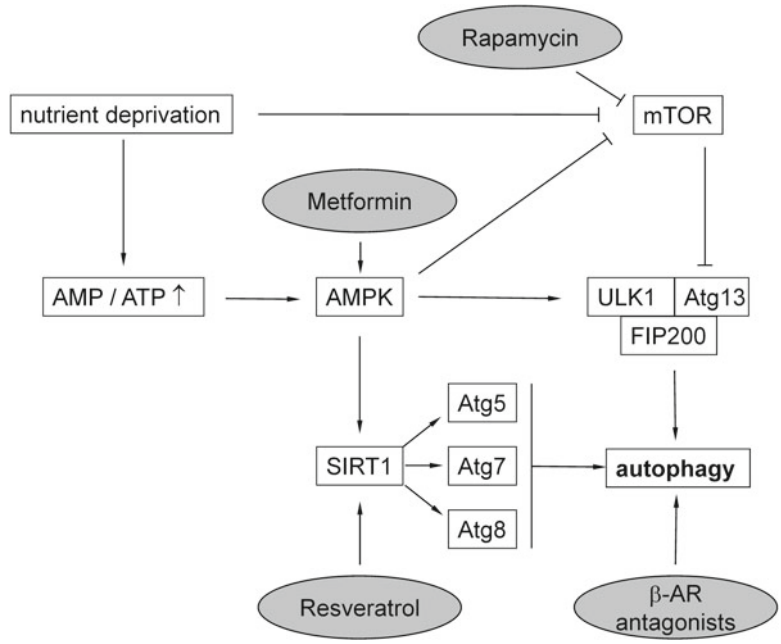

Fig. 22.3 Schematic overview of the regulation of autophagy and targets for therapeutic intervention. Under nutrient-rich conditions, mTOR is active and inhibits, through Atg13 hyperphosphorylation, the ULK1-Atg13-FIP200 complex required for the induction of autophagy. Nutrient deprivation leads to mTOR inactivation and stimulation of AMPK, which both induce autophagy. AMPK is as an energy-sensing kinase and is activated by increases in the cellular AMP to ATP ratio. Under these circumstances, AMPK promotes autophagy by activating ULK1 and by relieving the mTOR-mediated inhibition of autophagy. SIRT1, which can be activated by AMPK, deacetylates and activates several autophagy-related proteins, including Atg5, Atg7, and Atg8 (after [21]). Metformin activates AMPK, rapamycin inhibits mTOR, and resveratrol activates SIRT1. Although the long-term impact of β-AR antagonists on autophagy is not known, it might be clinically relevant

metabolic state of a cell. In the cardiovascular system, SIRT1 and SIRT3 have been mostly investigated. They are mainly located in the nuclei and mitochondria, respectively. Interestingly, SIRT1 and SIRT3 are potential regulators of longevity [41, 42].

These two sirtuins play a protective role in failing hearts because they induce protective autophagy (Fig. 22.3) and inhibit cell death [43, 44]. SIRT1, previously shown to extend the life span of lower organisms, is a promising target molecule to affect cardiovascular aging (*vide infra*) [45].

Sirtuins Inhibit Apoptosis

SIRT1 and SIRT3 have redundant functions to protect cells from apoptosis [46]. They deacetylate p53 and silence its proapoptotic activity [47, 48]. p53 deacetylation by SIRT1 seems to be crucial for cardiomyocyte survival. Indeed, in heart failure, increased activity of poly(ADP-ribose) polymerase-1 is associated with reduced SIRT1 activity and increased acetylation of p53 [49], resulting in cardiomyocyte death. SIRT1 also suppresses apoptosis via mechanisms independent of the deacetylase activity [50]. Moderate overexpression of SIRT1 retards aging of the heart by inducing resistance to oxidative stress and apoptosis, due to increased expression of antioxidants, such as catalase, through Forkhead box protein O1 (FOXO1)-dependent mechanisms [51].

Sirtuins Inhibit Necrosis

Sirtuins are involved in the regulation of the MPTP opening. The levels of intracellular ATP and ROS

and intramitochondrial Ca^{2+} determine the threshold of MPTP opening, and these factors are regulated by SIRT1 and/or SIRT3. p53 contributes to MPTP-mediated necrosis [52], but the impact of sirtuin-mediated regulation of p53 on MPTP opening remains to be determined. Aging significantly enhances the Ca^{2+} sensitivity of the MPTP in cardiac mitochondria from SIRT3-knockout mice [53], indicating that SIRT3 counteracts the increased sensitivity of the MPTP in response to cellular stress in failing and aging hearts.

Sirtuins Stimulate Autophagy

Autophagy induction by activation of the SIRT1–FOXO1 axis is an important adaptive mechanism in the failing heart [43]. SIRT1 regulates autophagy by deacetylating autophagy-related proteins Atg5, Atg7, and Atg8 (Fig. 22.3) [54]. SIRT1 is required for starvation-induced autophagy in cardiomyocytes, in which SIRT1-mediated deacetylation of FOXO1 plays a role [55]. FOXO1 maintains cardiac function after starvation. Furthermore, SIRT3 activates serine–threonine liver kinase B1, an upstream kinase of AMPK in cardiomyocytes [56]. Activated AMPK is a regulator of cell survival in response to pathological stress [43, 52, 57].

Implications for Heart Failure Therapy

Heart failure is predominantly a disorder of the elderly; its prevalence approximately doubles with each decade of life [7]. Failing hearts have significant systolic dysfunction and pathological left ventricular remodeling consisting of chamber enlargement and wall thinning. At the cellular level, there are abnormalities of cell signaling, Ca^{2+} handling, excitation–contraction coupling, contractile proteins, and the cytoskeleton [11, 30]. In addition, all three main types of cell death, apoptosis, autophagic cell death, and necrosis, have been observed during the progression of heart failure [11, 36, 43, 58]. Current pharmacological treatment of heart failure includes diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blockers, and digitalis [7]. Although treatments have improved, the development of novel therapies for patients with heart failure remains a major research goal. Pharmacological modulation of cell death and/or survival pathways, especially autophagy, might be a promising novel approach.

Compounds That Inhibit Apoptosis

Cardiomyocyte apoptosis can be targeted at multiple levels [9]: prior to the onset of death signaling (upstream signal transduction networks), at the uncommitted steps during the initiation of death signaling (death receptor or mitochondrial activation), or following apoptotic commitment (caspase activation).

ACE Inhibitors

At present, ACE inhibitors are the cornerstone in the therapy of heart failure. Whereas ACE inhibitors have multiple cardiovascular effects, they can also reduce oxidative stress and subsequent DNA damage due to inhibition of angiotensin II formation [59, 60], thereby preventing cardiomyocyte apoptosis.

β-Adrenergic Receptor Blockers

Similar to ACE inhibitors, β-adrenergic receptor (AR) blockers are currently used in heart failure therapy, and it has been shown that they reduce mortality in patients with heart failure. β-AR blockers show indirect effects on reducing cardiomyocyte apoptosis. Chronic sympathetic hyperactivity in heart failure causes sustained β1-AR activation, which can deplete Ca^{2+} in endoplasmic reticulum (ER) leading to ER stress and subsequent apoptosis [61]. β1-AR blockers largely prevent ER stress and protect cardiomyocytes against apoptosis. Alleviation of ER stress (and consequently preventing apoptosis) may be an important mechanism underlying the therapeutic effect of β1-AR blockers in heart failure [62].

Furthermore, stimulation of the β2-AR is antiapoptotic [63]. This may explain why prolonged

treatment with the β2-AR agonist fenoterol in combination with the β1-AR blocker metoprolol is more effective than β1-AR blocker alone with respect to survival and cardiac remodeling. Therefore, this combined regimen of a β2-AR agonist with a β1-AR blocker might be considered for clinical testing as alternative or adjunct therapy to the currently used drugs [64]. However, this combination therapy is somewhat controversial in the light of the proven clinical outcome of carvedilol, which is a non-selective β-AR blocker (blocking both β1-AR and β2-AR) that is successfully used in the treatment of heart failure patients [64].

Antioxidants

Notwithstanding antioxidants exert anti-apoptotic effects, their pleiotropic effects have to be considered as well [9]. Furthermore, although antioxidants have significant effects in vitro and in animal models, their efficacy in humans is questionable. There is now extensive evidence indicating that supplementing antioxidants has no significant effect on reducing cardiovascular risk [5, 65, 66].

Caspase Inhibitors and Apoptosis Blockers

Inhibition of apoptosis by caspase inhibitors improves heart function [67] and survival. On the other hand, it is known from autopsy studies that in situ neoplasia may exist in otherwise healthy individuals [68]. The potential effects of even transient, systemic inhibition of apoptosis in such individuals are concerning [9]. Because of these worries of long-term systemic anti-apoptotic therapies, it seems to be preferable to prevent progression of heart failure by targeting the low, but elevated, levels of apoptosis in the subacute stages of a large infarction. This approach prevents the large amount of apoptosis associated with index event and is probably the best initial target for anti-apoptotic strategies [9].

The apoptotic regulatory protein ARC (Apoptosis Repressor with Caspase recruitment domain) shows high concentrations in cardiac tissue. It blocks both extrinsic and intrinsic apoptotic pathways [69] and plays a protective role in adaptive responses to ischemia–reperfusion and biomechanical stress [70]. The degradation of ARC in response to oxidative stress is a trigger for cardiomyocyte apoptosis [69]. Because ARC is degraded by the proteasome, targeting this pathway might be an interesting approach [9].

Compounds That Inhibit Necrosis

Compounds that inhibit necrosis are scarce. Protection against necrotic death can be achieved by inhibition of the MPTP [6, 71]. The immunosuppressant cyclosporin A, which blocks the MPTP, confers cardioprotection by reducing myocardial infarct size in patients [72]. Also non-immunosuppressant MPTP inhibitors, such as NIM811, have been successfully used in animal studies [73]. A selective inhibitor of necroptosis (programmed necrosis) is necrostatin-1, which targets receptor interaction protein-1 RIP-1 [6, 74]. It is important to note that there are connections between cell death pathways [11]. If apoptosis can bring about necrosis, then inhibition of apoptosis may be working through inhibition of necrosis. Moreover, drugs that inhibit one pathway may shift death to another one, e.g., caspase inhibitors can shift apoptotic to necrotic cell death [75].

Compounds That Stimulate Autophagy

The development and use of therapies that upregulate the repair qualities of the autophagic process would be of great value in the treatment of heart failure [6, 30, 76]. Stimulation of autophagy by AMPK activation, mTOR inhibition, and/or sirtuin activation (Fig. 22.3) may represent novel therapeutic options in the treatment of heart failure [19, 77], focusing on cell survival of cardiomyocytes, as will be discussed below. However, the dosing should be carefully set in order to avoid (excessive) autophagic cell death.

AMPK Activators and mTOR Inhibitors

With regard to the regulation of autophagy, the mammalian target of rapamycin (mTOR) is a key regulator, linking the cellular nutritional state with the level of ongoing autophagy [78]. Under nutrient-rich conditions, mTOR is active and inhibits, through Atg13 hyperphosphorylation, the ULK1–Atg13–FIP200 complex required for the induction of autophagy (Fig. 22.3). Nutrient deprivation leads to mTOR inactivation and stimulation of AMPK, which both induce autophagy [78]. AMPK is as an energy-sensing kinase and is activated by increases in the cellular AMP to ATP ratio. Under these circumstances, AMPK promotes autophagy by directly activating ULK1 and by relieving the mTOR-mediated inhibition of autophagy [21, 78]. As discussed above, SIRT1, which can be activated by AMPK, deacetylates and activates several autophagy-related proteins, including Atg5, Atg7, and Atg8 [21].

The autophagy activators metformin (an AMPK activator) and rapalogs (rapamycin and its analogues/derivatives, which are mTOR inhibitors; Fig. 22.3) are already used clinically for other indications. Metformin is an oral antidiabetic drug, which diminishes all-cause mortality and myocardial infarction [79]. In animal models of ischemia and ischemia/reperfusion, beneficial effects of metformin by decreasing infarct size and blunting heart failure have been shown [6, 80].

The mTOR inhibitor rapamycin is used for the prevention of immunorejection following organ transplantation. Beneficial effects of mTOR inhibition in the cardiovascular system have been reported in the context of atherosclerosis [81–83] and the stabilization of vulnerable, rupture-prone plaques [84–86]. Moreover, pharmacological studies suggest a potential new application of rapamycin in attenuating cardiomyopathy [87]. In mice, suppression of TOR prevents lipofuscin accumulation in the heart [25]. The long-term benefits of rapamycin and its analogues/derivatives as candidate drugs for heart failure patients deserve to be investigated [88].

Sirtuin-Activating Compounds

Because sirtuins play a protective role in failing hearts by inhibiting cell death and inducing protective autophagy, as mentioned above, pharmacological activation of SIRT1 and/or SIRT3 might improve the outcome of heart failure during aging [5, 30, 43]. Resveratrol, a stilbene found in red wine, activates and/or upregulates SIRT1 in the cardiovascular system and might help in the treatment or prevention of the aging-related decline in heart function (Fig. 22.3). Resveratrol has shown beneficial effects against heart failure and aging. Several pathways that require the presence of functional SIRT1 mediate many of the beneficial cardiovascular effects of resveratrol [89]. For example, resveratrol induces manganese superoxide dismutase in cardiomyocytes via a SIRT1-dependent pathway [90], which acts to reduce oxidative stress and promotes cell survival in chronic heart failure. Moreover, resveratrol induces autophagy as a first line of protection against oxidative stress (Fig. 22.3) [91]. Due to its poor bioavailability, reformulated versions of resveratrol with improved bioavailability have been developed (resVida, Longevinex®, SRT501). Also molecules that are structurally unrelated to resveratrol (e.g., SRT1720, SRT2104, and SRT2379) stimulate sirtuin activities even more potently than resveratrol itself [37]. They are excellent protectors against metabolic stress in mammals, making SIRT1 an interesting target for therapeutic interventions [89].

β-Adrenergic Receptor Antagonists

As discussed above, it has been shown that β-AR antagonists can inhibit apoptosis of cardiomyocytes. It has been shown in patients that interventions known to exacerbate heart failure (e.g., beta-adrenergic receptor agonists) reduce autophagy in the heart, whereas interventions known to ameliorate heart failure, including β-AR antagonists, enhance autophagy in the heart [18, 92]. Although the long-term impact of β-AR antagonists on autophagy is not known, it might be clinically relevant, because patients use these drugs chronically in the treatment of heart failure.

Caloric Restriction

Autophagy can also be activated by caloric restriction (Fig. 22.3). In animal models, caloric restriction attenuates age-related changes in the heart, including hypertrophy, myocardial fibrosis, and apoptosis. In humans, caloric restriction improves diastolic function in healthy non-obese patients together with a reduction of myocardial stiffness [6, 7, 93].

Conclusion

All three main types of cell death, apoptosis, autophagic cell death, and necrosis, have been observed during the progression of heart failure. Pharmacological inhibition of apoptosis and necrosis improves heart function and survival. Currently used drugs in heart failure therapy, such as ACE-inhibitors and β-adrenergic receptor blockers, prevent apoptosis. However, complete inhibition of apoptosis might have adverse effects. Furthermore, compounds that "supplement" the decreased levels of autophagy during aging, such as AMPK activators, mTOR inhibitors, and/or sirtuin activators, might be of great value in heart failure therapy by preventing apoptosis and necrosis and stimulating cardiomyocyte survival. However, the dosing should be carefully set in order to avoid (excessive) autophagic cell death.

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23 Aging-Related Changes in Telomeres and Telomerases and Implications for Heart Failure Therapy

Pim van der Harst and Dirk J. van Veldhuisen

Introduction

In 2009, Dr. Elizabeth H. Blackburn, Dr. Carol W. Greider, and Dr. Jack W. Szostak jointly received the Nobel Prize in physiology or medicine for their pioneering research on telomeres and the enzyme telomerase. Telomeres located at the end of the chromosomes and are specialized DNA structures consisting of proteins and nucleotides. They have an important function as they provide protective caps by which they prevent the chromosomes to be recognized as DNA breaks alarming the damage-repair system, which will lead to cellular senescence or apoptosis [1, 2]. However, the most striking feature of telomeres is that they shorten with age and have been directly linked to the replicative capacity of the cell. In humans, telomere length has been explored as a proxy for biological aging and has been linked to various age-associated diseases. In this chapter, the function of the telomere complex and telomerase in relation to aging is explained. In addition, the potential implications of telomere biology to the development, progression, and treatment of heart failure are discussed.

P. van der Harst, MD, PhD (✉)
D.J. van Veldhuisen, MD, PhD
Department of Cardiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, Groningen, Netherlands
e-mail: p.van.der.harst@umcg.nl

Telomere Structure and Function

Telomeres are DNA structures that consist of tandem nucleotide repeats (TTAGGG in humans) and are located at the chromosomal ends (Fig. 23.1) [3]. The G-rich strand of the telomeres forms a so-called telomere loop (T-loop) in conjunction with a complex of specialized telomeric proteins. This protein complex is also named "shelterin," and the involved proteins include telomeric repeat-binding factor 1 (TRF1) and 2 (TRF2) and protection of telomerase 1 (POT1). TRF1 and TRF2 can bind directly to the double-stranded telomeric DNA. POT1 binds directly to single-stranded telomeric DNA. Other shelterin-associated proteins are repressor activator protein 1 (Rap1), TPP1, and TRF1-interacting nuclear factor 2 (TIN2) (Fig. 23.2) [3, 4]. The T-loop formation of the telomere–shelterin complex can conceal the terminal DNA ends from being recognized as DNA breaks resulting in the activation of p53 or $p16^{INK4a}$ pathway, which will lead to cellular senescence or apoptosis especially in stem and progenitor cells.

During each cell division, telomeres lose 30–150 base pairs, a phenomenon also known as the "end replication problem." This loss of telomeric base pairs at each cell division is caused by the failure of the DNA polymerase to completely replicate DNA to the final end of the 3′ strand. Further telomere erosion can occur in the presence of harmful environmental factors such as oxidative stress and factors that can be related to oxidative stress such as smoking and UV

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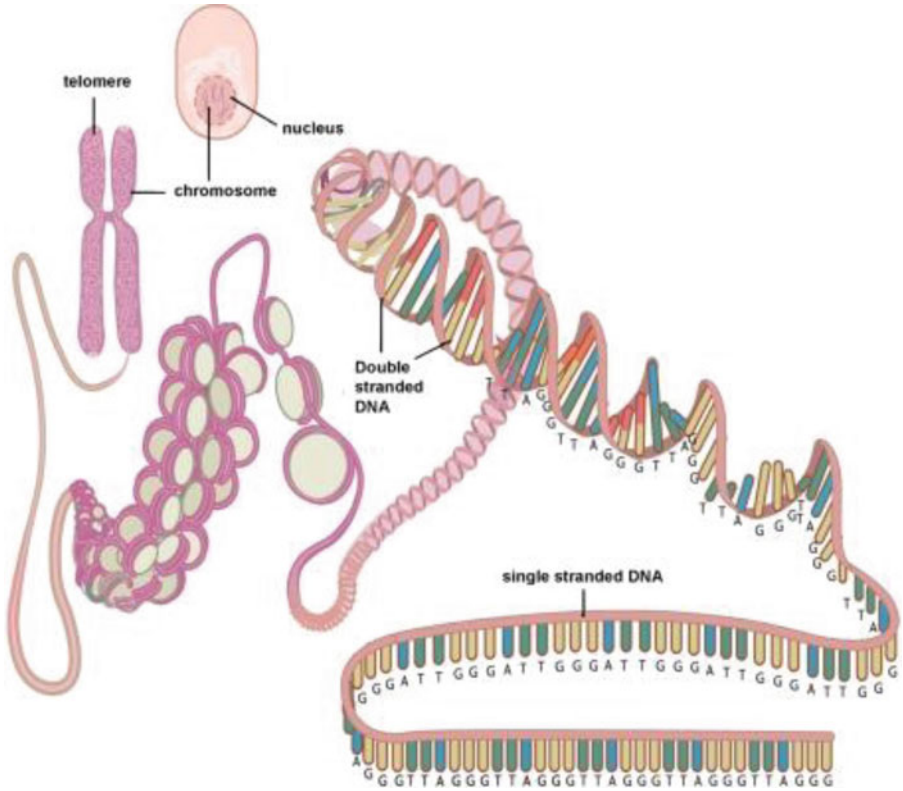

Fig. 23.1 Simplified scheme of the telomere structure and its chromosomal and cellular location (reprinted from Huzen J, van Veldhuisen DJ, van Gilst WH, van der Harst P (2008) Telomeres and biological ageing in cardiovascular disease. Ned Tijdschr Geneeskd 152: 1265-1270. With permission)

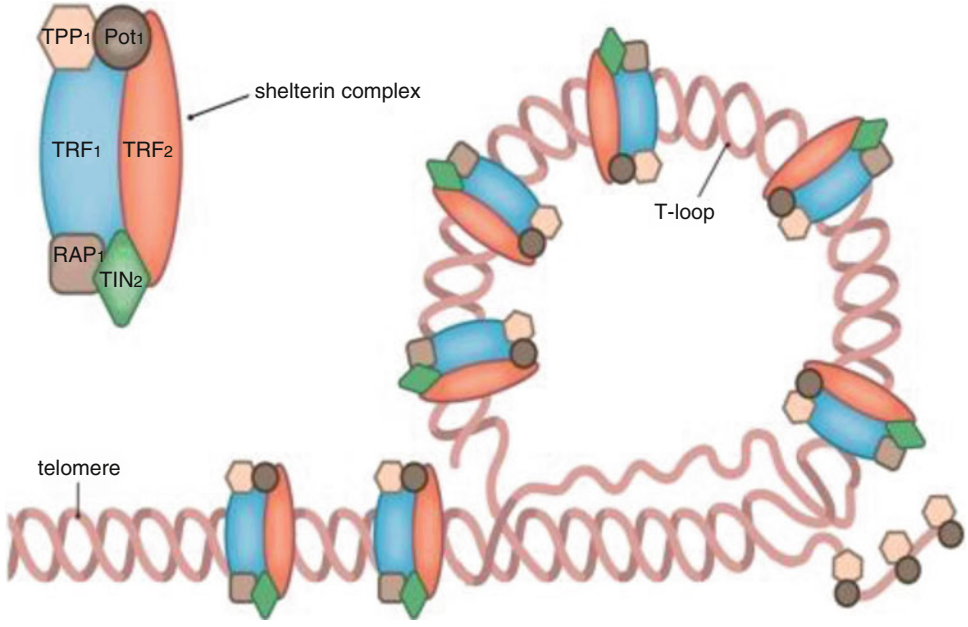

Fig. 23.2 Simplified scheme of the telomere–shelterin complex (reprinted from Huzen J, van Veldhuisen DJ, van Gilst WH, van der Harst P (2008) Telomeres and biological ageing in cardiovascular disease. Ned Tijdschr Geneeskd 152: 1265-1270. With permission)

radiation [5–7]. At a certain critical short length, the cell loses its ability to divide and can become senescent or dysfunctional [2]. Primary cultured cells usually reach a senescence state after approximately 50 population doublings [8]. In addition to the telomere length as such, also other disruptions of the telomere–shelterin complex can induce senescence or chromosomal instability [1]. Telomere biology also affects mitochondrial function, and short telomeres can lead to metabolic dysfunction [9].

It has long been thought that telomeres are transcriptionally silent. However, this is not the case. Telomeric repeat-containing RNA (named TERRA) is noncoding RNA fragment transcribed from the telomeres and expressed at heterogeneous lengths. TERRA has been located to the telomeric structure and is thought to be a structural component [10, 11].

Telomerase and Telomere Lengthening

Telomere length maintenance is of paramount importance for germ and stem cells and is key in cellular immortalization and tumor genesis. The majority of telomere length maintenance can be attributed to a specialized ribonucleoprotein named telomerase. Telomerase functions by adding telomere sequences to the telomere ends (Fig. 23.3) [3]. Telomerase is made up of three major components: a telomerase RNA component (TERC), telomerase reverse transcriptase (TERT), and dyskerin which stabilized the telomerase. The sequence of TERRA (noncoding RNA transcribed from the telomeres) is complementary to TERC, and it has been suggested that TERRA is involved in regulating telomerase activity [10, 11].

In addition to telomerase a mechanism named "alternative lengthening of telomeres" (ATL) exists. This mechanism is less well understood and is thought to depend on the homologous recombination machinery of the cell. This repair system providing the ATL is not considered an alternative to telomerase in cells without functional telomerase but usually acts concurrently to it [12]. Telomere elongation by ATL is more heterozygous among the different chromosomes [13].

Telomere Biology and Aging

In vitro, cells stop dividing after a certain number of passages and thereafter become senescent. This phenomena has been demonstrated in 1961 [8]. Shortening of telomeres has been identified as a major mechanism of replicative senescence [14]. Recently a connection was made to mitochondrial processes as well [9]. Master regulators of mitochondrial aging are also affected by short telomere length, providing also pathways to disease. Some severe human disorders of premature aging have been directly linked to mutations in telomerase. Dyskeratosis congenita is a striking example in which patients age prematurely and exhibit different characteristics, including short stature, hematopoietic defects, skin defects, bone marrow failure, infertility, hypogonadism, and premature death [15].

Telomere length has been considered as an integrated indicator of cellular cumulative replicative history and cumulative exposure to harmful

Fig. 23.3 Schematic overview of the action of telomerase (reprinted from Huzen J, van Veldhuisen DJ, van Gilst WH, van der Harst P (2008) Telomeres and biological ageing in cardiovascular disease. Ned Tijdschr Geneeskd 152: 1265-1270. With permission)

environmental factors both considered key factors of biological aging. Telomeres are important for humans and all animal species. However, there are several important considerations when discussing telomere length in relation to aging. At the level of comparison of species, a straightforward comparison between average life span of a species and their telomere length cannot be made. For example, inbred mice and rat species have relatively long telomeres compared to humans, and telomeres vary highly between different strains and also compared to outbred mice. No clear correlation exists between telomere length and life span, not even among closely related inbred mouse strains [16]. Another dimension of complexity is added by the fact telomere lengths are not the same for each chromosome. For example, in human cells, the chromosomes of 17p, 13p, and 19p have been reported to have considerable shorter telomere lengths compared to other chromosomes [17, 18]. Furthermore, telomere lengths are not only dissimilar within a single cell; they are also not comparable among different cell types or different tissues within an individual. This might be considered a consequence of different replicative histories and proliferation timings but can also be influenced by external factors to which a particular cell is exposed. However, to some extent there is synchrony of telomere lengths among different somatic tissues. This synchrony has been reported to be considerably stronger in the fetus [19] and newborn [20] compared to later in life as well [21].

Telomere length is associated with chronological age, but telomere length is highly variable at any age. Part of this variability is heritable. Multiple studies have reported associations between telomere length of an individual with the telomere length of their parents suggesting telomere length to be a heritable trait with a possible stronger effect of the father compared to the mother [22–24]. Interestingly, sperm telomere length, reflecting telomere length in the male germ cells, becomes longer with age [24–26]. As such the paternal age at conception has been suggested to be relevant to an individual telomere length [24–26]. Genome-wide association studies have mapped several genetic loci associated with telomere length on different chromosomes and also near the TERC component [27–29].

An important hypothesis in the aging field is that telomere attrition increases the likelihood of the onset of disease. Differences in telomere length among individuals have been used as a predictor for different diseases and outcome [21, 30–32]. Most data relating telomere length to aging and various pathologic conditions have been derived from telomere measurements in leukocytes. The use of leukocytes has clear advantages as they are easily obtainable, and processing them is relatively simple. However, there are several drawbacks that need to be recognized. Leukocytes are not a homogenous and stable population of cells. On the contrary, they consist of a varying heterogeneous population harboring different cell types. The different cell types that jointly are the leukocytes all have a replicative history. The relation between leukocytes and the disease of interest, for example, heart failure, might not be direct. For example, in the case of heart failure, the telomere length of the cardiomyocyte might be more important for the disease, and the leukocyte might only be a poor reflection. For other diseases, leukocytes might be more relevant.

Telomere Biology and Risk Factors of Heart Failure

Telomere length has been associated to several factors that predispose to the development of heart failure. Although the exact mechanism of associations all remain to be established, the factors associated with telomere length include hypertension, diabetes mellitus, atherosclerosis, and renin–angiotensin system activation.

Hypertension is an important risk factor for the development of heart failure. Telomere biology has been implicated in increased blood pressure in both human and animal studies. Telomerase activity and TERT expression were increased in aortae of spontaneous hypertensive rats before the blood pressure raises [33], and mice lacking functional active telomerase

(TERC$^{-/-}$) develop hypertension which is associated with increased circulating endothelin-1 levels [34]. Although not all data is consistent, it has been suggested that hypertension is linked to shorter telomere length in humans as well [35, 36]. When looking at normotensive subjects, the likelihood to develop hypertension is increased in subjects with shorter telomeres [37]. A feature of hypertension, and heart failure likewise, is activation of the renin–angiotensin system. In the Framingham Heart Study, higher renin/aldosterone ratios, as an indicator of renin-angiotensin system activation, have been associated to telomere length in hypertensive subjects [38].

Diabetes is caused by one or a combination of peripheral insulin resistance and pancreatic β-cell dysfunction. Diabetes is an important risk factor for atherosclerosis but also for heart failure. Reduced telomere length has been associated with diabetes in several larger studies [39, 40]. The reduced telomere length might be partially attributed to higher levels of oxidative stress in diabetes patients [40]. Adequate glycemic control appears to have a beneficial effect on telomere attrition in diabetic patients [41]. A small study even suggested that within type 1 diabetic patients, telomere length also predicted all-cause mortality [42]. This finding does require validation in larger-scale studies. Telomeres are also observed to be shorter in humans at the stage of impaired glucose tolerance [43]. A potentially causal link between impaired insulin secretion and glucose tolerance and telomere biology has recently been observed in telomerase-deficient mice (TERC$^{-/-}$) [44]. These mice show impaired glucose tolerance as their insulin secretion from pancreatic islets is reduced due to a diminished islet size as a consequence of impaired replication capacity [44]. Improving insulin sensitivity may even exert regulatory effects on cardiac telomere biology and consequently have desirable functional effects [45].

Atherosclerosis and myocardial infarctions are paramount in the development of heart failure. Coronary artery disease has been extensively linked to shorter telomere length [46–50]. It is interesting to note that even telomeres of offspring from coronary artery disease patients already have shorter telomere length compared to offspring of healthy individuals [51]. Although this observation can be confounded by environment, it also supports the hypothesis that shorter telomere length precedes the clinical manifestations of atherosclerosis. In almost any atherosclerotic plaque, senescent-positive endothelial cells can be found which have been linked to reduced telomere length [52]. As such telomere shortening of endothelial cells may play a critical role in the development of atherogenesis and its associated diseases. Also other manifestations of atherosclerosis have been linked to shorter telomere length but might be less relevant to heart failure [53–55].

Telomere Biology and Heart Failure

The incidence and prevalence of heart failure increase steeply with age. There exists a striking difference, however, in the age of onset of heart failure and its pace of progression. This difference cannot be completely explained by the presence of conventional risk factors and might be partially attributed to differences in biological age and aging [56]. Healthy myocardium constitutes of 20–25 % cardiomyocytes and a very large proportion of supporting connective tissue [57]. During aging the number of cardiomyocytes reduces, and the remaining become larger and polyploidy [58]. This is accompanied by an increase in the content of collagen, fibrosis, and "senile" depositions of both amyloid and lipofuscin [59–61]. Consequently the functional reserve of the heart decreases, and the vulnerability to cardiac dysfunction increases [62]. This reduction of functional reserve might be linked to telomere biology. In the Newcastle 85+ study, elderly subjects with shorter leukocyte telomere length had lower left ventricular ejection fraction [63]. One standard deviation of shorter telomere length was associated with approximately 5 % of lower left ventricular ejection fraction. In this study, telomere length alone could account for almost 12 % of the observed variability of left ventricular ejection fraction.

Cardiac biopsies taken from patients with heart failure have shown that their cardiomyocytes have considerable shorter telomeres, increased level of senescence, and a larger number of death cells [64]. Telomere length is reduced by approximately 25 % in cardiomyocytes derived from patients with dilated cardiomyopathies compared to cardiomyocytes derived from non-failing hearts [65]. This is associated with decreased expression of TRF2 and also with activation of checkpoint kinase 2 (Chk2), one of the DNA damage kinases. Cardiomyocytes that have short telomeres are also positive for the cellular senescence marker $p16^{INK4a}$.

The paradigm that human adult cardiomyocytes are terminally differentiated has been broken. Using carbon-dating techniques it has been established that DNA of cardiomyocytes continues to be synthesized many years after birth [66]. The level of cardiomyocyte DNA synthesis clearly decreases with age and models estimate a ~1 % cardiomyocyte renewal rate around the age of 25 years and less than 0.5 % at the age of 75 years. However, even considering this very low turnover rate, at the age of 50 years more than 50 % of the cardiomyocytes remain from the time around birth. Data derived from carbon-dating techniques does not allow the identification of the source of new cardiomyocytes. These could be derived locally or from a circulating pool of progenitor cells. The reduction of stem and progenitor cells is thought to drive the development of tissue and consequently organ dysfunction. Aging and also heart failure are indeed characterized by a progressive decrease in functionally competent cardiac stem cells [67]. Interestingly, human cardiac stem cells are regulated by telomerase activity and telomere length [68]. Although telomere length of circulating $CD34^+$ progenitor cells appears to be similar in heart failure compared to healthy subjects, their number is reduced and their function impaired [69, 70]. It can be expected that an imbalance between cardiomyocyte renewal and death can result in decreased cardiac performance and an increased vulnerability to develop cardiac dysfunction.

Leukocyte telomere length is considerably shorter in patients with heart failure compared to age- and gender-balanced control patients [69, 71]. Patients with more severe symptoms had shorter telomeres compared to other patients. In the subgroup of patients with ischemic etiology, telomere length was shorter compared to those with nonischemic etiology. Also the concomitant presence and extent of atherosclerotic disease manifestations were observed to be associated with even shorter telomeres [71]. Also other comorbidities in heart failure patients, such as decreased renal function or anemia, are related to shorter telomeres [72–74]. Patients with heart failure and shorter telomeres in their leukocytes are also at increased risk to be hospitalized for heart failure or to die earlier [21]. Also when studying telomere length in apparently healthy offspring of heart failure patients, telomere length is reduced compared to that of offspring of healthy control subjects [69].

One of the most important questions concerning all the associations reported between telomere length and heart failure in humans is its origin. It remains to be established whether telomere length, of any cell type, directly contributes to the development and progression of heart failure. Alternatively, heart failure itself might cause telomere attrition or a third phenomenon, e.g., oxidative stress or inflammation, which might have affect both. Casuistic data have been reported on patients with dyskeratosis congenita and who are also suffering from dilated cardiomyopathy and cardiac fibrosis [75]. Some noteworthy evidence has been derived from telomerase-deficient mice models. The fifth generation of these mice has severely reduced length of their telomeres [76]. These mice have increased p53 levels and suffer from severe heart failure, including increased end-diastolic left ventricular pressure, decreased maximal left ventricular pressure. These disturbed relaxation and contractility characteristics are similar to those observed in patients with dilated cardiomyopathies. Further animal experimental support has been provided by experiments in which telomeres were stabilized by TRF2 overexpression in mice [77]. In wild-type mice TRF2 overexpression prevents doxorubicin-induced cardiac apoptosis in contrast to telomerase-deficient mice.

Telomere Biology and Future Heart Failure Treatment

Therapeutic strategies to improve outcome in patients with heart failure are urgently needed. Telomere biology might play a role in the development of human heart failure, although definitive evidence is lacking. Currently the strongest evidence is animal experimental. The recognition that cardiomyocytes are not terminally differentiated cells and that the function of cardiac stem cells is regulated by telomere length and telomerase activity might have important clinical implications in the future treatment of heart failure [68]. Animal experimental data also suggest that reactivation of telomerase can extend telomeres and reduces the DNA damage signaling response allowing for the resumption and proliferation of cells restoring the degenerative phenotypes across multiple organs [78]. The ability of cardiac regeneration by autologous cardiac progenitor cells might be restricted by the patient's age and disease progression. In vitro restoration of telomere length, for example, by temporarily activating telomerase, might enhance expansion of the cardiac progenitor cell population and improve therapeutic efficacy [79]. Also some existing drugs also have been implicated in improving telomere function. Statins, for example, upregulates TRF2 and pioglitazone upregulates telomerase activity [80, 81]. Unfortunately, statins have not been proven beneficial in patients with heart failure [82]. The simplest strategies to modify telomere biology might only need to involve lifestyle changes such as increasing physical exercise or repetitive hyperthermia treatment [77, 83].

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24 Aging-Associated Alterations in Myocardial Inflammation and Fibrosis: Pathophysiological Perspectives and Clinical Implications

Arti V. Shinde and Nikolaos G. Frangogiannis

Introduction

Senescence is associated with a high prevalence of heart failure [1]. Almost 12 % of individuals 80 years or older have heart failure [2]. Moreover, heart failure is the most common cause of hospitalization for patients older than 65 years. As the population of individuals over 65 years of age is expected to grow rapidly in the United States, the burden of heart failure in the elderly will markedly increase. A study designed to forecast future costs of healthcare for cardiovascular disease projects a 25 % increase in the prevalence of heart failure in the United States within the next 20 years, primarily due to a rapidly aging population [3].

The etiology of heart failure in older individuals is multifactorial. The increased incidence of heart failure in the elderly is due to aging-associated increases in the prevalence of common risk factors for heart failure (such as coronary disease, hypertension, and diabetes). Moreover, a growing body of evidence suggests that direct effects of cardiac senescence on myocardial structure and function may significantly contribute to the development of heart failure in the elderly. Even in the absence of hypertension, apparently healthy elderly individuals exhibit age-associated increases in left ventricular wall thickness and impaired left ventricular filling. These structural and hemodynamic alterations limit exercise tolerance and reduce the quality of life by causing heart failure due to diastolic dysfunction [4]. Aging is also associated with impaired reparative mechanisms following cardiac injury; these defects may be responsible for more severe heart failure, accentuated adverse remodeling, and increased dysfunction in elderly individuals with myocardial infarction [5, 6].

Progressive cardiac fibrosis is a hallmark of cardiac senescence [5, 7, 8] and together with cardiomyocyte relaxation contributes to age-associated increases in cardiac stiffness [9]. The pathogenesis of cardiac fibrosis in the aging heart is often related to dysregulation of inflammatory cascades that promote activation of leukocytes and fibroblasts in the myocardium. This chapter deals with the mechanisms responsible for the development of fibrosis in the aging heart and discusses the role of inflammatory signals. Moreover, we discuss the involvement of age-associated alterations in the postinfarction inflammatory and reparative responses in mediating adverse remodeling of the infarcted heart. These concepts have major implications in designing therapeutic strategies to protect elderly patients from the development of heart failure.

A.V. Shinde, PhD
Department of Medicine (Cardiolology), Albert Einstein College of Medicine, 1300 Morris Park Avenue, Forchheimer G46B, Bronx, NY 10461, USA

N.G. Frangogiannis, MD (✉)
Department of Medicine (Cardiolology), Albert Einstein College of Medicine, Bronx, NY, USA
email: nikolaos.frangogiannis@einstein.yu.edu

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Fibroblasts and the Matrix Network in Normal Hearts

The adult mammalian myocardium contains both cellular elements (cardiomyocytes and non-cardiomyocytes) and an intricate network of extracellular matrix. In the normal adult mammalian heart, cardiac myocytes account only for 30–40 % of the total number of cells [10]; fibroblasts are generally considered the predominant non-cardiomyocyte cell type [11, 12]. In addition to their established role as matrix-secreting cells in cardiac repair, cardiac fibroblasts may also contribute to cardiac homeostasis by maintaining the matrix network and may regulate cardiomyocyte function through direct interactions [13].

Cardiac fibroblasts are enmeshed in the interstitial extracellular matrix. In the normal myocardium, the extracellular matrix provides a scaffold for cellular elements and blood vessels and maintains tissue architecture and the geometry of the heart. The matrix directly influences ventricular pump function by transmitting cardiomyocyte-generated force and electrically separates the atria from the ventricles [14]. Moreover, matrix proteins may transduce important cell survival signals in cardiomyocytes and may shield fibroblasts from mechanical stress, thus promoting a quiescent phenotype. The homeostatic effects of the matrix on myocardial cells are mediated through interactions between matrix proteins and cellular integrins; these actions are essential for contractile synchrony and cardiomyocyte function.

Reactive and Reparative Cardiac Fibrosis

Cardiac fibrosis is characterized by increased deposition of matrix proteins in the myocardial interstitium; the severity and morphology of the fibrotic lesions is dependent on the underlying pathophysiologic condition. Cardiomyocyte necrosis induces an intense inflammatory reaction that leads to extensive replacement of myocardium with fibrous tissue; this form of cardiac fibrosis is typically found in infarcted hearts and is termed "reparative fibrosis." On the other hand, the term "reactive interstitial fibrosis" is used to describe progressive expansion of the cardiac interstitial space in the absence of significant cardiomyocyte loss. In animal models of left ventricular pressure overload, reactive fibrosis is observed first in interstitial and perivascular areas and may initially progress without loss of cardiomyocytes. This initial reactive perivascular and interstitial fibrosis is accompanied by cardiomyocyte hypertrophy and is part of an adaptive response aimed at preserving cardiac output while normalizing wall stress. Eventually, however, reparative fibrosis is noted as cardiomyocytes undergo necrosis and apoptosis [15]. One possible mechanism of cardiomyocyte death is that the thickening of the extracellular matrix around hypertrophied cardiomyocytes may result in a mismatch between supply and demand of nutrients, leading to cell death. Interstitial fibroblasts respond to activating signals released by dying cardiomyocytes by synthesizing matrix proteins in order to replace the dead cells.

Aging Is Associated with Fibrotic Myocardial Remodeling

Healthy elderly individuals usually have preserved cardiac systolic function but often exhibit impaired myocardial compliance [16, 17]. Although senescence is associated with a reduction in the total number of cardiomyocytes, left ventricular mass progressively increases in the aging heart [18] in both experimental models and human patients. Animal model experiments provide consistent evidence of aging-related cardiomyocyte hypertrophy accompanied by an increase in myocardial collagen content. Histological analysis of the non-hypertensive aging hearts reveals progressive loss of cardiomyocytes due to necrotic and apoptotic cell death [19]. While the absolute number of myocytes decreases in aging hearts, the remaining cardiomyocytes undergo hypertrophy [20]. Eghbali and coworkers demonstrated that left ventricular collagen content increased from 5.5 % of total protein in young Fischer 344 rats to approximately 12 %

in senescent animals [21]. Age-associated increases in collagen content have also been reported in sheep [22], in normocholesterolemic rabbits [23], and in mice [24]. Similar findings were observed in human hearts. Collagen content increased with age in normal human hearts [25]; myocardium from senescent individuals exhibited increased collagen deposition and thicker endomysial and perimysial collagen fibers [26].

Aging-associated cardiac hypertrophy and fibrosis are, at least in part, due to peripheral vascular stiffening. Age-related arterial stiffening increases hemodynamic load, contributing to the development of cardiomyocyte hypertrophy [27] and leading to enhanced collagen deposition in the interstitial and perivascular space.

Collagen Turnover in the Aging Myocardium

Myocardial collagen levels in the heart are determined by the balance between matrix-preserving and matrix-degrading signals [28]. Resident cardiac fibroblasts are the key regulators of myocardial collagen content, not only by secreting collagen but also by modulating the balance between synthesis and degradation. When stimulated by fibrogenic growth factors, such as transforming growth factor (TGF)-β, cardiac fibroblasts synthesize matrix proteins and express protease inhibitors (such as the tissue inhibitors of metalloproteinases/TIMPs) that preserve the matrix [29]. In contrast, proinflammatory mediators such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β stimulate matrix metalloproteinase (MMP) expression by cardiac fibroblasts activating matrix-degrading pathways [30, 31]. Evidence suggests that in the aging heart, increased collagen synthesis may not be the main culprit of fibrosis. Using radiolabeled proline assays, Mays and coworkers estimated that in the heart of 1-month-old rat, about 20 % of collagen is newly synthesized per day. Synthesis remains high in 15-month-old rats and is significantly decreased (2 % per day) in 24-month-old animals [32]. Similarly, mRNA expression of collagens I and III is reduced in the aging rat myocardium [33, 34]. Robert et al. suggested that, in contrast to hypertensive fibrotic remodeling, aging-related fibrosis in rats is associated with attenuated MMP expression [35]. Hypertension induced by systemic aldosterone infusion caused significant perivascular fibrosis and was associated with a 40 % increase in MMP-2 expression and activity. Marked interstitial fibrosis was noted in nonhypertensive senescent rats; however, in contrast to the observations made in the model of aldosterone infusion, aging was associated with reduced MMP-2 and MMP-1 expression and activity [35]. These findings suggested that in normal aging, fibrosis may be primarily due to a reduction in the proteolytic activity of matrix MMPs; increased expression of TIMP-1 may be a possible regulatory factor. Thus, the mechanisms leading to cardiac fibrosis in hypertension and aging appear to be different: increased collagen synthesis may be responsible for the accumulation of collagen in models of hypertension, whereas attenuation of matrix-degrading pathways may account for excessive collagen deposition in the aging heart.

Collagen Cross-Linking in the Aging Myocardium

Procollagen is synthesized by fibroblasts and secreted into the pericellular space, where it forms collagen fibrils that assemble into fibers. Covalent cross-linking of collagen stabilizes fibrillar collagen, increasing its tensile strength and limiting its degradation. Accumulation of cross-linked collagen may contribute to the pathogenesis of diastolic dysfunction in the aging heart. The degree of collagen cross-linking may be measured in tissue by assaying hydroxylysylpyridinoline (HP) residues after hydrolysis [7]. The concentration of ventricular HP increases approximately fivefold in senescent Fischer 344 rats compared to sedentary young animals [36]. Interestingly, collagen cross-linking is significantly lower in old trained rats, compared with their sedentary counterparts [36, 37]. Glucose can react nonenzymatically with myocardial collagens and link them together, producing

advanced glycation end products (AGEs) [38]. Protein cross-linking through AGEs may be important in the pathogenesis of diastolic dysfunction in the aging heart. However, experimental studies testing this hypothesis have produced contradictory results. Treatment with the AGE breaker ALT-711 attenuated age-related left ventricular stiffness [39] in normal aged dogs, suggesting a significant role for accumulation of AGE cross-links in promoting the decreased cardiovascular compliance of aging. In contrast, a more recent study showed no effects of the same AGE breaker on diastolic ventricular function in elderly hypertensive canines and suggested that AGE accumulation and AGE cross-link breaker effects were confined to the vasculature without evidence of myocardial actions [40].

Functional Consequences of Cardiac Fibrosis in Elderly Patients

Because increased myocardial collagen content and collagen cross-linking are associated with accentuated myocardial stiffness, aging-related fibrotic remodeling of the ventricle may be involved in the pathogenesis of diastolic dysfunction in the elderly. Clinical studies have provided convincing evidence supporting the relation between aging and diastolic dysfunction. The Framingham Heart Study [41] and the Baltimore Longitudinal Study of Aging [27] have demonstrated that, in healthy populations, there is an age-dependent increase in the prevalence of left ventricular hypertrophy accompanied by a decline in diastolic function. These changes are associated with reduced exercise capacity; however, systolic function at rest is relatively preserved. Diastolic dysfunction plays a dominant role in the pathogenesis of heart failure and impaired exercise tolerance in elderly individuals [42, 43]. In addition to fibrotic changes, senescent subjects also exhibit significant alterations in cardiomyocyte function that may result in impaired relaxation. Thus, the contribution of fibrotic remodeling to the aging-associated impairment in diastolic function remains unknown.

Although fibrosis in senescent hearts is primarily associated with a stiffer ventricle and diastolic dysfunction, fibrotic remodeling may also induce impaired systolic function. Activation of matrix-degrading pathways leads to the development of ventricular dilation and systolic failure [44]. Although systolic hypocontractility is not observed in healthy aging hearts, aging-associated fibrotic remodeling of the ventricle may contribute to the pathogenesis of systolic dysfunction in the presence of other conditions, such as hypertensive or diabetic cardiomyopathy. Disturbance of the collagen network in the fibrotic heart may cause systolic dysfunction through several distinct mechanisms. First, fibrosis may suppress systolic function through disruption of the coordination of myocardial excitation–contraction coupling [45]. Second, loss of fibrillar collagen may impair transduction of cardiomyocyte contraction into myocardial force development, resulting in uncoordinated contraction of cardiomyocyte bundles [46]. Third, interactions between endomysial matrix components (such as laminin and collagen) and their receptors may play an important role in cardiomyocyte homeostasis [47]. Finally, fibrotic remodeling of the cardiac interstitium is often associated with MMP activation and enhanced matrix degradation, resulting in sliding displacement (slippage) of cardiomyocytes and leading to a decrease in the number of muscular layers in the ventricular wall. These changes may promote left ventricular dilation [48].

In addition, the fibrotic process may have profound effects on the cardiac conduction system. An autopsy study of 230 noncardiac patients demonstrated increased fibrosis and fat within the cardiac conduction system of elderly patients [49]. Fibrotic ventricular remodeling may also promote arrhythmogenesis through impaired anisotropic conduction and subsequent generation of reentry circuits [50, 51].

Mechanisms of Fibrosis in the Aging Heart

Cellular Effectors of Cardiac Fibrosis

Fibroblasts are the main effector cells in cardiac fibrosis. In fibrotic conditions, fibroblasts are activated and undergo phenotypic transition into

"myofibroblasts" [52]. These cells combine ultrastructural and phenotypic characteristics of smooth muscle cells, acquired through formation of contractile stress fibers, with an extensive endoplasmic reticulum, a feature of synthetically active fibroblasts [52, 53]. Expression of α-smooth muscle actin (α-SMA) is considered a major characteristic of differentiated myofibroblasts, but is not a requirement for the myofibroblast phenotype. At the early stages of fibrotic and reparative responses, myofibroblasts have stress fibers that may lack α-SMA and are composed of cytoplasmic actins; these cells are termed proto-myofibroblasts [54]. Proto-myofibroblasts develop mature focal adhesions containing β- and γ-actin microfilaments that are associated with nonmuscle myosin [54].

Generation of α-SMA-positive differentiated myofibroblasts requires the cooperation between TGF-β signaling, mechanical stress, and specialized matrix proteins, such as the ED-A fibronectin variant [54]. Mechanical stress directly stimulates α-SMA transcription through Rho/Rho kinase signaling [55], but is not sufficient to induce myofibroblast transdifferentiation in the absence of TGF-β. In normal hearts, fibroblasts are generally protected from mechanical stimuli by a stable cross-linked matrix network. Once the structural integrity of the myocardium is disrupted, exposure of the cells to mechanical stress contributes to proto-myofibroblast transdifferentiation [54]. Whether aging-related fibrosis is associated with myofibroblast transdifferentiation has not been systematically studied.

The origin of fibroblasts in the fibrotic myocardium remains controversial. The traditional view is that activated myofibroblasts in fibrotic hearts originate from resident fibroblasts through proliferation and activation. However, investigations that tracked proliferating cell populations during cardiac hypertrophy and reactive interstitial fibrosis showed proliferating fibroblast-like cells only in the neighborhood of blood vessels [56]. Several studies have suggested that proliferating fibroblasts in sites of injury may be recruited from other cellular sources such as endothelial cells [57], pericytes [58], or circulating bone marrow-derived progenitor cells [59–62]. Fate-mapping studies have demonstrated that while there is no significant endothelial contribution to the fibroblast population in the normal adult heart, up to 30 % of fibroblasts in damaged myocardium may be of endothelial origin [57], suggesting that EndMT play a significant role in cardiac fibrosis. A recent study has suggested that EndMT may contribute to profibrotic responses during myocardial fibrosis in aged mouse hearts and that this process may involve constitutive TGF-β signaling [63]. In this study, Ghosh et al. used a mouse model of age-associated cardiac fibrosis that develops in the absence of plasminogen activator inhibitor-1 (PAI-1). PAI-1 plays a significant role in regulation of fibrosis by inhibiting collagenase activity and by protecting matrix proteins from proteolytic degradation [64]. Paradoxically, mice lacking PAI-1 develop age-dependent cardiac fibrosis; the mechanism responsible for this phenomenon is incompletely understood [65]. Ghosh et al. showed that aged hearts from PAI-1 null mice had increased inflammation, elevated TGF-β expression, and activation of TGF-β-mediated profibrotic responses. Moreover, PAI-1-deficient endothelial cells are more susceptible to EndMT in response to TGF-β via induction of both Smad and ERK1/2 MAPK pathways. These findings suggest that physiologic PAI-1 levels may protect the heart from age-dependent fibrogenesis [63]. Bone marrow-derived progenitor cells may be an additional source of fibroblasts in the fibrotic heart. However, their role in aging-associated fibrosis has not been established.

Molecular Signals Involved in Aging-Associated Fibrosis (Fig. 24.1)

The Role of Inflammatory Cascades

The involvement of inflammatory cascades has been clearly demonstrated in many fibrotic responses, in particular when significant cellular necrosis is observed. For example, a close association between the inflammatory and fibrotic processes is well established in the reparative fibrosis following myocardial infarction. In other cases, the link is weaker. The potential involvement of the inflammatory response in aging-associated

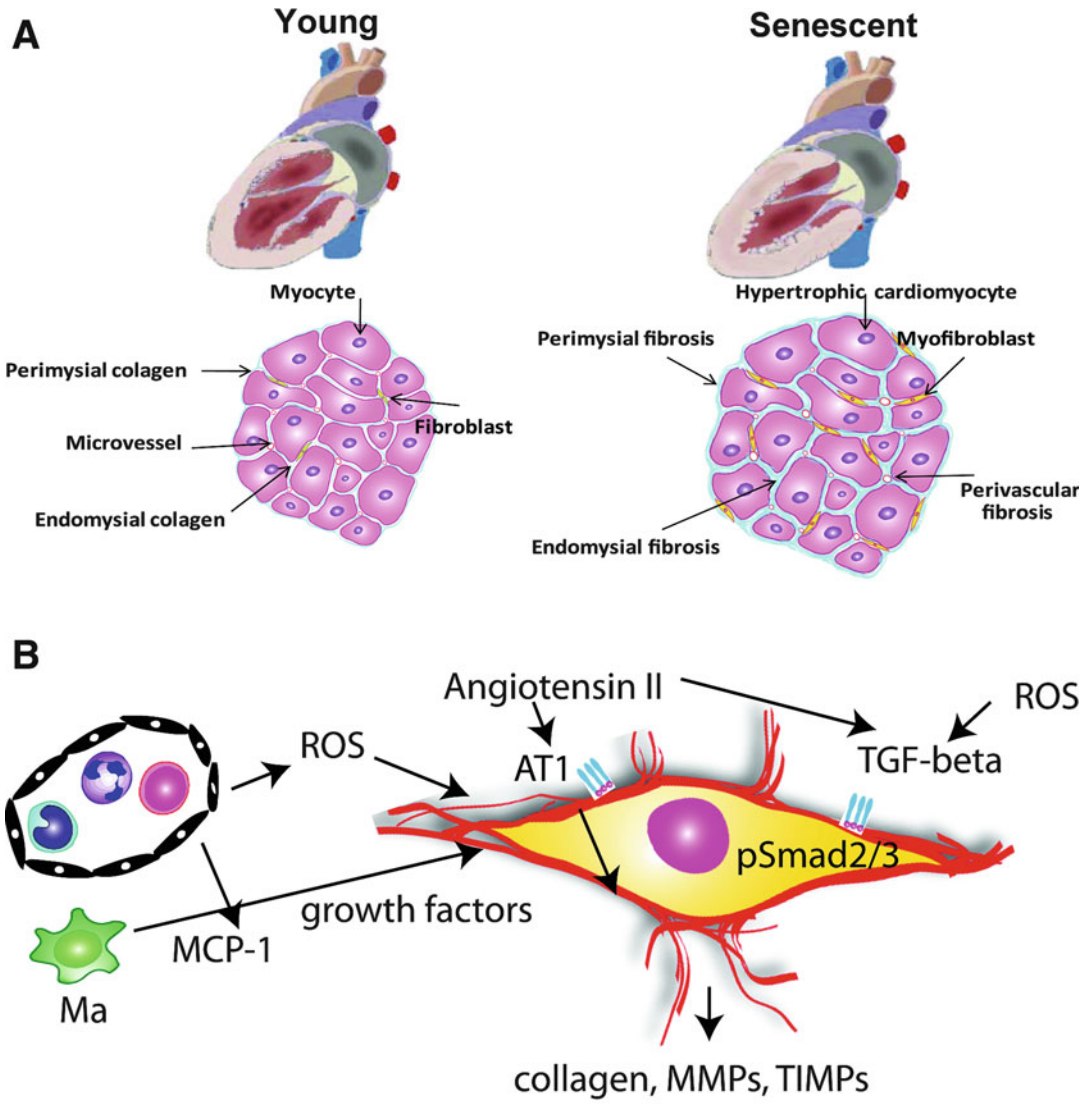

Fig. 24.1 *Pathways involved in age-associated cardiac fibrosis*. (**a**) Senescence is associated with cardiac fibrosis and hypertrophy. (**b**) Angiotensin II (ANG II), reactive oxygen species (ROS), and transforming growth factor-β (TGF-β) signaling play an important role in mediating fibrotic remodeling of the aging heart. ANG II exerts pro-fibrotic actions through the ANG II type 1 receptor (AT1) and indirectly through TGF-β upregulation. Aging-associated mitochondrial dysfunction is a major source of ROS in the myocardium. Inflammatory cytokines may induce and activate matrix metalloproteinases (MMPs) enhancing matrix degradation. TGF-β/Smad2/3 signaling promotes myofibroblast transdifferentiation and enhances the production of extracellular matrix proteins. Symbols: *Ma* macrophage; *MCP-1* monocyte chemoattractant protein-1

fibrosis is primarily supported by descriptive and associative studies. Recent experiments suggested that interstitial fibrosis in senescent mice may arise from age-dependent immunoinflammatory dysregulation [66]. In C57BL/6 mice, cardiac fibrosis and diastolic dysfunction were present at the end of the first year of life and became progressively worse as the mice aged up to 30 months. These morphological and functional alterations were associated with increased myocardial expression of the chemokine monocyte chemoattractant protein (MCP)-1/CCL2,

accentuated synthesis of the profibrotic cytokines interleukin (IL)-4 and IL-13, and accumulation of CD45+ myeloid-derived fibroblasts that correlated temporally and quantitatively with the degree of fibrosis and the development of diastolic dysfunction. MCP-1 may induce fibrosis through recruitment of monocytes with fibrogenic properties [67] or through chemoattraction of fibroblast progenitors. Although both animal and human studies have suggested a significant role for MCP-1/CCL2 in ischemic cardiac fibrosis [67–69], its involvement in aging-associated fibrotic cardiac remodeling has not been investigated. The potential role of other chemokines with fibrogenic and anti-fibrotic properties [69–71] in regulation of aging-related fibrosis remains unknown.

IL-13 is known to exert profibrotic actions in vivo [72, 73]; however, its role in the aging heart has not been examined. Elevation of IL-4 and IL-13 expression in the aging mouse heart suggests a shift to a Th2 phenotype. Age-associated changes in immune function characterized by a shift from Th1 (IL-12, IFN-γ) to Th2 (IL-13, IL-4) cytokines have been shown in animal studies [74] and in human aging [75] and may be important in senescence-associated fibrosis.

The Renin–Angiotensin–Aldosterone System in Aging-Associated Fibrosis

Extensive evidence suggests that activation of Renin–Angiotensin–Aldosterone System (RAAS) may play a central role in cardiac aging and in age-associated fibrotic remodeling. Angiotensin (ANG) II concentrations increase significantly in aged rodent hearts [76], probably due to an increase in tissue levels of angiotensin II converting enzyme (ACE) [77]. ANG II promotes cardiomyocyte hypertrophy [78] and stimulates fibroblast proliferation and expression of extracellular matrix proteins [79]. ANG II exerts its effects directly through the ANG II type 1 receptor (AT1) and indirectly through induction of TGF-β1 [80]. Long-term inhibition with angiotensin receptor blockers, or AT1 gene disruption, reduces age-dependent cardiac pathology and prolongs rat [81] and mouse [82] survival. In contrast, knock-in mice with a gain-of-function mutation of AT1A develop progressive cardiac fibrosis with increased expression of collagen [83]. Stein et al. showed that chronic RAAS inhibition resulted in the reduction of both interstitial and patchy fibrosis in the senescent mouse heart. Interestingly, a significant reduction in the susceptibility to arrhythmias was observed after RAAS inhibition and was directly correlated to the reduction of patchy fibrosis [84].

The Role of β-Adrenergic Signaling

Activation of β-adrenergic signaling increases heart rate, contractility, and afterload, enhancing cardiac metabolic demand. Chronic activation of β-adrenergic signaling is deleterious to the heart; several clinical trials have demonstrated that inhibition of β-adrenergic signaling by β-blockers provides survival benefit in patients with heart failure. Mice with disruption of adenylate cyclase type 5 (AC5), a major mediator of β-adrenergic signaling in the heart, had prolonged life span and were protected from cardiac aging, exhibiting reduced age-dependent cardiac hypertrophy and attenuated fibrosis [85]. However, the potential involvement of β-adrenergic signaling in the pathogenesis of aging-associated fibrosis has not been investigated.

Reactive Oxygen Species as Mediators of Age-Associated Cardiac Fibrosis

Experimental studies have demonstrated increased generation of ROS in the aging heart. Within the cells, ROS are produced in multiple compartments; however, mitochondria contribute to the majority of ROS generation as a by-product of electron transfer during oxidative phosphorylation. Mitochondrial DNA, lipids, and proteins are therefore at the highest risk from free radical-induced damage and dysfunction. Several studies have documented an age-dependent impairment

of mitochondrial function associated with increased production of ROS. The heart, with its high metabolic demand, is rich in mitochondria and is particularly vulnerable to mitochondrial oxidative damage. Impairment of mitochondrial function has been widely documented in heart failure in both human patients and mouse models [86]. Moreover, a significant increase in superoxide radical production was seen in mitochondria prepared from aging rat hearts [87]. Studies in mice overexpressing catalase targeted to the mitochondria (mCAT) provided direct evidence on the critical role of mitochondrial ROS in cardiac aging. Overexpression of mCAT prolonged murine life span [88] and attenuated age-associated cardiomyocyte hypertrophy, cardiac fibrosis, and diastolic dysfunction [89]. These protective actions were associated with attenuated mitochondrial oxidative damage [89].

Recent investigations have focused on the role of mitochondrial NAD-dependent deacetylase sirtuin-3 (SIRT3) in cardiac senescence. Overexpression of SIRT3 in cultured cells decreased ROS generation. SIRT3 knockout mice showed accelerated signs of cardiac aging exhibiting premature cardiac hypertrophy and fibrosis at 13 months of age. SIRT3 knockout mice are also more vulnerable to the effects of pressure overload, exhibiting increased mortality, cardiac hypertrophy, and fibrosis following transverse aortic constriction. The findings suggest that SIRT3 activity is necessary to prevent mitochondrial dysfunction and cardiac hypertrophy during aging [90].

Although a growing body of evidence suggests an important role for ROS in the pathogenesis of aging-associated cardiac fibrosis, the pathways responsible for ROS-induced fibrotic remodeling in the aging heart remain poorly understood. ROS may exert fibrogenic actions both through direct effects on cardiac fibroblasts and through modulation of cytokine signaling. Oxidative stress regulates the quantity and quality of extracellular matrix by modulating both collagen synthesis- and metabolism [91]. In addition, ROS mediate cytokine- and ANG II-induced effects on fibroblasts [92]. On the other hand, ROS are capable of inducing expression of inflammatory and fibrogenic mediators that may play an essential role in aging-associated fibrosis. ROS-mediated upregulation of CC chemokines (such as MCP-1/CCL2), accompanied by induction of adhesion molecules in the microvascular endothelium [30], may promote recruitment of mononuclear cells and fibroblast progenitors in the aging myocardium creating a fibrogenic milieu [70, 93].

The Role of TGF-β

TGF-β appears to be an essential profibrotic signal in cardiac fibrotic conditions [94–96]. TGF-β may mediate aging-associated cardiac fibrosis by inducing myofibroblast transdifferentiation [97] and by enhancing matrix protein synthesis by cardiac fibroblasts [29]. In addition, TGF-β may exert potent matrix-preserving actions by suppressing the activity of MMPs and by inducing synthesis of protease inhibitors, such as PAI-1 and TIMPs [98, 99]. The canonical signaling pathway for TGF-β involves the Smad family of intracellular effectors [100]. The receptor-associated R-Smads, Smad2, and Smad3 are phosphorylated directly by the TGF-β type 1 receptor kinase, after which they heterooligomerize with Smad4, translocate to the nucleus, and, together with their binding partners, activate or repress their target genes. Several studies have shown that TGF-β can also signal in a Smad-independent fashion, activating extracellular signal-regulated kinase (ERK), c-Abl, or TAK-1 pathways [101].

TGF-β1-overexpressing mice exhibited enhanced beta-adrenergic signaling and significant cardiac hypertrophy accompanied by interstitial fibrosis [102]. On the other hand, loss of one TGF-β1 allele in TGF-β1 heterozygous mice appears to ameliorate age-associated myocardial fibrosis and improve left ventricular compliance [103]. Both ROS and ANG II may activate TGF-β signaling pathways in the senescent heart. ROS activate TGF-β and upregulate its downstream fibrogenic effector [104], connective tissue growth factor (CTGF)/CCN2 [105]. In addition, ANG II markedly upregulates TGF-β1 synthesis by cardiac fibroblasts and myofibroblasts [106, 107].

ANG II-induced TGF-β upregulation is followed by the development of cardiac fibrosis [45]; however, the dependence of the profibrotic actions of ANG II on TGF-β has not been established [79].

Aging and Cardiac Repair

Patients aged 65 years and over account for about 50 % of hospital admissions and 80 % of deaths from acute myocardial infarction [108]. Aging increases the incidence of postinfarction heart failure, and adverse ventricular remodeling is more common in elderly patients. The age-related increase in postinfarction mortality and morbidity cannot be explained by larger infarcts [109]. Thus, distinct responses of the senescent heart to cardiac injury may play a role in aging-associated heart failure. Aging modulates repair of the infarcted heart and promotes adverse remodeling, reducing survival and increasing the likelihood for development of heart failure [108].

Aging and the Postinfarction Inflammatory Response

Healing of the infarcted heart is dependent on an inflammatory reaction that ultimately results in formation of a scar [110]. Inflammatory cascades direct the reparative response in the infarcted heart, modulating deposition, and metabolism of extracellular matrix proteins in the wound [111, 112]. These actions ultimately determine the mechanical properties and the geometric characteristics of the infarcted ventricle by affecting the tensile strength of the scar.

We have recently tested the hypothesis that aging-related changes in inflammatory mediator expression and impaired responsiveness of senescent reparative cells to growth factors may be responsible for defective infarct healing and adverse remodeling of infracted heart. Using a mouse model of reperfused infarction, we compared the inflammatory and fibrotic response between young (3–4-month-old) and old C57BL/6 J mice (>24-month-old) [113]. Aging was associated with suppressed postinfarction inflammation, decreased and delayed neutrophil and macrophage infiltration, reduced cytokine and chemokine expression, and impaired phagocytosis of dead cardiomyocytes. Despite comparable scar size, reperfused infarction in young mice induced intense inflammation after 24 h and replacement with granulation tissue within 72 h, whereas healing in the older mice was delayed (Fig. 24.2). Decreased phagocytotic activity [114] and diminished oxidative responses to activating signals [115] displayed by senescent macrophages and neutrophils may explain the impaired clearance of dead cardiomyocytes in the infarcted myocardium. The suppressed inflammatory reaction was followed by decreased myofibroblast infiltration and markedly attenuated collagen and matricellular protein deposition in senescent mouse infarcts, resulting in formation of a scar containing loose connective tissue. The reduction in scar collagen content in old animals was associated with increased dilative remodeling and markedly enhanced systolic dysfunction following infarction.

Because of the critical role of the Smad2/3 pathway in mediating fibrogenic TGF-β responses [94, 116], we hypothesized that defective fibrous tissue deposition in senescent infarcted hearts may be due to impaired responses of aged mouse fibroblasts to growth factor stimulation. Young mouse cardiac fibroblasts exhibited a robust increase in Smad2 phosphorylation after stimulation with TGF-β1. In contrast, fibroblasts isolated from senescent hearts showed a blunted response to TGF-β stimulation [113], suggesting that aging results in impaired fibroblast responses to growth factors. The blunted response of senescent fibroblasts to fibrogenic mediators may not be limited to TGF-β stimulation. The stimulatory effect of ANG II on matrix synthesis is reduced in rat fibroblasts isolated from senescent hearts in comparison with fibroblasts harvested from young hearts [117].

Therefore, the enhanced baseline activation of fibrogenic pathways and increased collagen deposition in senescent hearts may be associated with an impaired reparative reserve, due to blunted responses of mesenchymal cells to stimulatory signals (Fig. 24.2). Defective scar formation may

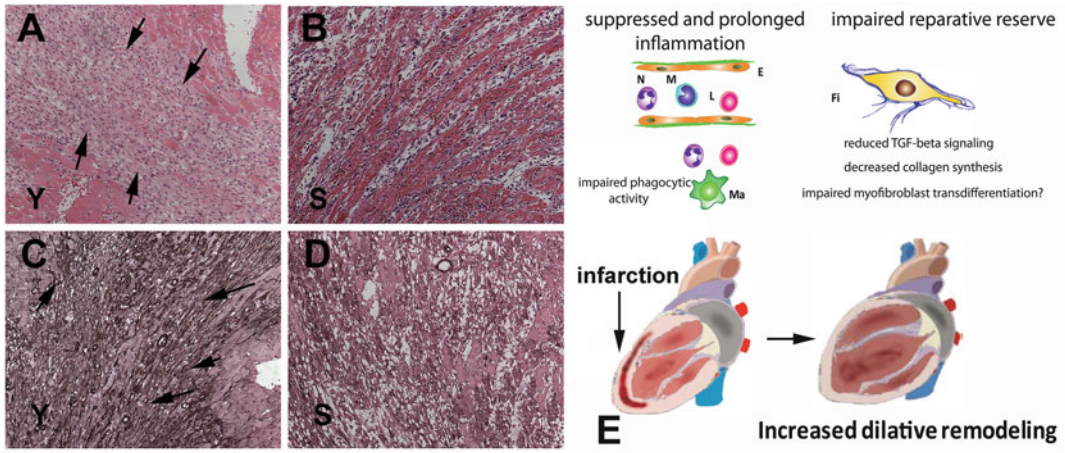

Fig. 24.2 *Senescence is associated with defects in the postinfarction inflammatory and reparative response that may be responsible for adverse remodeling*. Although aging is associated with enhanced baseline inflammation and increased fibrosis, acute infarction results in suppressed, but prolonged, inflammatory reaction, impaired cardiomyocyte phagocytosis, a defective fibroblast response, and markedly diminished collagen deposition in the scar. (**a–b**) Senescence is associated with delayed phagocytosis of dead cardiomyocytes in the infarcted heart. Hematoxylin–eosin staining shows that, after 1 h of ischemia and 72 h of reperfusion, young mice (Y, 2–4 months of age) exhibit replacement of dead cardiomyocytes with granulation tissue (**a**). In contrast, in senescent mice (>2 years of age), at the same timepoint, dead cardiomyocytes remain. (**c–d**) Senescent hearts exhibit impaired infiltration of the infarcted myocardium with myofibroblasts. α-smooth muscle actin (α-SMA) immunohistochemistry identifies myofibroblasts in the infarct after 72 h of reperfusion (*arrows*). Young mouse hearts exhibit infiltration with abundant myofibroblasts (**c**); in contrast, senescent hearts have markedly lower myofibroblast density (**d**). (**e**) Senescent mouse infarcts have a decreased and prolonged inflammatory response and impaired reparative reserve characterized by defective fibroblast responses to TGF-β. Decreased collagen deposition in senescent mouse infarcts may reduce tensile strength of the scar and increase dilative remodeling. Symbols: *E* endothelial cell; *Fi* fibroblast; *L* lymphocyte; *Ma* macrophage; *M* monocyte; *N* neutrophil

play a key role in the pathogenesis of adverse remodeling and heart failure in senescent subjects. In model of heart failure induced by right ventricular tachypacing in sheep, collagen depletion was observed in aged hearts [22]. Thus, impaired matrix-synthetic and enhanced matrix-degrading responses may be consistent and clinically important features of injury-site fibroblasts in failing senescent hearts.

Therapeutic Targets to Attenuate Fibrotic Remodeling in Senescent Hearts

Targeting mediators involved in the pathogenesis of aging-associated fibrosis may reduce diastolic dysfunction and prevent heart failure in elderly patients. MCP-1 inhibition, targeting of the TGF-β cascade, attenuation of ROS signaling, and administration of AGE breakers may be reasonable therapeutic approaches to prevent progression of cardiac fibrosis in the elderly. However, several important concerns dampen enthusiasm about the potential usefulness of these strategies:

a) Whether cardiac fibrosis can be reversed remains controversial. It has been suggested that established fibrotic changes may no longer be reversible due to the absence of cellular mediators that could produce proteases to degrade the collagen-rich tissue [118]. In addition, the formation of cross-linked matrix proteins in advanced lesions of senescent hearts may prevent reversal of the fibrotic process. Thus, effective inhibition of age-related cardiac fibrosis may require early and prolonged treatment, exposing patients to the adverse consequences of therapeutic agents that interfere with immune function, matrix homeostasis, and tissue repair.

b) Blockade of fibrogenic pathways may in many cases also inhibit adaptive processes with

protective effects on the aging heart. For example, chronic MCP-1 inhibition may not only exert anti-fibrotic actions but may also reduce arteriogenesis, interfering with collateral vessel formation. TGF-β inhibition, on the other hand, may interfere with immune responses and with matrix-preserving effects that maintain geometry in the heart and in the vasculature [95].

c) Because senescence is also associated with cardiomyocyte changes that lead to impaired relaxation, it is unknown to what extent age-associated fibrosis contributes to diastolic dysfunction in elderly patients. Thus, the clinical significance of age-associated cardiac fibrosis in patients without concomitant conditions (such as diabetes, hypertension, or coronary atherosclerotic disease) is not well defined. Attenuation of the modest fibrosis noted in healthy elderly individuals may not confer clinically significant benefits. Thus, it seems more reasonable to focus on specific subpopulations of elderly patients who are at a high risk for development of fibrotic remodeling and diastolic dysfunction due to the presence of hypertensive, diabetic, or ischemic heart disease. Beyond the established beneficial effects of ACE inhibitors and angiotensin receptor blockers in patients with hypertension that may be due, at least in part, to attenuation of cardiac fibrosis, other anti-fibrotic strategies (such as AGE breakers, anti-MCP-1 strategies, or TGF-β inhibitors) may exert beneficial actions in high-risk elderly patients with diastolic heart failure.

Targeting Age-Associated Defects in Cardiac Repair to Correct Impaired Reparative Reserve

A much more appealing and realistic therapeutic goal may be to target specific age-associated healing defects in senescent patients with myocardial infarction, in order to prevent adverse remodeling and to protect from the development of heart failure [119–121]. In senescent mice, a suppressed postinfarction inflammatory response results in delayed replacement of dead cardiomyocytes with granulation tissue [113], while blunted responses of senescent fibroblasts to fibrogenic growth factors markedly decrease collagen deposition in the scar, resulting in decreased tensile strength and enhanced ventricular dilation. These findings suggest that age-associated adverse remodeling of the infarcted ventricle may not be due to enhanced inflammatory injury, or increased fibrosis, but rather results from a defective fibroblast response and impaired formation of the reparative matrix network, necessary to mechanically support the infarcted heart. Elderly subjects may have impaired reparative reserve. Thus, strategies aiming at enhancing reparative responses following cardiac injury through the cautious administration of growth factors along with injection of smart biomaterials [122] may represent new therapeutic opportunities for preventing the development of heart failure in elderly patients with acute myocardial infarction. However, such approaches have not yet been tested in experimental models of senescence-associated post-infarction heart failure.

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Aging-Related Changes in Extracellular Matrix: Implications for Ventricular Remodeling Following Myocardial Infarction

Nguyen T. Nguyen, Andriy Yabluchanskiy, Lisandra E. de Castro Brás, Yu-Fang Jin, and Merry L. Lindsey

Abbreviation

ECM	Extracellular matrix
LV	Left ventricle
MMP	Matrix metalloproteinase
MI	Myocardial infarction
OPN	Osteopontin
SPARC	Secreted protein acidic and rich in cysteine
TSP	Thrombospondin
TIMP	Tissue inhibitors of metalloproteinase
TGF	Transforming growth factor
VEGF	Vascular endothelia growth factor

N.T. Nguyen, MS • Y.-F. Jin, PhD
San Antonio Cardiovascular Proteomics Center, Department of Electrical and Computer Engineering, University of Texas at San Antonio, San Antonio, TX, USA

A. Yabluchanskiy, MD, PhD • L.E. de Castro Brás, PhD
San Antonio Cardiovascular Proteomics Center and Mississippi Center for Heart Research, Department of Physiology and Biophysics, University of Mississippi, Jackson, MS, USA

M.L. Lindsey, PhD (✉)
San Antonio Cardiovascular Proteomics Center and Mississippi Center for Heart Research, Department of Physiology and Biophysics, University of Mississippi, Jackson, MS, USA

Department of Physiology and Biophysics, University of Mississippi Medical Center, 2500 North State Street, Room G351-04 Jackson, MS 39216–4505, USA
e-mail: mllindsey@umc.edu

Introduction

Age is a major risk factor for cardiovascular disease, with a reported 81 % of deaths occurring in adults over 65 years of age [1, 2]. Additionally, morbidity and mortality rates for heart failure following myocardial infarction (MI) increase significantly with age [3]. Survival post-MI declines as a function of age, with 30-day survival rates falling from ~90 % for patients under 65 years of age to ~60 % for patients over 80 years of age [4]. Because of the poor clinical outcome for elderly patients with MI, understanding the effects of aging on the left ventricle (LV) will help us to develop better therapies to treat MI in the elderly [5–8].

During the normal aging process, the cardiovascular system undergoes a continuous resetting of homeostasis that induces changes in the structure and function of the LV. In humans, the major LV changes with age include impairments in endothelial function, acute response to stress, and cardiovascular reserve, while vascular intimal thickness, vascular stiffness, LV wall thickness, and left atrial size all increase [9–11]. In mice, similar LV changes occur a reduced level,

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since these changes are not accompanied by vascular changes. Mice do not get hypertension with age [12]. Therefore, the aging mouse is an excellent model to examine cardiac changes that are not superimposed on vascular changes.

Under normal conditions, the extracellular matrix (ECM) provides a three-dimensional structure to coordinate cell adhesion, proliferation, and migration and maintain normal cardiac performance. In this setting, the ECM communicates with myocytes, endothelial cells, and fibroblasts by binding to integrins and other cell surface receptors [13]. In the post-MI setting, LV ECM also interacts with macrophages and fibroblasts to regulate the inflammatory and remodeling phases of the wound healing process [14].

In this chapter, we briefly summarize the age-related changes in ECM that occur in the absence and presence of MI, evaluate the effects of current clinical therapies on ECM, and discuss novel ECM therapeutic options for the treatment of MI in the setting of an aging LV.

Age-Related Changes in Cardiac ECM

Age-related changes in cardiac ECM include alterations in collagens, other glycoproteins, proteoglycans, glycosaminoglycans, and matricellular proteins, as well as integrins, matrix metalloproteinases (MMPs), and growth factors (Table 25.1).

Collagens

As a major component of cardiac ECM, total collagen is the combination of several collagen subtypes, all of which exhibit different structures, functions, and properties. Included in the list of collagens are fibrillar types I, III, and V, basement membrane type IV, and microfibrillar type VI collagens. During normal aging, total collagen content, insoluble collagen, collagen fibril diameter, types I–III collagen ratio, and the extent of collagen cross-linking all increase [15–17].

Table 25.1 Summary of ECM changes with aging (references in the text)

ECM components		Changes	Location	Species
Collagen	Type I	↑	LV myocardium	Human
	Type III	↓	LV myocardium	Balb-c mice
Procollagen	Type I	↓	LV free wall	Fischer rats
	Type III	↓	LV free wall	
Glycoproteins	Fibronectin	↓ ↑ ↓	LV	Balb-c mice Wistar
	Laminin-α2	↓	LV	Wistar rats
	Periostin	↑	LV	C57BL/6 J mice
Proteoglycans	Versican	↓	LV	C57BL/6 J mice
Glycosaminoglycan	Hyaluronan	↓	LV	Sprague–Dawley rats
		↑	Right ventricle	
Matricellular proteins	SPARC	↑	LV	C57Bl6/SV129 mice
	TSP-2	↑	LV	C57BL/6 J mice C57Bl6/129SvJ/EMS + Ter mice
	Tenascin	↑	Chordae tendineae	Human
	OPN	↑	Aorta	F344xBN rats
Cell surface receptors	Integrin-α1	↓ ↑	LV	Balb-c mice
	Integrin-α5	↑		
	Integrin-β1	↓		

(continued)

Table 25.1 (continued)

ECM components			Changes	Location	Species
MMPs	MMP-2		↑	Aorta	F344xBN rats
				Epicardial coronary arteries	F344xBN rats
				Right atrial appendage	Human
	MMP-9		↑	Right atrial appendage	Human
	MMP-28		↑	LV	C57BL/6 J mice
	TIMP-2		↓	Epicardial coronary arteries	F344xBN rats
				Right atrial appendage	Human
	MMP-2	*Insoluble*	→	LV	CB6F1 mice
		Soluble	→		
	MMP-3	*Insoluble*	↑		
		Soluble	↓		
	MMP-7	*Insoluble*	–		
		Soluble	→		
	MMP-8	*Insoluble*	→ ↑ ↑		
		Soluble	→		
	MMP-9	*Insoluble*	↓ → ↑		
		Soluble	↓ → →		
	MMP-12	*Insoluble*	→ → ↑		
		Soluble	↓		
	MMP-13	*Insoluble*	–		
		Soluble	↓		
	MMP-14	*Insoluble*	→ ↑ ↑		
		Soluble	↓ ↓ ↑		
	TIMP-1	*Insoluble*	–		
		Soluble	↓ → →		
	TIMP-2	*Insoluble*	–		
		Soluble	→		
	TIMP-3	*Insoluble*	→ ↓ ↓		
		Soluble	→		
	TIMP-4	*Insoluble*	→ → ↓		
		Soluble	→		
Growth factors	TGF-β		↑	Right atrial appendage	Human
				Aorta	F344xBN rats
	VEGF		↓	LV	Wistar rats

↑ increased, ↓ decreased, → unchanged, – very low levels. In the changes column, the presence of a single arrow represents general age-related changes. The double arrows represent changes from young to middle-aged (*first arrow*) and from middle-aged to old animals (*second arrow*). Triple arrows represent changes between young to middle-aged (*first arrow*), young to old (*second arrow*), and middle-aged to old animals (*third arrow*). More details can be found in the text

Collagen types I and III form fibrils to support resident cells in the LV. The accumulation of collagens, primarily types I and III, contributes to LV wall thickening [10]. Collagen type I increases and collagen type III decreases in the aged mouse myocardium, leading to an increase in the relative proportion of types I–III collagen [18, 19]. The tensile strength of type I collagen is comparable to steel, while type III collagen has less tensile strength and higher distensibility. An increased ratio of types I–III collagen, therefore, increases LV wall stiffness. Further, cardiac collagen content doubles in senescent mice compared to young hearts [20]. Since collagen is about 800–1,000 times stiffer than the muscle, increased collagen content contributes significantly to increased LV stiffness with aging, which in turn impairs the biomechanics of the LV [21, 22].

While collagen deposition increases in the LV with age, the mRNA expression of procollagen types

I and III actually declines in the LV, demonstrating that the increased collagen with aging is more likely due to translational or posttranslational regulation rather than increased transcription [12, 23].

Glycoproteins

In addition to collagens, other ECM glycoproteins include fibronectin, laminins, and periostin. Interactions between cells and glycoproteins mediate multiple functions, including adhesion, migration, growth, and differentiation.

Fibronectin binds to cells through integrins and other cell surface receptors such as syndecan 4, and fibronectin interacts with other ECM proteins including collagen, fibrin, heparin, and heparan sulfate [24]. The combined presence of fibronectin, collagen type IV, heparan sulfate proteoglycan, and laminin constitutes the basal lamina in normal LV. Fibronectin levels are lower in middle-aged 12-month-old Balb-c LV compared to 2–3-month-old LV, and fibronectin increases in 20-month-old LV compared to the middle-aged LV [16]. In the LVs of adult 7.5–10-month-old Wistar rats, fibronectin levels are also lower than young 2–3-month-old LVs [25, 26].

Laminins connect basement membrane to adjacent cells by binding cell surface receptors such as CD44. A steady decrease in the level of laminin-α2 mRNA is observed with aging in humans and rats [25]. Deficiency of laminin-α2 causes muscular dystrophy, which is commonly accompanied by cardiomyopathy characterized by the functional and structural deterioration of the myocardium [27].

Periostin is a multifunctional secreted protein that regulates cell adhesion and migration and collagen fibrillogenesis. Expressed in collagen-rich connective tissues, periostin exhibits dynamic changes in developmental and actively remodeling adult tissues [28]. Elevation of periostin has been observed with aging, as mRNA levels of periostin increase 85 % in senescent murine LV compared to young [12, 29].

Hyaluronan and Proteoglycans

Hyaluronan is an extracellular and cell surface-associated glycosaminoglycan that interacts with proteoglycans as well as cell surface receptors including CD44, link proteins, and tumor necrosis factor (TNF)-α-stimulated gene 6 [30]. The interaction of hyaluronan with the cell surface receptor CD44 is essential for embryonic heart development, in which atrioventricular canal morphogenesis is regulated by a signaling pathway involving hyaluronan, CD44, and ErbB receptors/ligands [31]. The expression and location of hyaluronan differ between newborn and adult animals, in which hyaluronan in newborn rats displays stronger staining in the LV than in the right ventricular wall, and vice versa for rats older than one month old [32].

Versican is a very large proteoglycan that interacts with hyaluronan to form a polymeric structure in ECM [33]. Versican in the mouse myocardium reaches the highest mRNA levels during the fetal period, decreases steadily to very low levels by birth, and reduces further with age [29, 34].

Matricellular Proteins

Matricellular proteins are a group of ECM proteins that mediate cell–matrix interactions and include secreted protein, acidic and rich in cysteine (SPARC), thrombospondins (TSPs), tenascins, and small integrin binding ligands N-linked glycoproteins. In the mouse myocardium, SPARC was found to increase with age, and this increase correlated with an increase in post-synthetic collagen processing to form mature cross-linked insoluble collagen [35]. The association between SPARC and post-synthetic procollagen processing suggests that increased SPARC expression with aging might be a plausible cause of age-dependent increase in myocardial fibrillar collagen content and the decline in diastolic function.

The TSP family consists of two subgroups: TSP-1 and -2 (homotrimers) and TSP-3, -4, and -5 (homopentamers). In mice, TSP-2 transcription and protein levels increase 3.4- and 3.6-fold, respectively, in older hearts compared with young hearts [29, 36]. Increased expression of TSP-2 in aged hearts may protect against dilation.

The tenascin family consists of four multimeric secreted proteins including tenascin C, R, X, and W that regulate cell differentiation and

adhesion. In mouse models, tenascin C is elevated 30 % in senescent LV compared to younger counterparts [12]. Increased levels of tenascin C in the LV may be a result of the increase in stiffening seen during aging.

Osteopontin (OPN) is expressed in many cell types, including cardiomyocytes and fibroblasts. In mice, gene expression of OPN drops 34 % in senescent LV compared to young [12]. Ventricular OPN mRNA content in normal adult rat hearts also displays a 2.5-fold decrease compared to neonatal rat hearts [37].

Integrins

As cell surface receptors, integrins regulate the attachment between cell and ECM proteins including fibronectin, laminin, and collagen. Consistent with the temporal profiles of fibronectin and collagen, integrins undergo dynamic changes with aging. The α1 integrin, a fibronectin-binding integrin, is significantly lower in 12-month-old middle-aged mouse hearts compared to 2-month-old young and 20-month-old mice. The α5 integrin, another fibronectin-binding integrin, increases significantly with age. In contrast, the β1 integrin level in old mouse hearts is significantly less than that of middle-aged and young mice [16].

MMPs

MMPs are a family of zinc-dependent enzymes involved in ECM turnover. MMP activity is inhibited by tissue inhibitors of metalloproteinases (TIMPs), and both MMP and TIMP levels change as a function of age, concomitant with the decrease in LV diastolic function [38]. Compared to 3-month-old young CB6F1 mice, MMP-3, MMP-9, MMP-12, MMP-14, and TIMP-1 decrease and TIMP-3 increases in the 15-month-old middle-aged LV. MMP-13, MMP-14, and TIMP-4 decrease in middle age. Compared to middle-aged levels, MMP-3, MMP-9, and MMP-14 increase and TIMP-4 decreases in 23-month-old LV [20]. In senescent C57BL/6 J mice (26–34 months old), MMP-3 increases twofold, MMP-9 increases 83 %, and MMP-14 increases 41 % compared to younger LV levels [12]. Protein expression of MMP-28, the newest member of the MMP family, is upregulated in the LV of aged mice [29].

Growth Factors

Several growth factors, including transforming growth factor (TGF) and vascular endothelial growth factor (VEGF), stimulate tissue remodeling and cell growth, proliferation, and differentiation. TGF-β, a class of polypeptide growth factors, is crucial in the pathways involved in the accumulation of collagen in the aged heart [39]. TGF-β induces the transdifferentiation of fibroblasts to myofibroblasts and stimulates collagen synthesis. TGF-β mRNA levels in human right atrial appendage have been shown to increase with age [17]. Similar age-related changes in TGF-β_1 have also been observed in rat aortas [40, 41]. VEGF is a major regulator of angiogenesis. Impaired angiogenesis with aging has been associated with reduced VEGF expression in the LV of aged rats [11, 42].

ECM Changes Following MI

Cardiac ECM coordinates a series of remodeling events as part of the LV response to injury. These events occur in three distinct but overlapping phases of infarct healing, namely, inflammation, proliferation, and maturation. In Table 25.2, we have listed the temporal changes in ECM proteins observed in mouse and rat models as well as humans.

Collagens

Within a few days post-MI, the existing ECM within the infarct region is degraded and new collagen synthesis and deposition begins in the infarcted area. With time, the infarcted tissue is replaced by a scar comprised primarily of collagen. Collagen type I mRNA levels increase fivefold at day 2 and collagen type III mRNA levels increase 15-fold at day 4 post-MI [43]. Collagen types I and III mRNA remain elevated in the infarcted rat LV. A delayed upregulation of both collagen types I and III is seen in the non-infarcted regions of the LV and the right ventricle beginning at

Table 25.2 ECM changes post-MI (references in the text)

ECM components		6 h	12 h	d1	d2	d3	d4	d7	d14	d21	d28	d35	d56	d40	d84	d112
Collagen	[A,S]Type I[1]			–		↑										
	[A,S]Type III[1]			–		↑										
Procollagen	[A,W]Type I[1]						↑								↑	
	[A,W]Type III[1]				↑					↑						
Glycoprotein	[A,CS]Fibronectin[2]			–		↕										
	[B,CS]Laminin[3]			–		↑										
	[A,F]Periostin[2]						↑									
Glycosaminoglycan	[B,C]Hyaluronan[3]			–		↑		↓								
Matricellular proteins	[A,CS]SPARC[2]			–		↕										
	[B,C]TSP-1[1]	↕		–		–		–								
	[B,C]OPN[3]			–		↑		↓								
Cell surface receptors	[A,S]Integrin-β1[1,2]					↑		↑	↓		↓					
	[A,SH]Integrin-β1[2]					↑										
	[A,S]Integrin-β3[1,2]					↑		↑	↓		↓					
MMPs	[A,S]MMP-2[1]			↑				↑	↑			↓	–	–	–	–
	[A,CS]MMP-3[1a,soluble]			–		↓										
	[A,C]MMP-7[2]							↑								
	[A,S]MMP-8[2p]			–				–	↑			↓	↓			↑
	[A,S]MMP-8[1]	↑	↑	↓		↓										
	[A,S]MMP-9[1]	↑	↑	↑		↓										
	[A,S]MMP-9[2]			↑				↑	↑			↓	→	↑	↓	↑
	[A,S]MMP-14[2p]							–	–			–	–			↑
	[A,S]MMP-13[2a]							↑	↑			↓	–			–
	[A,S]MMP-13[2p]							↓	-			↑	↑			↑
	[A,S]TIMP-1[1]			↑				↓	↓			↓	↑	↓	↑	↓
	[A,S]TIMP-1[2]			–				–	↑			–	–			↑
	[A,S]TIMP-2[1]			↑				↑	↓			–	–	–	↓	–
	[A,S]TIMP-2[2]			–				–	↑			↓	–			↑
	[A,S]TIMP-4[2]			–				↓	–			–	↑			–
Growth factors	[A,S]Ang II							↑								
	[A,W]Ang II									↑						
	[A,S]TGF-β1[1]	–	↑	↑		↑										
	[A,S]TGF-β2[1]	–	↑	↑		↓										
	[A,S]TGF-β3[1]	–	–	–		↑										
	[A,S]VEGF[1]			↑		↓		↓								
	[A,S]VEGF[1,2]		↓	↓		↓		↓	↓	↓						

[A]permanent occlusion, [B]ischemia/reperfusion,[C]C57BL/6 mice, [CS]C57/BL6/SV129 mice, [F]FVB mice, [S]Sprague–Dawley rats, [SH]129x black Swiss hybrid mice, [W]Wistar rats. [1]mRNA, [2]protein, [3]immunoreactivity, [a]active form, [p]pro form. ↑ increased and ↓ decreased compared to sham control, ↕ increased compared to control day 0, → unchanged, – very low levels

day 4 after MI. In a reperfused mouse model, collagen content peaks in the infarcted region after 14 days [44]. The increased expression of cross-linking enzymes, such as lysyl oxidase, during the maturation phase helps to increase overall LV stiffness [44, 45].

Glycoproteins

Intense fibronectin staining is observed in the infarcted area at day 2 post-MI in rats and steadily decreases from days 3 to 7 [46]. Consistent with an increase in total fibronectin,

there are five and tenfold increases in insoluble and soluble fibronectin, respectively, at day 3 in the LV infarct region [47]. Fragmentation of the laminin network has been seen after 1 h of occlusion and 24 h of reperfusion through 7 days of reperfusion [44]. Periostin is highly expressed in the infarct of both human and mouse hearts following MI [48].

Hyaluronan

Hyaluronan undergoes fragmentation into low molecular weight species shortly after ischemia is initiated [49]. The hyaluronan network in the infarcted area appears fragmented after 1 day of reperfusion, and increased hyaluronan expression persists through 7 days of reperfusion [44].

Matricellular Proteins

In mice, soluble and insoluble SPARC protein levels increase 60 and 36 %, respectively, in the LV infarct region at day 3 post-MI [47]. Tenascin C is also strongly induced in the infarcted LV of mice, consistent with a major role in stimulating myofibroblast differentiation during the early stages of tissue repair [50]. Murine TSP-1 is increased in the infarct region, particularly in the border zone. This localization in the border zone suggests a crucial role in suppressing post-MI inflammatory response, inhibiting angiogenesis, and limiting expansion of granulation tissue into the non-infarcted area [51]. OPN is detected in mouse infarcts after 1 day, peaks at day 3, and decreases after 7 days of reperfusion [44].

Integrins

An increase is observed in mRNA and protein expression of integrin β1 and β3 at the site of MI at day 3, peaks at day 7, and decreases thereafter [52]. Immunoblot analysis shows that levels of intact integrin β1 increase 3 days after MI [53].

MMPs

Following MI, all MMPs and TIMPs evaluated have at least modest changes, and these changes in MMP and TIMP levels facilitate ECM degradation and permit inflammatory cell recruitment to remove the necrotic cardiomyocytes.

MMP-2 mRNA in rats increases at day 1 post-MI, peaks at day 14, and decreases to baseline after 10 weeks post-MI [54]. The soluble active form of MMP-3 is downregulated twofold by day 3 in the LV infarct region [47]. MMP-7 protein levels are upregulated threefold in both remote and infarct regions at 7 days post-MI [55]. Increased MMP-8 mRNA can be detected 6 h post-MI in the infarct region and reaches a peak after 12 h [56]. In a rat permanent occlusion model, MMP-8 protein is found to increase after 2 weeks and remains high at 16 weeks post-MI [54]. MMP-9 is actively expressed within 24 h and remains elevated until week 16 post-MI [54, 56]. In a dog model, MMP-9 can be seen as early as 15 min after reperfusion and is localized primarily (but not exclusively) to neutrophils [57]. In a rat model of MI, MMP-14 protein levels are significantly increased only at 16 weeks post-MI [54]. TIMP-1 mRNA levels increase early, reaching a peak during 1–7 days, and stay elevated through day 21 post-MI [54, 58, 59]. TIMP-2 mRNA increases during the first 3 weeks post-MI, while protein levels increase at weeks 2, 5, and 16 post-MI [54]. In contrast, TIMP-3 expression is significantly reduced in the hearts of patients and in rodent models of MI [59]. TIMP-4 protein levels decrease at weeks 1 and 8 post-MI [54].

Growth Factors

Marked upregulation of TGF-β is seen in the post-MI scar region, particularly in the infarct border zone [56]. TGF-β_1 and TGF-β_2 mRNA levels increase steadily in the infarcted myocardium, beginning at 12 h after MI. TGF-β_2 mRNA expression reaches a peak at 24 h post-MI and declines thereafter. An increase in TGF-β_3 mRNA can be

detected at day 3 post-MI. Angiotensin II (Ang II) levels increase in the infarct area of the LV at 7 days post-MI and fall to below detection by day 28 [60, 61]. In a rat model of MI, VEGF protein and mRNA levels decline below baseline level beginning at 6 h after ligation and continue to decline over the 4-week time course evaluated [62].

ECM Changes with Aging and MI

Most animal studies of experimental MI use very young animals (e.g. 8–12-week-old mice), while MI in humans prevails in the older aged groups. In addition, LV remodeling outcomes post-MI worsen as a function of age. However, over the past years, there has been only limited research on ECM changes post-MI in an aging environment.

Following ischemia/reperfusion in mice, collagen deposition decreases in healing infarcts of senescent (>24-month-old) mice, compared to young (2–3-month-old) mice. Collagen content does not differ in the infarct regions of middle-aged 12-month-old mice compared to 3-month-old young counterparts, indicating that the differences in collagen begin after middle age [63, 64]. Of note, levels of cross-linked collagen are higher in middle-aged mice compared to young mice, which may provide an infarct that is more resistant to rupture but also stiffer [63].

OPN mRNA expression declines in the infarct regions of senescent mice that are over 2 years old, compared to young 2–3-month-old mice [64]. TGF-β_1, TGF-β_2, and TGF-β_3 mRNA levels do not differ significantly in the infarct regions of young 2–3-month-old and senescent over 24-month-old mice [64].

A common ground in ECM changes seen with aging, in the absence of clinically significant cardiovascular disease, and ECM changes seen post-MI include increased collagen content and cross-linking, increased expression of growth factors such as TGF-β, and an imbalance between MMPs and TIMPs in the LV. The elevation of collagen content, ratio of collagen type I to type III, and cross-linking contribute to increased LV stiffness. Meanwhile, the upregulation of TGF-β stimulates the synthesis of fibrous connective tissue in the myocardium, which also decreases the flexibility of the myocardium and increases myocardial stiffness. In addition, the imbalance between cardiac MMPs and TIMPs may result in cardiac dilation due to excessive matrix degradation in the LV. These changes in ECM components can lead to diastolic dysfunction and, eventually, heart failure. Essentially, aging changes the baseline myocardial environment, such that the LV response to injury will be different. One outcome of this is that the reestablishment of homeostasis will be more difficult in the aging LV.

Clinical Relevance

To date, only limited progress has been achieved in targeting specific ECM components in the post-MI heart. There are, however, a number of medications that are commonly used to treat MI patients that possess direct and indirect effects on the ECM. These therapeutic agents include angiotensin-converting enzyme (ACE) inhibitors, Ang II receptor antagonists, aldosterone antagonists, beta-adrenergic receptor blockers, and statins [65, 66]. In Table 25.3, we list the effects of post-MI medications on ECM proteins.

Table 25.3 Effects of current therapies in post-MI patients on the expression and production of ECM proteins

Medication	Effect on ECM proteins
ACE inhibitors	↓ Collagen type I ↑ Collagen type III ↑ Fibronectin ↓ Osteopontin ↓ Thrombospondin-4 ↓ MMP-1, -2, -3, -9
Angiotensin II receptor antagonists	↓ Collagen type I ↑ Thrombospondin-1 ↓ Fibronectin ↓ MMP-2, -3, -9
Aldosterone antagonists	↓ Collagen type I and III ↓ Fibronectin ↓ MMP-1, -2, -9
Beta-blockers	↓ Collagen type I and III ↓ Collagen degradation ↓ Fibronectin ↓ Thrombospondin-4 ↓ MMP-2, -9
Statins	↓ Collagen type I ↓ MMP-9

↑ increased, ↓ decreased

ACE inhibitors exert positive effects on post-MI mortality and morbidity rates [67]. ACE inhibitors decrease fibronectin levels in the plasma and improve LV function [68]. ACE inhibitors also mollify the progression of fibrosis by modulating collagen, OPN, and proteoglycan synthesis as well as blocking MMP activity [69–73]. Many ACE inhibitors, due to their structural specificity, have high affinity for gelatinases and act as direct and indirect inhibitors of several MMPs [74, 75].

Ang II receptor antagonists are used as an alternative approach to blocking the renin–angiotensin–aldosterone system. Ang II receptor antagonists selectively inhibit Ang II by competitive antagonism for the Ang II receptors [76]. Ang II receptor antagonists indirectly alter several ECM components. Specifically, Ang II receptor antagonists upregulate the expression of TSP-1 and downregulate the expression of collagen type I, fibronectin, MMPs, and connective tissue growth factor [77–79]. Ang II receptor antagonists attenuate cardiac remodeling in experimental in vivo models of MI and in clinical trials in post-MI patients [80, 81].

Aldosterone antagonists block aldosterone receptors leading to a decreased reabsorption of Na^+ and increased secretion of K^+, Mn^{2+}, and Ca^{2+} ions [82]. Aldosterone antagonists inhibit aldosterone-associated myocardial fibrosis and reduce collagen turnover [83, 84]. In vivo studies suggest that aldosterone antagonists reduce mRNA levels and protein expression of fibronectin, vimentin, and MMPs, decrease collagen types I and III mRNA levels, and decrease cardiac fibrosis to improve LV function [85, 86].

Beta-adrenergic antagonists inhibit β-adrenergic receptors (B1, B2, and B3) [87]. Beta-blockers have beneficial effects on ECM remodeling by inhibiting collagen and fibronectin expression, therefore reducing fibrosis [88, 89]. Beta-blockers also lower TSP levels post-MI [90]. These effects correlate with experimental data showing that beta-blockers reduce MMP activity to prevent ventricular stiffening and cardiac dysfunction [91].

Statins reduce high cholesterol levels, oxidative stress, and vascular inflammation, inhibit smooth muscle cell proliferation and migration, and are broadly used in post-MI patients [92]. In vivo models demonstrate the ability of statins to decrease collagen I synthesis by cardiac fibroblasts [93]. Similarly, in humans, statins have been reported to attenuate collagen synthesis and show anti-fibrotic effects by reducing the pro-fibrotic growth factor secretion [94]. In vitro studies also suggest statins to attenuate the production of MMP-9 in human cardiac fibroblasts [95].

In clinical practice, post-MI patients usually receive a combination of the above therapies. These combinations, in turn, could possibly act in synergism to improve the effects on ECM.

Conclusion

Aging changes the baseline cardiac ECM environment in subtle but significant ways, and the LV response to injury is different in the old compared to the young myocardium as a consequence of these changes. A better understanding of age-related changes in the structural and functional properties of cardiac ECM will likely reveal novel therapeutic options to improve outcomes in elderly patients with MI.

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Calcium-Handling Defects and Changes in Cardiac Function in the Aging Heart

26

Adriana Adameova, Nirankar S. Neki, Paramjit S. Tappia, and Naranjan S. Dhalla

Introduction

The aging state as reflected by the decline of functional capacity and stress resistance is different in every individual and has been referred to as the disablement process [1]. While many definitions for aging have been suggested, there is still no general agreement on the age at which a person becomes old. According to the World Health Organization WHO, senility is defined as the age of >60 years, while in the USA, it is considered as 65 years of age. However, gerontologists have distinguished three subsets of senility: younger older people (60–74 years of age), older people (75–85 years of age) and very old people (>85 years of age) [2]. It is known that the chronological age does not in general represent the "real" age of an individual, the so-called biological age; however, in view of the existing literature on aging for both females and males, individuals at 70 years or older can be considered among the aging population. Older age is considered to be a risk factor for many diseases, including cardiovascular disease (CVD) [3, 4]. Clinical studies have revealed that more than 80 % of all acute myocardial infarction (MI)-related deaths occur in persons aged 65 years or older [5–7] and with each 10-year increase in age, the odds for death in hospital following coronary artery event is augmented by 70 % [8]. In addition, the elderly account for more than 75 % of patients with heart failure and greater than 70 % patients with congestive atrial fibrillation [9]. These data imply that intrinsic cardiac aging per se is a major risk factor for CVD and is defined as slowly progressive age-dependent degeneration and decline in function that increases the vulnerability of the heart to stress [10].

It is estimated that by the year 2035, one in four of the global population will be 65 years of age or older. Thus, in view of the development of aging-associated cardiovascular complications, understanding how the aging process contributes to changes in cardiac structure and function is an enormous challenge for the cardiovascular research community. Indeed, it is difficult to study the exact mechanisms of effects of aging on

A. Adameova, PharmD, PhD
Department of Pharmacology and Toxicology, Comenius University, Odbojarov 10, Bratislava 832 32, Slovak Republic

N.S. Neki, MD, FRCP, FACP (USA), FAMS
Department of Internal Medicine, Government Medical College and Guru Nanak Dev Hospital, House No. 88, Street 4 Gopal Nagar, Majitha Road, Amritsar 143001, Punjab, India

P.S. Tappia, Ph.D.
Office of Clinical Research, Asper Clinical Research Institute, St. Boniface Hospital Research, CR3129-369 Tache Avenue, Winnipeg, MB, Canada R2H 2A6

N.S. Dhalla, PhD, MD (Hon), DSc (Hon) (✉)
Department of Physiology, Faculty of Medicine, Institute of Cardiovascular Sciences, University of Manitoba, St. Boniface Hospital Research, 351 Tache Avenue, Winnipeg, MB, Canada R2H 2A6
e-mail: nsdhalla@sbrc.ca

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the heart per se, because many comorbidities, including diabetes, hypertension, and dyslipidemia, exist in older individuals and thus can confound the aging process. In addition, factors that can contribute to the age-induced changes in cardiac structure and function such as ischemia and lack of physical activity should also be considered in defining the mechanisms for reduced function of the aging heart. Likewise, gender (sex hormones) may also have a significant impact on the progression of structural and functional changes in the aging heart. Therefore, distinguishing between the normal aging-induced changes and alterations due to disease is an important step in defining the mechanisms responsible for depressed function of the aging heart.

Aging-Induced Changes in Heart and Their Impact on Cardiac Function

A diverse range of aging-induced morphological and cellular changes has been identified in the senescent heart. Epicardial fat deposition and intracellular lipofuscin deposits appear to be symptomatic aging-induced changes without any overt adverse effects on heart function [11, 12]. On the other hand, aging-induced changes in myofilament activation, gene expression, lower capillary density, denervation, development of cardiac fibrosis, and reduced adrenoceptor sensitivity have been proposed as likely candidates for reduced function of the aging heart [10, 12–15]. Lakatta and Sollott [4] have suggested that changes in cardiac output are developed as an adaptive response to greater arterial stiffening. In the elderly, heart rate has been found to be lower, whereas left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVSV) are increased. These changes are accompanied by elevated left ventricular end-diastolic pressure (LVEDP), decreased maximal rate of pressure development (+*dP*/*dt*) and decay (−*dP*/*dt*), as well as blunted ejection fraction, indicating a significant impairment of cardiac contractile function and cardiac remodeling in the aging heart [7, 16–19]. It has also been shown that aging-induced cardiomyocyte hypertrophy occurs due to increased hemodynamic load and neurohumoral factors. Myocyte length and volume as well as the amount of collagen in the myocardial tissue progressively increase with senescence. On the other hand, the number of cardiomyocytes in the left ventricle of the aging heart has been reported to be reduced [16, 20] as a consequence of necrosis, apoptosis, impaired autophagic process, and reduced cardiomyocyte renewal [21].

Aerobic capacity in the heart declines with advancing age that is attributable to impaired redistribution of blood flow to working muscles, impaired oxygen extraction per unit muscle, a decrease in muscle mass and increase in body fat [4]. Interestingly, cardiac dysfunction due to aging has been reported to exhibit similar characteristics as of the failing heart due to MI [22]. Although abnormalities in mitochondrial function, oxidative stress, and loss of cytoprotective signaling have been implicated in the phenotype of the aging heart, altered Ca^{2+}-homeostasis seems to play a crucial role in this process, and in fact both these aspects are closely related to each other. Indeed, increased production of mitochondrial reactive oxygen species (ROS) has been shown to result in defects in cardiomyocyte Ca^{2+}-handling and subsequent disturbances in excitation–contraction coupling (ECC), excitation–metabolism coupling (EMC), and excitation–transcription coupling (ETC) (Fig. 26.1). The role of fluctuation of Ca^{2+} in the pathogenesis of cardiac dysfunction in the aging heart is supported by findings from studies investigating ischemia/reperfusion injury and heart failure, showing that intracellular Ca^{2+} overload results in mechanical and electrical dysfunction [23, 24]. Thus, impairment of Ca^{2+}-homeostasis may be one of the mechanisms for reduced performance of the aging heart.

Altered Ca^{2+}-Homeostasis in the Aged Heart

The kinetics of cellular reactions, which are involved in ECC in the aging heart, has been shown to be reduced. As a consequence, the

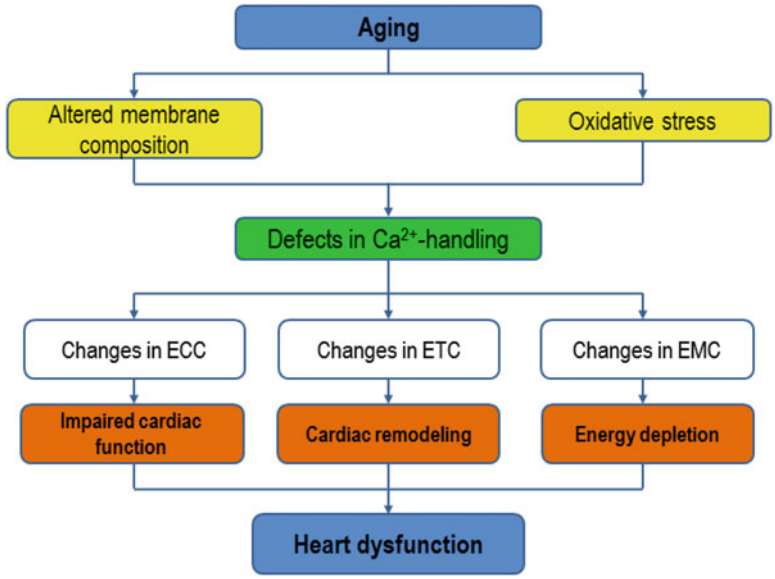

Fig. 26.1 *Defects in cardiomyocyte Ca^{2+}-handling and subsequent disturbances in excitation-coupling mechanisms leading to heart dysfunction*. It is proposed that changes in membrane lipid composition as well as the development of oxidative stress lead to Ca^{2+}-handling abnormalities in the aging heart. Thus, the occurrence of intracellular Ca^{2+}-overload plays a critical role in inducing alterations in gene expression, myocardial metabolism, and cardiac function in the aging heart. *ECC* excitation–contraction coupling, *EMC* excitation–metabolism coupling, *ETC* excitation–transcription coupling

action potential duration and contraction are prolonged. An increase in the magnitude of L-type Ca^{2+}-current (I_{Ca}) and Ca^{2+}-transient amplitude in the aging heart [25, 26] can contribute to the prolonged relaxation time of cardiomyocytes in the senescent heart. A slower inactivation of I_{Ca} in addition to the reduction in peak transient outward K^+ current can provide an explanation of prolonged action potential observed in the aging heart [27, 28]. Interestingly, unlike in male mice, no age-related changes in cardiomyocyte I_{Ca} characteristics were observed in female mice [29]. In contrast, the peak I_{Ca} and integrated Ca^{2+} entry were significantly greater in aged than in younger cardiomyocytes isolated from female sheep [25]. In addition, molecular studies have also revealed a reduction in the density of L-type Ca^{2+} channels in the sarcolemmal (SL) membrane of the aging heart [30].

The prolonged relaxation time of the senescent heart may also be related to a transient increase in cytosolic Ca^{2+} due to diminished sarcoplasmic reticulum (SR) storage that prolongs contractile protein activation. Prolongation of Ca^{2+} elevation can occur due to the lower protein levels of SR Ca^{2+}-pump (SERCA2) [3, 31] reflecting decline in expression of SERCA2 gene along to a reduced SR Ca^{2+}-pump activity [32–35]. These changes suggest that the lower SR Ca^{2+}-uptake may, in part, explain the impaired relaxation of the senescent heart. In support of this contention, overexpression of SERCA2a in the aging heart has been shown to improve cardiac function [36]. However, it should be pointed out that data regarding the changes in SERCA2 due to aging are not consistent. Although reduced SERCA activity has been reported, the protein levels were found to be unchanged in the aged heart [34, 35]. In addition, recently published data have revealed that despite no changes in SERCA2 protein expression in aged cardiomyocytes, diastolic dysfunction was still evident in C57BL/6 mice [26]. These changes in gene and protein expression of SERCA2 are unlikely to be related to species. Moreover, inconsistencies in SERCA2 density have also been seen in different

mice strains (FVB versus C57BL/6). Although similar features were detected in the failing cardiomyocytes from different strains of mice, Western blot analysis revealed different results regarding protein contents [26, 31]. Importantly, Ca^{2+}-calmodulin kinase II (CaMKII)-mediated phosphorylation of phospholamban (PLB), which leads to release of the inhibitory action on the SERCA2, was also significantly decreased by 25–40 % in the aged compared with adult rat hearts. In addition, CaMKII-mediated phosphorylation of Ca^{2+}-release channel or ryanodine receptor (RyR2) was also downregulated with senescence. The total amount of CaMKII was also approximately 50 % lower and the stimulatory effect of calmodulin on Ca^{2+} uptake was also reduced in the aging heart [34]. This suggests that not only intrinsic properties of the SR Ca^{2+} regulatory proteins are changed, but their activation by CaMKII is also impaired in the senescent heart.

In addition to SERCA, the Na^+–Ca^{2+} exchanger (NCX) at the SL membrane is considered to be another mechanism for lowering the cytoplasmic concentration of Ca^{2+}. As with other Ca^{2+}-handling proteins, changes of NCX protein in the senescent heart are conflicting. In rats, the cardiac mRNA level for NCX has been found to be initially decreased and then increased with the progression of age [37]. On the other hand, the NCX protein levels have been observed to be downregulated in the hearts failing due to aging [18, 38, 39]. No differences in the gene and protein expression of NCX between young and aged hearts have been reported [15, 31, 33]. A recent study has revealed an age-related increase in NCX (forward mode activity) that may provide an explanation for the late action potential prolongation [40]. From the information available in the literature, it appears that the increase in SL NCX may serve as an adaptive mechanism for lowering the cytoplasmic concentration of Ca^{2+} at initial stages of aging myocardium, whereas depression in its activity may contribute in the development of intracellular Ca^{2+}-overload at late stages of the aging heart.

Ca^{2+}-release from the SR is mediated by the RyR as well as through the inositol trisphosphate receptor ($InsP_3R$); any changes in their expression and function can cause systolic and diastolic dysfunction. The protein content of the total RyR [41] and its CaMKII-mediated phosphorylated form [34] have been reported to be reduced in the aging heart. In accordance, in senescent rat cardiomyocytes lower Ca_i^{2+}-transient amplitude has been observed, which was also correlated with a reduced Ca^{2+} content in the SR [42]. Likewise, frequency of spontaneous Ca^{2+} sparks in cardiomyocytes isolated from senescent hearts has been shown to be increased [42, 43]. This would seem to suggest that the increased Ca^{2+} leak from the SR may explain both systolic and diastolic dysfunction due to a lower Ca^{2+}content available for release and a slower decrease of the Ca_i^{2+} transient, respectively. Although an impaired function of RyR in the aging heart has been reported, it appears to be independent of any age-related differences in gene transcription [33] and protein expression levels [34]. Aging causes an increase in $InsP_3R$ mRNA level that has been suggested to account for the age-related enhanced susceptibility of $InsP_3R$ to proteolytic degradation that is compensated for by increased synthesis of $InsP_3R$ protein through increased $InsP_3R$ mRNA [35].

The myocardial abundance of other Ca^{2+}-handling proteins, which regulate Ca^{2+} homeostasis within the SR (calsequestrin and PLB), is reported to be unchanged during the aging process [34]. On the other hand, the Na^+–K^+ -ATPase activity and number of ouabain-binding sites in the SL membrane have been found to be decreased in the senescent heart, which was also found to be related to a lower threshold for onset of arrhythmias [44]. Furthermore, the number of ventricular and supraventricular premature beats and the incidence of atrioventricular block are increased in the senescent heart [45]. Although Na^+–K^+ -ATPase does not directly influence cytosolic Ca^{2+} levels, inhibition of Na^+–K^+ -ATPase by cardiac glycosides leads to Ca^{2+} influx and produces positive inotropic effects. Thus, decreased density of SL Na^+–K^+ -ATPase could explain cardiac dysfunction and a higher arrhythmogenicity of the aging heart. From the foregoing discussion, it is evident that intrinsic cardiac aging is a

complex of Ca^{2+}-dependent events that can underlie impaired mechanical function, increased sensitivity to arrhythmias, and cell death.

Mechanisms Causing Disturbances in Ca^{2+}-Homeostasis due to Advancing Age

Cardiomyocytes of senescent hearts exhibit a reduced threshold for abnormalities due to Ca^{2+} loading under conditions known to increase Ca^{2+}-influx such as excessive production of catecholamines, reperfusion of postischemic tissue, and oxidative stress [24, 46]. The relative Ca^{2+} intolerance in the aging heart is mainly caused by changes in the Ca^{2+} regulatory proteins, which may, in part, be due to altered gene expression, activity, and changes in the membrane composition. It has been shown that with age, the $n-6$ polyunsaturated fatty acid (PUFA) content of rat cardiac cell and inner mitochondrial membrane is increased, whereas $n-3$ PUFA content is decreased. However, it remains to be demonstrated whether alterations in mitochondrial membrane with respect to PUFA content are responsible for inducing changes in mitochondrial function. Nonetheless, these changes are associated with abnormal cell Ca^{2+} balance that results in increased Ca^{2+}-dependent arrhythmogenesis during reperfusion following ischemia [47]. In addition to changes in membrane composition, intracellular generation of ROS is likely to contribute to impaired Ca^{2+}-homeostasis as a consequence of alterations in the membrane composition of both SL and SR. In fact, perfusion of isolated rabbit hearts with hydrogen peroxide has been shown to increase cytosolic Ca^{2+} levels [48]. With respect to the aged hearts, it has been reported that increased ROS formation by mitochondrial electron transport chain or NADPH oxidase promotes a pro-oxidative shift in redox balance [49, 50]. In fact, the content of thiol groups, as a marker of oxidative damage of proteins, has been found to be decreased, while lipid peroxidation measured as conjugated diene formation has been shown to increase in the hearts of senescent rats [51]. On the other hand, it has been shown that lifelong constitutive overexpression of antioxidative enzymes prevents age-dependent diastolic dysfunction indicating that oxidative stress is involved in the pathogenesis of cardiac dysfunction of the aging heart [10, 52]. Thus, it can be postulated that increased production of ROS in the aging heart may interact and damage various cellular components, including Ca^{2+} regulatory proteins, and thereby contribute to alterations in Ca^{2+}-homeostasis and subsequent Ca^{2+}-dependent events including proteolysis, energy depletion, and cellular necrosis.

Aging-induced ROS production has been associated with depression of SERCA2 activity [53, 54]. Likewise, Rueckschloss et al. [15] have shown increased NADPH oxidase activity and expression, decelerated shortening/relengthening, and the increased amplitude of Ca^{2+}-transients in the aged cardiomyocytes. These changes were accompanied by a reduced Ca^{2+} sensitivity of myofilaments, but not by altered density of RyR2, PLB, calsequestrin, nor L-type Ca^{2+}-channel, indicating that aging changes the contractile phenotype of cardiomyocytes involving altered Ca^{2+}-homeostasis and myofilament function. Of note, reduced Ca^{2+} sensitivity of myofilaments of aged cardiomyocytes was reversed by the superoxide scavenger tiron. In addition, pharmacological inhibition of NADPH oxidase by apocynin normalized deceleration of shortening/relengthening of aged cardiomyocytes, clearly indicating a link between superoxide formation, age-dependent alterations in Ca^{2+}-handling and contractility [15]. Although, in this study, a short-term antioxidant treatment attenuated age-dependent alterations in cardiomyocyte mechanical function, the efficacy of antioxidants in older humans to correct cardiac dysfunction is questionable as clinical trials have failed to show consistent beneficial effects of vitamin E on age-induced myocardial changes [55]. In addition to characteristic changes in Ca^{2+}-handling proteins, the increased vulnerability of the senescent heart to stress (ischemic events) may also be linked to a concomitant attenuation of endogenous cytoprotective mechanisms [56, 57].

Potential Interventions Leading to Prevention and Delay of Cardiac Dysfunction due to Age

Interventions that can partially reverse some of the reported changes of the aging heart are summarized in Table 26.1. For example, modification of lifestyle has been shown to improve cardiac function in the elderly. In fact, exercise training of sedentary old mammals produced an upregulation of the SERCA and a faster cardiac relaxation [58]. In addition, it has been suggested that the risk of Ca^{2+}-overload in the senescent heart can be prevented by antioxidants to reduce oxidative stress and by dietary measures to reverse altered membrane composition through normalization of the $n-6$ PUFA to $n-3$ PUFA ratio [59, 60]. Likewise, caloric restriction (40 % energy reduction) has recently been reported to ameliorate age-associated deterioration in intracellular Ca^{2+} -handling and enhance autophagy [61]. It has been suggested that caloric restriction can upregulate sirtuins (SIRT). SIRT3, located in the mitochondria, has been found to abolish aging-induced oxidative stress due to activation of MnSOD [59]. In addition, SIRT3 is likely to inhibit cardiomyocyte death because of the modulation of cyclophilin D, a modulatory and structural protein of mitochondrial permeability transition pore (mPTP), the opening of which induces apoptosis. SIRT3 activity progressively declines with the aging process and leads to hyperacetylation of cyclophilin D, which increases mitochondrial permeability transition and thereby induces cardiomyocyte apoptosis [62]. Thus, it appears that activation of SIRT3 is necessary to prevent impairment of mitochondrial function as well as cardiac dysfunction due to aging. Maintenance of endogenous cardioprotective mechanisms, which are activated during preconditioning and postconditioning in a healthy heart but attenuated in the senescent heart [56, 57], may be additional targets to delay aging-induced defects in heart function. In addition, gene therapy, pertaining to normalization of SERCA expression may also be a promising intervention to restore Ca^{2+} regulatory proteins in the senescent heart. Figure 26.2 summarizes the major consequences of aging-induced Ca^{2+}-overload and a cascade of events that leads to heart dysfunction.

Table 26.1 Interventions that can prevent or delay cardiac aging

Intervention	Mechanisms underlying attenuation of cardiac dysfunction due to age
Diet	Increasing the content of omega-3 PUFA in cellular membrane in which Ca^{2+} regulatory proteins reside
Caloric restriction	Attenuation of oxidative stress due to increase in activity of MnSOD Inhibition of apoptosis due to prevention of mPTP opening
Physical activity	Increasing SERCA activity/expression and improvement of cardiac relaxation
Antioxidants	Attenuation of oxidative stress by reducing ROS production and/or direct ROS scavenging activity

Conclusion

Understanding the effects of aging on cardiovascular system assumes greater clinical relevance as the global population ages. Although considerable effort has been made to identify the mechanisms of cardiac remodeling and dysfunction in the senescent heart, the molecular basis for such age-related changes is not fully understood. The interpretation of some of the reported changes in the senescent heart is contentious because of limited knowledge on the interaction between age, comorbidities, lifestyle-related risk factors, and diminished intrinsic endogenous cytoprotective mechanisms. Although a number of different mechanisms have been suggested to play a role in the pathogenesis of the aging heart, changes in Ca^{2+}-homeostasis appear to be crucial in the increased sensitivity to the development of myocardial abnormalities. Alterations in Ca^{2+}-handling proteins (Ca^{2+} channels and Ca^{2+}-pumps located at both SL and SR membranes as well as NCX in the SL membrane) at the molecular level as well as protein density and activity can underlie cardiac systolic and diastolic dysfunction and prolongation of the action potential duration and induce hypertrophic and apoptotic processes. It is

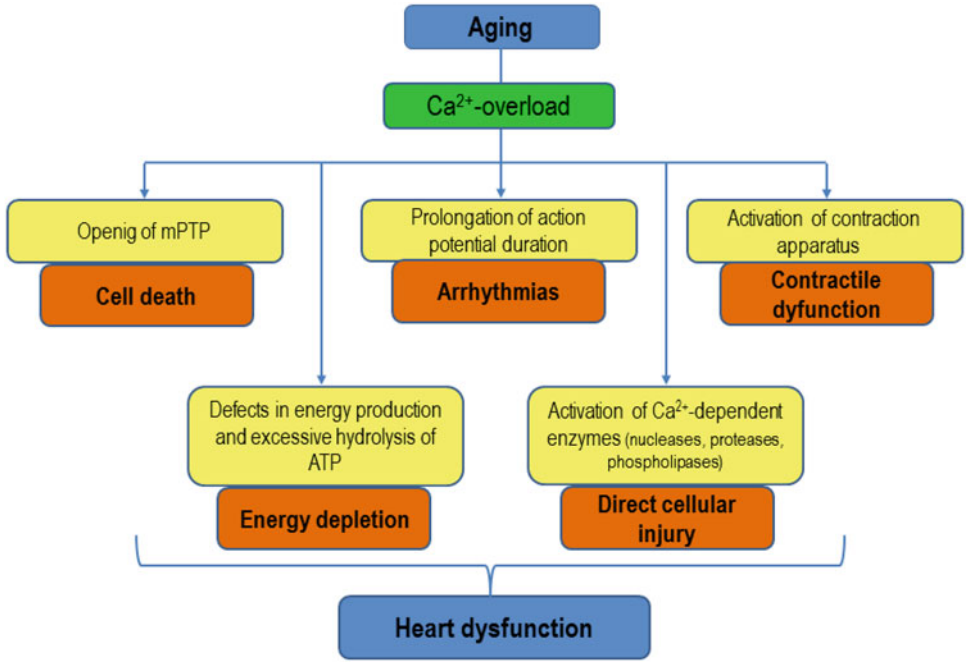

Fig. 26.2 *Mechanisms of Ca^{2+}-overload induced defects leading to impaired function of the aging heart.* The development of cardiac dysfunction in the aging heart is proposed to be occurring due to the development of intracellular Ca^{2+}-overload as a consequence of defects in Ca^{2+}-handling proteins in cardiomyocytes. A wide variety of mechanisms such as apoptosis, necrosis, energy depletion, proteolysis, and arrhythmias are associated with cardiac dysfunction due to intracellular Ca^{2+}-overload

assumed that altered Ca^{2+} homeostasis due to aging is closely related to mitochondrial dysfunction, sensitivity to oxidative stress, and altered membrane composition, and thus detailed insights into these processes might advance our understanding of the biology of senescence. Particularly, alterations in both SR and SL membranes due to oxidative stress may be of critical importance in determining their Ca^{2+}-handling characteristics of aging cardiomyocytes. Such information will be of value for the development of pharmacological interventions to prevent or reduce the higher sensitivity of the aging heart to ischemic injury and failure.

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Integrins: Implications for Aging in Heart Failure Therapy

27

Laura L. Daniel, William L. Joyner, Mahipal Singh, and Krishna Singh

Introduction

Integrins are multifunctional heterodimeric transmembrane receptor proteins comprised of α and β subunits [1]. They are capable of signaling bidirectionally across the cell membrane and are the main receptors used for cell binding and responding to changes in the extracellular matrix (ECM). Signals originating inside the cells can influence the ability of integrins to bind to the ECM. Integrins are found in most nucleated cell types and are involved in many signaling processes such as development, immune response, wound healing, cell migration, cell proliferation, and survival [2]. In the heart, integrins are vital for the development of heart and its function. They respond to a variety of pathophysiological stresses such as pressure overload and myocardial infarction and play a significant role in myocyte survival [3]. Here we will describe the general structure and function of integrins, discuss age-associated changes in the expression of integrins in the heart, and evaluate the role of integrins in myocardial remodeling in failing heart.

L.L. Daniel, BS • W.L. Joyner, PhD • M. Singh, PhD
Department of Biomedical Sciences, East Tennessee State University, Johnson City, TN, USA

K. Singh, PhD (✉)
Department of Biomedical Sciences, East Tennessee State University, PO Box 70582, Johnson City, TN 37614, USA
e-mail: singhk@etsu.edu

General Structure and Function

Integrin heterodimer is composed of noncovalently associated one α and one β subunit. Each polypeptide consists of >1,600 amino acids [1, 4]. They contain a large extracellular domain of 700–1,100 amino acids, a small single-pass transmembrane domain, and a short cytoplasmic domain of 20–60 amino acids [5]. Eighteen different α subunits have been identified in mammals, each one containing ~1,000 amino acids. Eight β subunits have been identified in mammals, with a size of ~750 amino acids. Together, these subunits can form >24 distinct pairs [6]. The partnership between specific α and β subunits determines the ligand specificity of the large extracellular domain which binds a variety of different components of the ECM. For example, pairing of α_3, α_6, or α_7 subunit with the β_1 subunit forms the major laminin-binding receptors in mammals. Pairing of α_1, α_2, α_{10}, or α_{11} subunits with the β_1 subunit forms collagen receptors. In addition, α_{IIb}, α_v, α_5, and α_8 can combine with β_1, β_3, β_5, β_6, and β_8 subunits to form receptors for ECM proteins that contain a ARG-GLY-ASP (RGD) motif [4]. Integrin expression changes depending on the type of cell, the developmental stage, or the pathological status [7]. The cytoplasmic domain of integrin is linked to actin-based microfilament system which gives the cell a mechanical connection to the ECM [4]. Binding of the cytoplasmic domain of integrins to the cytoskeletal proteins and to the components of the ECM

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allows integrins to function as mechanotransducers. Mechanotransduction is the process of sensing an external mechanical force and converting it into an internal cellular response. Being able to sense mechanical forces and respond is important in the cardiovascular system. Cardiac hypertrophy, atherosclerosis, atrial fibrillation, heart failure, and hypertension are all associated with disruption in mechanotransduction [8].

Integrins are bidirectional signaling molecules. When integrins bind to ECM proteins, they can transmit a signal to the inside of the cell with the help of non-receptor kinases; this is termed "outside-in" signaling. This could be a signal for survival, proliferation, or migration. It has been established that integrin binding to the ECM is necessary to transmit survival signals via PI3-kinase and Akt and also to stimulate cell cycle progression via ERK1/2 and cyclin D1 [4]. Following mechanical stimulation, integrins take part in the formation of focal adhesion complex (FAC) which contains an upward of 50 different proteins [9]. Among those proteins are a couple of non-receptor tyrosine kinases, focal adhesion kinase (FAK) and Src, which play a major role in transmitting signals from the outside environment via their link with integrins [10]. In addition, integrins are also bound to a variety of cytoskeletal proteins within the FAC, such as talin, vinculin, paxillin, and $p130^{CAS}$ [11, 12]. When integrins bind their ligand, autophosphorylation of FAK at Y397 occurs, providing a docking site for Src which allows it to phosphorylate FAK at Y576 and Y577, increasing the activation of FAK. Src can also create a SH2 domain on FAK by phosphorylation of FAK at Y861 and Y925. Proteins such as Grb2 will bind the SH2 domain of FAK, linking FAK activation to Ras and the MAPK pathway [10].

In addition to "outside-in" signaling, integrin binding to ECM proteins is regulated by intracellular signals, termed "inside-out" signaling. Binding of a ligand such as growth factor to its receptor initiates an intracellular signaling cascade which can impact expression of integrins, their clustering patterns (avidity), and also their affinity for their ligand. Under normal conditions, some integrin heterodimers do not productively bind their ligand. This is necessary for cells in the immune system. For example, under normal conditions, leukocytes do not bind to endothelial cells; they will roll along the vasculature via selectins. β_2 integrins are located on leukocytes and exist in a closed conformation in which they do not bind their ligand. Once the leukocytes are exposed to chemokines or other inflammatory mediators, the "inside-out" signaling activates the integrins, enabling them to bind their ligand located on the endothelial cells [13]. Integrin activation is in part due to the translocation of talin to the cytoplasmic tail of the β integrin which causes a conformational change in the integrin receptor allowing it to bind its ligand [14].

Integrins are capable of modulating the signaling cascades activated by growth factors, such as platelet-derived growth factor receptor, epidermal growth factor receptor, insulin-like growth factor-1 receptor, and vascular endothelial growth factor receptor [15]. They can play a major role in the activation of growth factors such as transforming growth factor-β (TGF-β). Inactive TGF-β has an integrin-binding domain and an ECM-binding domain. Evidence has been provided that interaction of integrins such as $\alpha_v\beta_6$ and $\alpha_v\beta_8$ promotes TGF-β activation. In turn, TGF-β activation increases the expression of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, and several β_1 integrin partners [16]. Mice lacking β_6 integrin subunit or a TGF-β knock-in mutation of ARG-GLY-GLU (RGE) for RGD, which prevents integrins from binding to the RGD sequence, have a similar phenotype of TGF-$\beta1^{-/-}$ mice, suggesting that integrin binding to TGF-β might be necessary for its activation [16].

Integrin Expression in the Heart

The α integrin subunits that are expressed by myocytes are α_1, α_3, α_5, α_6, α_7, α_9, and α_{10}. Cardiac myocytes predominantly express β_1 subunit [3]. However, expression of β_3 is described in feline myocytes [17]. The expression of integrins in the heart changes depending on the developmental or the pathological state of the heart. For example, α_1 and α_5 are expressed in fetal and neonatal cardiac myocytes but are not in the adult cardiac

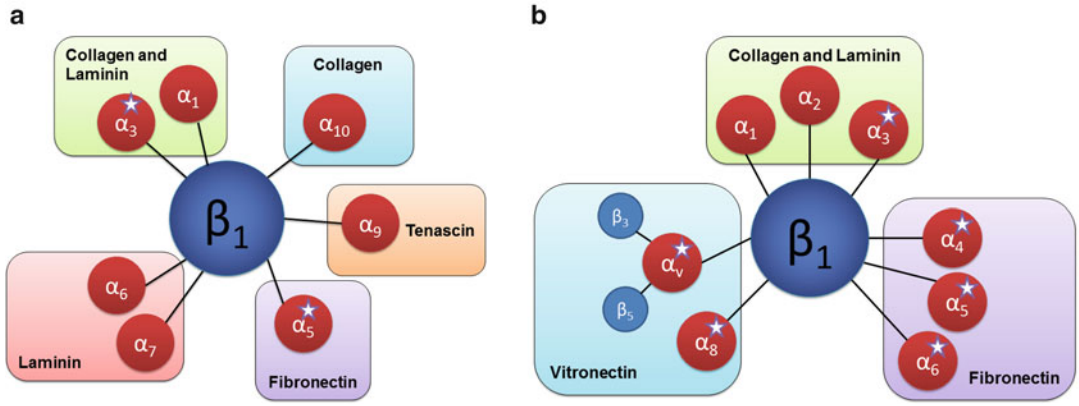

Fig. 27.1 Diagram illustrating integrin heterodimers and their ECM ligands in cardiac myocytes (**a**) and fibroblasts (**b**). *Star* represents integrin subunits for fibronectin

myocytes. Pressure overload, however, induces expression of these integrins in the adult heart [3]. The main binding partner of the α subunits in myocytes is β_{1D}. Integrin β_{1D} is a splice variant of β_1 integrin. It has a unique cytoplasmic domain of 50 amino acids with the last 21 amino acids being replaced by 24 amino acids encoded by an additional exon. Of these 24 amino acids, 11 are conserved when compared to β_{1A} isoform, but 13 are unique [18, 19]. Both β_{1D} and β_{1A} are shown to be functionally similar with regard to integrin signaling in skeletal muscle cells. Adenovirus-mediated expression of either β_{1A} or β_{1D} augmented phenylephrine-induced hypertrophic response in neonatal cardiac myocytes, whereas overexpression of free β_1 integrin cytoplasmic domains, representing β_1 shedding, inhibited the effects [20]. The integrins that can be found in cardiac fibroblasts include α_1, α_2, α_3, α_4, α_5, α_8, α_v, β_1, and β_3. Of note, certain integrin subunits remain specific to certain cell types. For example, α_v and α_2 are expressed by fibroblasts but are not expressed by myocytes [3]. Figure 27.1 describes the ligand binding of integrins to the different components of ECM in myocytes and fibroblasts.

In cardiac fibroblasts, integrins are found at focal adhesion points [21]. In myocytes, integrins are localized to the costameres and in the intercalated discs [22]. The cytoskeleton and the ECM are connected together through integrins providing proper placement of cardiac myocytes, a conduit for transmitting information about mechanical forces, and support to the contracting cardiac muscle cells [23]. Because of the importance of integrins in anchoring cardiac myocytes to the ECM, they have been the focal point of many studies involving structural remodeling both in the development and disease.

The Aging Heart and Integrins

Development of heart disease is a large concern for the elderly. In 2006 ~80 % of all deaths for individuals over 60 years were attributed to cardiovascular diseases in the USA. The causes of heart failure are multifactorial. Accumulation of collagen (fibrosis) within the ECM is considered as a major contributor of reduced ventricular compliance [24]. The increase in fibrosis not only affects the mechanical properties of the heart but has also been proposed to affect the myocardial electric conductivity which may lead to arrhythmias and sudden cardiac death. Since integrins mechanically couple the ECM with intracellular cytoskeleton, their disruption is proposed as a potential target for the arrhythmias [25]. With numerous changes occurring in the ECM of aging heart, it is reasonable to speculate age-associated changes in integrin expression are an underlying cause. Aged Balb-c mice express higher levels of α_1 and α_5 integrins and decreased β_1 integrin when compared to middle-aged or

young mice. The aged mice also exhibit increased levels of collagen and fibronectin [26]. It is interesting to note that fibronectin is the initial matrix upon which the collagen is laid [27]. Age-associated decrease in β1 integrin was also observed in the myocardium of Wistar-Kyoto rats [28]. Adult cardiac fibroblasts express lower levels of β1 integrins when compared to neonatal cardiac fibroblasts [29]. Aged myocytes exhibit decreased levels of β_1, α_3, and $\alpha_3\beta_1$ integrins when compared to adult myocytes [30].

Integrins and Myocardial Remodeling

Change in size, shape, structure, and function of the heart after an injury to the heart is described as myocardial remodeling. Myocardial remodeling typically occurs following myocardial infarction (MI). However, it also occurs following mechanical overload as well as hypertensive cardiomyopathy, valvular cardiomyopathy, familial hypertrophy, and dilated cardiomyopathy [31]. MI is the leading cause of congestive heart failure, and its prevalence increases with age [32]. The remodeling process includes infarct expansion, hypertrophy, fibrosis, and ventricular dilation. The following sections describe expression and role of integrins in myocardial remodeling, including their role in mechanotransduction, and myocyte hypertrophy and apoptosis.

Integrin Expression and Role in Myocardial Remodeling

The non-infarcted heart expresses low basal levels of β_1 and β_3 integrins. The expression of these integrins in the mouse heart increases in the infarct area 3 days post-MI and peaks at day 7 [33]. In addition, peri-infarcted and non-infarcted areas exhibit increased α_5 subunit expression. Increase in α_1 subunit was only observed in the peri-infarct area, while α_3 showed no change in expression in the heart post-MI. Along with the changes in α integrin expression, there was also an increase in both collagen and fibronectin. At day 42 following MI, expression of α_5 and fibronectin was decreased; however, the expression of the α_1 and collagen remained higher [34]. It should be noted here that these studies were carried out in adult mice and no comparison was made between adult and aged mice following MI. A comparison between young and aged mice post-MI demonstrated a decrease and delayed neutrophil and macrophage infiltration, reduced cytokine and chemokine expression, and impaired phagocytosis of dead myocytes in the aged mice. Aged mice also exhibited a decrease in myofibroblast density and collagen deposition in the scar [35]. Given integrin role in activation of growth factors, such as TGF-β1 [36], it is tempting to speculate that integrins may play a major role in the inflammatory phase of the infarct healing post-MI. Of note, $\alpha_4\beta_1$ and $\alpha_5\beta_1$ integrins are suggested to function as cell adhesion molecules in mediating recruitment and migration of neutrophils following endotoxin-induced lung injury [37].

Examination of non-infarct LV region from patients with ischemic cardiomyopathy (ICM) showed decreased β_{1D} integrin expression; however, there was no change in β_{1D} integrin shedding or mRNA production. Interestingly, corresponding to β_{1D} regulation, FAK and phosphorylated FAK decreased in ICM patients when compared to normal patients. In addition Akt kinase activity, a downstream signaling pathway of FAK, was also decreased when compared to control. The reason for the decrease in β_{1D} integrin protein levels is unclear. However, this study suggests an insufficient adaptation of the heart to the mechanical demands during integrin deficiency [38]. Using Cre-Lox technology to inactivate the β_1 integrin gene exclusively in cardiac myocytes, Shai et al. (2002) demonstrated that β_1 integrins play an important role in myocardial fibrosis and cardiac failure [39]. Using β_1 integrin heterozygous KO mice, our laboratory has shown that deficiency of β_1 integrins associates with increased cardiac myocyte apoptosis and enhanced LV dysfunction and dilation after MI when compared to WT [40]. Together, these studies suggest a pivotal role for β_1 integrins in

cell survival and maintenance of the heart function. Reduction in β_1 integrins seen in the aging heart could, in part, be responsible for the exacerbated condition following MI in the elderly.

Integrins and Mechanotransduction

Integrins are clearly one of the receptors involved in mechanotransduction coupling in the heart. It is believed that the ability of cells to sense and respond to mechanical stimuli is altered with age [8]. Prior to mechanical stimulation, some integrin heterodimers are not bound to their ligand. Integrins that are responsible for responding to mechanical stretch, like $\alpha_5\beta_1$, mediate signaling by binding to RGD domain in the ECM [22]. When the heart experiences torsional stress, this causes structural alterations in the ECM, exposing the RGD motif. Integrins then bind to the ECM, and signaling molecules are recruited onto the cytoskeleton to form FAC [22]. Kinase recruitment to the FAC is then required for initiation of intracellular signaling and downstream gene expression [41]. The disruption of integrin binding with the ECM is believed to be the turning point from compensated to decompensated heart failure in the animal model [42]. The reasons for this disruption are not clearly understood. However, it may involve shedding of the extracellular domain of integrin due to a class of enzymes called sheddases which include A disintegrin and a metalloproteinase (ADAMs) and matrix metalloproteinases (MMPs) [43, 44]. MMPs are considered major players of the remodeling process of the heart post-MI [45]. Changes in the expression of ADAMs have also been observed in the heart post-MI [44]. Expression of ADAM-15, a novel regulator of inflammatory response, was increased in the rat heart at day 1 post-MI, reaching to a maximum at day 3. Immunohistochemical analysis showed cardiac myocytes as a source of ADAM-15 in the border area [46]. β_1 integrin shedding is suggested to correlate with the transition from cardiac hypertrophy to heart failure [47]. Release of myocytes from their normal attachment sites to collagen and/or fibronectin via disruption of $\alpha_5\beta_1$ integrin could trigger myocyte apoptosis [48]. In isolated adult rat ventricular myocytes, expression of cytoplasmic domain of β_1 integrin (present as a result of integrin shedding) led to activation of caspase-8 and myocyte apoptosis [49].

Integrins and Apoptosis

Cardiac myocyte death due to apoptosis is linked to the pathogenesis of the heart [50, 51]. Cardiac myocytes in the aged heart are susceptible to apoptosis [52]. It is believed that as many as 30 % of myocytes are lost as a function of aging in normal heart [47]. Heart failure associates with increased sympathetic nerve activity in the myocardium [53]. MI also causes sympathetic activation [54, 55]. Aging, itself, associates with alterations of sympathetic nervous system [56]. The chronic stimulation of the sympathetic nervous system induces release of catecholamines which signal via β-adrenergic receptor (β-AR) leading to adverse remodeling of the myocardium [57]. When β_1-AR and β_2-AR are coupled to the stimulatory G protein ($G\alpha_s$), proapoptotic signaling cascade is activated via a cAMP-dependent protein kinase (PKA). However, when β_2-AR is coupled to the inhibitory G protein ($G\alpha_i$), synthesis of cAMP is inhibited [58] and an antiapoptotic signaling cascade is activated [59]. Evidence has been provided that integrins, specifically β_1 integrins, can alter β-AR signaling and influence myocyte phenotype with respect to hypertrophy as well as apoptosis. β_1 integrin signaling has been shown to act in opposition to the proapoptotic actions of β-AR stimulation to protect cardiac myocytes both in vivo and in vitro [60, 61]. Our laboratory has shown that interaction of MMP-2 with β_1 integrins interferes with survival signals induced by β_1 integrin [62, 63]. In addition, chronic β-AR stimulation induces β_1 shedding and associates with increased myocyte apoptosis in the mouse heart [49, 61]. The antiapoptotic β_1 integrin signaling pathway may involve activation of Akt (a survival kinase) and inactivation of c-Jun N-terminal kinase (JNKs, apoptotic kinase; Fig. 27.2) [57].

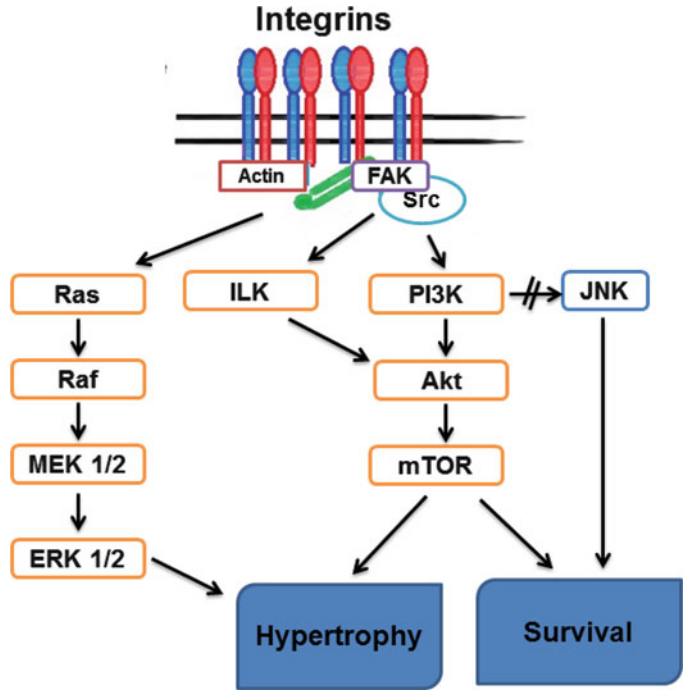

Fig. 27.2 Summary diagram illustrating integrin signaling involved in cardiac myocyte hypertrophy, survival, and apoptosis. *MEK* mitogen-activated protein kinase kinase; *mTOR* mammalian target of rapamycin; *ERK* extracellular signal-regulated kinase; *PI3K* phosphoinositide 3 kinase; *ILK* integrin-linked kinase; *JNK* c-Jun NH2 terminal kinase; *FAK* focal adhesion kinase

Integrins and Hypertrophy

Myocyte hypertrophy is an important pathological change that occurs in the heart following MI and during heart failure. Aging, itself, associates with ventricular hypertrophy [64]. Hypertrophy is a compensatory mechanism in response to hemodynamic overload to preserve cardiac output. However, if prolonged, it is a maladaptive process that can lead to sudden cardiac death or progression towards heart failure [65]. Tight regulatory processes are required to initiate a signaling cascade in response to hypertrophic stimuli. The cytoskeleton must be able to adapt to the changes in myocyte size and increased sarcomeres while maintaining heart function. Integrins are suggested to play a central role in recognizing and responding to the initial signals, thereby promoting activation of early genes involved in myocyte hypertrophy. Mechanical stimulation alone is suggested to activate integrins [22]. The expression of integrins changes in the heart during hypertrophic remodeling. There is an increased expression of β_1 integrin in fibroblasts and in myocytes [66, 67]. There is also an increase in α_1 and α_5 integrin levels in myocytes following abdominal aortic coarctation-induced hypertrophy. During the initial phase of pressure overload, expression of $\alpha_5\beta_1$ and its ligand fibronectin increases in parallel. During the later stages of the hypertrophic response, there is a disruption of cell-ECM and/or cell-cell interactions which may be one of the contributing factors for myocyte apoptosis due to anoikis [42].

β_1 integrin is accepted as an important participant in the hypertrophic signaling [15]. Overexpression of β_1 integrin in vitro augments the myocyte hypertrophic response assessed by protein synthesis and atrial natriuretic factor production, a marker of hypertrophic induction [20]. β_1 integrin-deficient mice exhibit lower myocyte cross-sectional area, a measure of myocyte hypertrophy, following β-AR stimulation. In addition there was more apoptosis in β_1 integrin-deficient mice when compared to WT mice [40, 61]. β_3 integrin expression is upregulated in pressure overload-induced hypertrophy, and formation of FAC appears to be β_3 integrin specific [68]. These studies provide evidence for the role of this integrin subunit in myocardial

hypertrophy. The downstream signaling pathway activated by β_1 and β_3 integrins may involve activation of PI3-kinase/Akt, Ras-ERK1/2, and mammalian target of rapamycin (mTOR; Fig. 27.2) [22]. It should be noted that lack of β_3 integrin in mice results in moderate spontaneous cardiac hypertrophy and systolic and diastolic dysfunction; and these abnormalities were exacerbated 7 days after transverse aortic constriction [69]. In contrast, lack of β_3 integrin reduced myocardial hypertrophy 4 weeks after transverse aortic constriction [70]. These contrasting findings may relate to the time of observation, inflammatory response, myocyte loss, and/or myocyte size.

Treating the Aging Heart

Heart failure is mainly a disease of the elderly. Angiotensin-converting enzyme (ACE) inhibitor, β-AR blockers, and angiotensin receptor blockers are shown to have favorable effects on parameters of LV remodeling with improved clinical outcomes in patients with heart failure [71]. A few studies now provide evidence for the role of integrins in the improvement of heart function. For example, treating hypertensive patients with ramipril, an ACE inhibitor, results in reduced risk of death, myocardial infarction, stroke, and congestive heart failure, independent of blood pressure changes [72]. Treatment of rat cardiac fibroblast with angiotensin II (Ang II) increases the expression of α_v, β_1, β_3, and β_5 integrin, enhances cell attachment to ECM proteins, and induces FAK phosphorylation, leading to cell survival. These effects were inhibited by irbesartan, an Ang II type 1 receptor antagonist. In addition, treatment with antibodies against β_3 or $\alpha_v\beta_5$ attenuated Ang II-mediated cell adhesion [73]. Treatment of spontaneously hypertensive rats with losartan, an Ang II type 1 receptor antagonist, attenuated the increased integrin (α_v and β_5) expression and hypertrophic response [73]. Elucidation of role of integrins and mechanism by which integrins may participate in the favorable effects in response to ACE inhibitors, β-AR blockers, and angiotensin receptor blockers may help identify novel therapeutic potential of integrins in failing heart.

Other therapeutic potential of integrins may involve targeting fibrosis. TGF-β is considered as a powerful pro-fibrotic cytokine [24]. It increases fibrosis by stimulating ECM deposition and decreasing its degradation. Deficiency of TGF-β1 in mice is shown to associate with decrease in age-related fibrosis and preserved diastolic function [74], linking the increase in fibrosis to heart dysfunction. Integrins play an important role in the activation of TGF-β [75]. Therefore, targeting integrins to prevent TGF-β activation may serve as an interesting therapy to age-associated increases in fibrosis and LV dysfunction.

Gene transfers using viral vectors directly into the myocardium and myocytes may also serve as an important therapeutic mechanism. However, in vivo gene transfers using adenoviruses are less efficient in the aging myocardium when compared to adult hearts [76]. Decreased β1 integrin levels is suggested as a key mechanism accounting for the decreased viral infectivity in the aged myocytes/myocardium [30]. A better understanding of why gene transfer is less efficient in aging myocytes and heart may have implications for treatment of heart failure in elderly patients.

Monitoring changes in integrin expression during the repair processes of the heart, specifically after MI, may help provide important prognostic information. This could aid in targeting a treatment for post-MI patients, tailoring each treatment to the severity of the MI. Sherif et al. (2012) used (18)F-galacto-RGD, a positron emission tomography tracer, to evaluate $\alpha_v\beta_3$ expression in rat hearts following MI. The uptake for this tracer was increased in the infarct area 1 week after MI. Most of the tracer uptake was found to be associated with capillary density as $\alpha_v\beta_3$ is highly expressed on endothelial cells during angiogenesis. Interestingly, animals with larger MI exhibited lower uptake of this tracer when compared to animals with smaller MI. This uptake in the MI area inversely correlated with LV dilation and directly correlated with worsening of systolic function [77]. Thus, integrins can be used as potential biomarkers of myocardial repair processes post-MI.

Conclusion

Heart failure is primarily a disease of the elderly. With elderly population on the rise, it is becoming imperative to discover treatments. Understanding the changes that are associated with age-related cardiomyopathies is the first step towards developing an intervention. Integrins are complex bidirectional signaling molecules. They have the potential to interact and influence signaling of a variety of growth factors in the heart. Significant strides have been made to understand the role of integrins in the heart and myocardial remodeling. However, most studies involving cardiovascular diseases were performed on young animals. Further investigations are needed to clarify the role of integrins in the aging heart and the repair processes of aged heart after MI. This information may help develop effective therapeutics for the treatment of heart failure in elderly.

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Adipokines as Novel Biomarkers in Aging and Heart Failure

28

Ken Shinmura

Introduction

The last decade of animal studies has rewritten previous knowledge regarding white adipose tissue (WAT), which is considered merely as excess energy deposits, as in obese individuals [1]. Increasing evidence indicates that WAT is an active tissue that can produce a wide variety of factors known as adipokines, and these molecules participate in a range of physiological and pathophysiological processes, including metabolism, immunity, inflammation, satiety, and cellular fate via endocrine, paracrine, autocrine, or juxtacrine cross talk. Adipokines in a broad sense include classic pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, both secreted from adipocytes, but synthesized mainly by immune cells infiltrating WAT such as macrophages. These pro-inflammatory cytokines contribute to the low-grade inflammation, closely associated with the development of atherosclerosis and myocardial dysfunction. Specific adipokines secreted by WAT include leptin, adiponectin, resistin, and visfatin, which even play a role in the cardiovascular system.

Adipokines mainly exert metabolic effects on most organs including the heart, although they have also been found to have direct as well as indirect cardiovascular effects on target tissues [2]. Furthermore, these peptides have received substantial attention because of their potential role as biomarkers of cardiovascular diseases (CVDs) including heart failure (HF) [2]. Mounting evidence demonstrates that the circulating levels of some adipokines increase in patients with HF, and this increase is associated with the severity and consequently the prognosis of HF. Identification of adipokines as potent biological molecules and useful biomarkers for CVDs has had a major impact in the fields of endocrinology and cardiology. Additionally, adipokines have also received attention in the area of geriatrics and gerontology because their biological functions are considered important contributors to longevity. Both quantitative and qualitative changes in WAT are inevitable with aging, and therefore, the production of most adipokines in WAT is affected by aging. Accordingly, when we discuss the role of adipokines as biomarkers of CVD, we should focus on the influence of the age as well as gender, comorbidities, and body composition.

In terms of the categories of their exact roles in different stages of HF, biomarkers can act either as risk factors for use in screening vulnerable individuals among apparently "healthy" populations or as diagnostic markers to identify patients with suspected disease. In patients with identified HF, a biomarker can be used as a prognostic indicator for monitoring the progression or outcome of the disease or the efficacy of a therapeutic

K. Shinmura, MD, PhD, FAHA (✉)
Division of Geriatric Medicine, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjyuku-ku, Tokyo 1608582, Japan
e-mail: shimmura@z5.keio.jp

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modality. In this chapter, the potential of each adipokine as a biomarker of aging and HF is mainly discussed through the corresponding clinical design studies. In addition, the possible mechanisms by which each adipokine acts in the cardiovascular system are discussed based on information obtained from both clinical and experimental studies.

Leptin

Among the adipokines, the 16-kDa protein leptin has received primary attention. Leptin is chiefly secreted by adipocytes, but is also produced by many tissues including the heart [2, 3]. The production of leptin in cardiomyocytes increases by both endothelin-1 and angiotensin II (ang II), suggesting that leptin plays a paracrine or autocrine role in the regulation of cardiac function under pathological conditions. The primary cardiac response to leptin in terms of physiological function appears to be a negative inotropic effect mediated by nitric oxide (NO) produced endogenously. Circulating levels of leptin are generally positively related to body mass index (BMI). Thus, leptin is traditionally recognized as a product of adipocytes. However, it is difficult to ignore the role of local leptin production in peripheral tissues including cardiomyocytes on the progression of CVD. In obese individuals, circulating leptin exists primarily in the free form, whereas in lean individuals, it circulates bound to plasma proteins. The effects of leptin are mediated by the binding of this peptide to its specific receptors, termed OBR (or LEPR or LR). These receptors are abundantly expressed in many different cells including cardiomyocytes. The intracellular domain of OBRb (long form of OBR) belongs to the Janus kinase signal transduction and translation system (Jak2/STAT3). Moreover, it has been reported that leptin activates various kinases, including Ras homolog gene family; member A/Rho-associated, coiled-coil-containing protein kinase (RhoA/ROCK); extracellular signal-regulated kinase (ERK)1/2; p38 mitogen-activated protein kinase (MAPK); phosphoinositide 3-kinase (PI3K)/Akt; and protein kinase C (PKC) in cardiomyocytes [2, 3]. Leptin can exhibit various cardiovascular effects directly through these signaling pathways or through secondary responses mediated by the central nervous system (Fig. 28.1). Fundamentally, leptin can protect cardiomyocytes from apoptosis, indicating that it is cardioprotective under acute settings. However, increasing evidence indicates that both excessive and insufficient leptin signaling results in adverse cardiovascular effects. To maintain a homeostatic environment, a feedback system exists to prevent excess leptin activity, but leptin resistance may occur when this feedback system is impaired. Leptin resistance leading to hyperleptinemia occurs in obese individuals. Whether the heart becomes leptin resistant under pathological conditions or not remains unclear. One study demonstrated that cardiomyocytes isolated from rats subjected to dietary sucrose feeding for 10 weeks, which lead to hyperleptinemia and insulin resistance, have impaired leptin signaling, suggesting the development of leptin resistance [4]. Most of leptin's cardiovascular effects seem to be detrimental rather than cardioprotective under chronic hyperleptinemic conditions. Therefore, it is likely that some of the cardiovascular pathology observed in obese individuals might reflect excess leptin signaling rather than cardiovascular leptin resistance. It is also possible that specific leptin-mediated effects develop into leptin resistance, whereas others remain leptin sensitive.

Finally, the effect of aging on circulating leptin levels remains controversial. Some studies showed that the elderly had higher leptin levels in the elder in proportion to a greater fat mass [5]. Others reported that this population group had lower leptin levels and that leptin and changes in body fat with aging were not correlated [6]. However, it seems definite that lower leptin levels in the elderly are closely associated with cachexia independent of its cause [7]. Further, circulating leptin levels definitely differ between men and women after adjustment for BMI [8].

Leptin as a Biomarker of HF

Leptin has been proposed as a potential link between obesity and CVD and HF. Circulating

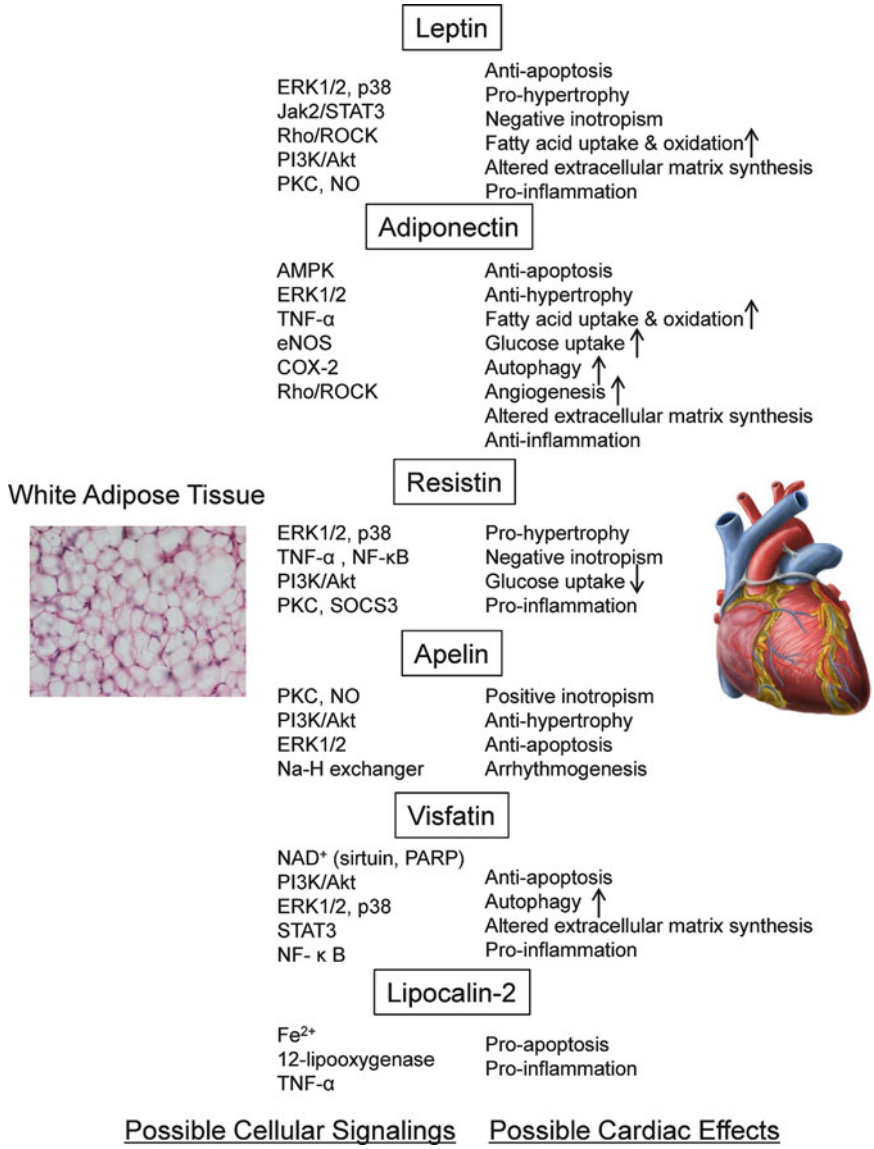

Fig. 28.1 Summary of possible cellular signalings downstream of each adipokine and its possible cardiac effects. *COX-2* cyclooxygenase-2; *SOCS3* suppressor of cytokine signaling 3

leptin levels were examined at routine visits to evaluate the risk of developing chronic HF or CVD in a study of 818 elderly patients [8]. Higher leptin levels in women were strongly correlated with BMI and were associated with a higher risk of incident CVD events and chronic HF. However, this association was no longer significant after adjustment for BMI. In addition, a U-shaped, nonlinear, relationship between leptin and mortality was suggested for the elderly. In this regard, Lehtonen et al. also reported that serum leptin levels did not predict mortality in elderly men in a longitudinal 10-year study [9]. A prospective study involving 4,080 men aged 60–79 years without diagnosed HF who were followed up for 9 years showed that the relationship between leptin and HF depended on the presence or absence of coronary heart disease (CHD) [10]. Increased BMI was associated with an increased risk of HF in men with and without preexisting

CHD (myocardial infarction or angina) after adjustment for cardiovascular risk factors. Further, increased leptin levels were significantly associated with an increased risk of HF in men without preexisting CHD. In contrast, no association between these parameters was observed in those with CHD. This finding is consistent with that of the Heart and Soul Study, in which obesity was found to be associated with a higher risk of HF independent of leptin and C-reactive protein (CRP) in CHD patients [11]. However, on the basis of the available data, we do not have a clear explanation for why leptin acts as a mediator in the development of HF in non-CHD, but not in CHD patients.

The serum levels of leptin and soluble leptin receptor were reported to be increased in patients with advanced HF [12]. The elevated levels of leptin correlated with increased serum levels of TNF-α. However, the prognostic value of this finding remains unclear. A clinical study was performed to elucidate the effect of leptin and resistin (another adipokine discussed later) on the progression of HF in patients with nonischemic dilated (DCM) and inflammatory (DCMi) cardiomyopathy [13]. Plasma levels of leptin and resistin, but not their cardiac expression, were significantly elevated in patients with DCM and DCMi. A multivariate linear regression model revealed that the high circulating levels of leptin and resistin in these patients were associated with HF progression, independent of immune response. The authors speculated that resistin and leptin are responsible for the progression of cardiac dysfunction by increasing oxidative stress, activating nuclear factor (NF) κ–B, and upregulating TNF-α and IL-6 within the myocardium. Another study that included an equal number of ischemic ($n=5$) and nonischemic ($n=5$) cardiomyopathy patients in the failing heart group demonstrated that cardiac expression of leptin and its receptor was increased in failing human hearts [14]. Mechanical unloading of the failing heart with a ventricular assist device (VAD) resulted in a marked decrease in the expression of cardiac leptin and its receptor. Thus, the increase in the expression of cardiac leptin and its receptor might be a compensatory mechanism in the failing heart.

Adiponectin

Among the adipokines, adiponectin, also referred to as ACRP30 and AdipoQ, is the most abundant plasma protein secreted by adipocytes; its plasma levels range between 3 and 30 μg/mL [15]. It exists in human and mouse plasma in different oligomeric forms: trimeric, hexamer, and high molecular weight (HMW). These different oligomeric forms of adiponectin bind to the specific adiponectin receptors, adipoR1 and adipoR2, in a distinct manner, activating different signaling pathways and exerting distinct effects on target tissues. AdipoR1 has been identified as a major receptor for adiponectin-mediated signaling in cardiomyocytes. Transduction of adiponectin-mediated signaling downstream of these receptors involves the activation of AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor (PPAR)-α, and PPAR-γ. Adiponectin contains a collagen-repeat domain at the N-terminus and a globular domain at the C-terminus that shows sequence homology to compliment factor C1q. Adiponectin is processed by proteolysis, and fragments including the globular domain have been detected in both human and mouse plasma, although their plasma levels are usually extremely low. More recently, it has become clear that extensive posttranslational modifications of adiponectin are required for efficient multimerization and secretion [16]. For example, during the transit of adiponectin through endoplasmic reticulum (ER), thiol-mediated retention of this adipokine occurs via direct interactions with chaperones including ERp44 and DsbA-L, and this process facilitates multimerization and secretion. Thus, it is possible that ER stress is responsible for the decrease in circulating levels of total and HMW adiponectin in obese patients and patients with type 2 diabetes mellitus (T2DM).

The adiponectin transcript is mainly expressed in adipose tissue (AT). Many adipokines are positively regulated by adiposity, but plasma adiponectin levels are negatively regulated by accumulation of body fat, especially visceral AT. In this regard, adiponectin levels

are lower in obesity and insulin-resistant states, and loss of its protective effects might contribute to the greater cardiovascular risk observed in these conditions.

Multiple mechanisms of adiponectin signaling exist, and the mechanism used varies with the cellular sites of action [15, 17]. Adiponectin ameliorates the progression of microvascular disease in rodents; this observation is consistent with the correlation of this adipokine with improved vascular outcomes, which has been shown in epidemiological studies. Adiponectin protects the myocardium from oxidative stress and ischemia/reperfusion injury and attenuates cardiac remodeling induced by pressure overload or after myocardial infarction. The favorable effects of adiponectin are associated with accelerated angiogenesis, anti-inflammatory effects, an antiapoptotic effect, an anti-hypertrophic response, and inhibition of interstitial fibrosis (Fig. 28.1) [15, 17]. Thus, adiponectin is considered a good-natured adipokine, and it could be a promising therapeutic molecule for managing CVDs. On the other hand, evidence demonstrates that adiponectin is involved in pro-inflammatory processes in patients with rheumatoid arthritis, chronic liver disease, chronic kidney disease, sepsis, etc [18]. These findings may make the role of adiponectin obscure as a screening biomarker for incident CVD and longevity in a prospective cohort study.

Adiponectin in Aging and Longevity

Plasma levels of adiponectin in women are significantly higher than those in men [19, 20]. In addition, the levels in women do not change with age after menopause, but those in men increase linearly with age [20]. Since it is well known that a decline in renal function increases plasma levels of adiponectin, the decline in renal function with aging might contribute, at least in part, to the age-associated increase in adiponectin levels. In addition, the redistribution of body fat and loss of skeletal muscle mass and strength (sarcopenia) with physiological and pathological aging might influence adiponectin levels in the elderly [21].

Mounting evidence from epidemiological studies demonstrates the divergent associations of circulating levels of adiponectin with the prevalence and incidence of CHD and with mortality [21–26]. In population-based studies of apparently healthy men and women, elevated adiponectin levels were associated with a lower risk of CHD [22–24]. At the same time, these studies revealed that increased adiponectin levels were closely associated with not only all-cause mortality but also CHD mortality in either sex [21, 22, 24–26]. This association seems to be particularly strong in the elderly [21, 26] and in patients at high risk for CHD [22, 25]. A prospective study of 4,046 elderly men aged 60 to 79 years confirms the results of previous studies that high adiponectin levels are associated with significantly increased mortality in elderly patients with HF [21]. Furthermore, this study expanded the link between high adiponectin levels and total mortality to the general older population of men without diagnosed CVD or HF. Another prospective study of 3,075 well-functioning men and women aged 69 to 79 years indicated the association between high adiponectin levels and increased risks of both total and CVD mortality in the elderly [26]. More recently, Kizer et al. evaluated the joint association of plasma adiponectin levels and interval changes in adiponectin and inflammatory markers (CRP and IL-6) with mortality in 840 older adults participating in a population-based study [27]. Higher levels or larger interval change in adiponectin and inflammatory markers predicts increased mortality in this population independent of each other, although the association appears inverse below 20 mg/L for adiponectin.

In asymptomatic healthy subjects, adiponectin levels are associated not only with brain natriuretic peptide (BNP) but also with left atrial diameter (LAD) and/or left ventricular wall thickness as evaluated by echocardiography [28, 29]. In this regard, the association between 2 circulating adipokines (adiponectin and resistin) and 3 echocardiographic parameters was evaluated in 2,615 participants in the Framingham Offspring Study [30]. Serum adiponectin levels were found to be inversely related to left ventricular mass (LVM), and serum resistin levels were

inversely related to fractional shortening (FS). Thus, it is possible that the higher levels of adiponectin in the elderly could be attributed, at least in part, to impaired LV diastolic function related to LV hypertrophy.

In contrast to these prospective studies, cross-sectional studies performed in 3 different countries—Poland [31], USA [32], and Japan [33]—demonstrated that adiponectin levels in centenarians (survivors over 100 years of age) were significantly greater than those in the very elderly (below 95 years) and in the early elderly (below 70 years). Although it is difficult to clarify whether the increase in adiponectin levels is a cause or a result of longevity, those investigators concluded that altered adiponectin production in centenarians might play a role in the mechanisms contributing to prolonged survival. A recent case-control study on generally apparent population in the Baltimore Longitudinal Study demonstrated that serum levels of adiponectin in their sixties did not predict longevity [34]. However, the directional difference between long- and short-lived individuals was obtained when multiple biomarker dysregulation was considered.

From these clinical studies, we expect that the contamination of asymptomatic patients with wasting and malnutrition due to complicated chronic inflammatory diseases and with LV diastolic dysfunction increases mortality in the elderly with higher adiponectin levels but that healthy elderly individuals showing high adiponectin levels due to genetic background and/or life style modification have the potential for longevity.

Adiponectin as a Biomarker of HF

Higher levels of adiponectin in patients with HF have been identified in many case-control studies. In a prospective study of 195 HF patients (average age, 69 years), higher levels of adiponectin were found to be a predictor of mortality independent of HF severity risk markers including age, systolic blood pressure, systolic LV dysfunction, HF duration, and creatinine clearance [35]. The hazard ratio of mortality for the value in the 2 upper tertiles relative to the lowest tertile (adiponectin levels $\leq$ 11.6 mg/L) was 3.23 ($P = 0.032$). However, this association became insignificant after additional adjustment for N-terminal proBNP (NT-proBNP). High levels of adiponectin were closely associated with increased mortality and severity, expressed as New York Heart Association (NYHA) Class I–IV, in patients with HF including DCM [21, 36–41]. Patients with HF and cachexia showed remarkably increased plasma adiponectin levels compared with those with HF but not cachexia [42]. These results suggest that the increase in adiponectin levels is associated with the wasting process that occurs in cachectic patients with HF. The association between adiponectin levels and HF mortality was found to be significant in the elderly with HF [21, 36] and in HF patients with normal BMI (21–25 kg/m^2) [41].

In addition to obesity and the complication of T2DM, genetic factors also determine the circulating levels of adiponectin. The adiponectin gene *ADIPOQ* is considered the major gene influencing adiponectin levels with single-nucleotide polymorphisms (SNPs) in its coding region and promoter. However, Masson et al. demonstrated that higher adiponectin levels, but not genetic variants, were consistently associated with a poor prognosis in patients with HF [43]. Interestingly, all studies in which NT-proBNP or BNP was simultaneously measured indicated a strong positive correlation between adiponectin and NT-proBNP or BNP levels [35–42]. In addition to BNP, plasma adiponectin levels were associated with plasma TNF-α [38, 42] and oxidized low-density lipoprotein levels [40] in patients with HF.

In addition to circulating levels of adiponectin, local production of adiponectin and the expression of its receptors in cardiomyocytes seem to play an important role in the development of HF [17]. More recently, using human cardiac tissue undergoing heart transplantation, Yin et al. found that the expression of adiponectin, but not leptin and resistin, was significant in cardiomyocytes and positively correlated with the severity of HF [44]. They also reported that

among 3 adipokines, plasma levels of adiponectin alone showed prognostic value in patients with chronic HF. Khan et al. evaluated 3 circulating adipokines (leptin, adiponectin, and resistin), the expression of adiponectin and its receptors in cardiac tissue in patients with advanced HF before and after VAD implantation [45]. Although their serum levels were significantly higher in patients with advanced HF, only serum adiponectin levels were reduced by VAD implantation. Cardiac expression of adiponectin significantly decreased after VAD implantation. In contrast, the expression levels of adipoR1 and adipoR2 were found to be suppressed in the failing hearts, but they recovered to the control levels after VAD implantation. Schulze et al. evaluated the changes in insulin resistance and plasma levels of adipokines in patients with acute decompensated and chronic stable HF [46]. Plasma levels of adiponectin, visfatin, leptin, resistin, and TNF-α were elevated in patients with chronic stable HF and further increased in patients with acute decompensated HF, compared with control subjects. Similarly, homeostasis model assessment-insulin resistance (HOMA-IR) was increased in chronic stable HF and further increased in patients with acute decompensated HF. However, at the time of discharge, the plasma levels of TNF-α, adiponectin and visfatin, and HOMA-IR decreased to the levels in patients with chronic stable HF.

The improvement in cardiac function by treatment with either nitroglycerin or carperitide (atrial natriuretic peptide = ANP) for 7 days reduced the plasma levels of adiponectin together with those of BNP [47]. The decrease in serum adiponectin levels in response to treatment has been identified to predict a good prognosis in acute decompensated HF [48]. In addition to total adiponectin levels, HMW adiponectin levels at admission and its larger decrease would be signs of favorable responsiveness to treatment in acute decompensated HF [49]. Greater attention should be paid to the use of β-blockers when estimating plasma adiponectin levels as diagnostic and prognostic biomarkers. Treatment with carvedilol for more than 6 months also decreased plasma adiponectin levels, and this decrease was associated with the improvement of LV ejection fraction (EF) in patients with HF [50]. Carvedilol treatment decreased plasma BNP and norepinephrine levels as well. β-blocker treatment was correlated with lower adiponectin levels, especially in non-obese patients with chronic HF [51]. In addition, it has been reported that the prognostic value of adiponectin is significantly affected by β-blocker treatment in patients with chronic HF [52].

The most possible explanation for the association between increased adiponectin levels and high mortality in patients with HF is the compensatory upregulation of adiponectin production against excess inflammatory cytokine production and oxidative stress with the existence of "adiponectin resistance" [15, 17]. However, increased circulating adiponectin might promote weight loss in patients with advanced HF, resulting in the development of cardiac cachexia. In addition, it is possible that increased adiponectin production is involved not only in metabolic remodeling but also in structural remodeling during the development of HF [37].

Two prospective studies provide important information regarding the correlation between adiponectin and incident HF. A total of 946 men of average age 70 years, who were free of CHF at the baseline, underwent follow-up examinations for 9 years [53]. The adiponectin concentration was not found to be significantly associated with incident CHF after adjusting for all CHF risk factors. Further, in the Framingham Offspring Study, 2,739 participants underwent follow-up examinations for 6 years [54]. This study found that increased circulating resistin levels were associated with incident CHF, but neither high nor low adiponectin levels were associated with the new onset of CHF. The association between adiponectin and the risk of HF was also evaluated in a prospective nested case-control study of US male physicians (Physician's Health Study) [55]. A J-shaped association between them was observed in this study, indicating that moderate levels of adiponectin is beneficial for a cardiovascular risk and extremely high levels of adiponectin might reflect homeostatic dysregulation of this adipokine and/or the presence of chronic inflammation.

Resistin

Resistin is a 12.5-kDa polypeptide that belongs to a unique family of cysteine-rich C-terminal domain proteins known as resistin-like molecules [56]. In mice, resistin is primarily secreted by adipocytes, and it has been shown to be a link between obesity and T2DM via insulin resistance. Human resistin is 64 % identical to its mouse counterpart at the mRNA level and 56 % at the protein level. Unlike mouse resistin, human resistin is produced mainly by monocytes/macrophages. In human AT, resistin is predominantly expressed in non-adipocyte-resident inflammatory cells and stromal cells. The lack of human resistin expression in adipocytes might be due to the loss of a genomic binding site for PPAR-γ in the enhancer region, which regulates the adipocyte-specific expression of the *Retn* gene in mice [57]. The involvement of human resistin in inflammation has been well established [56]. Resistin increases TNF-α, IL-6, and IL-12 levels in mononuclear cells, macrophages, and cardiomyocytes by activating NF-κB (Fig. 28.1). In a cross-sectional study on the Japanese population, plasma levels of resistin were found to be associated with age, female sex, low high-density lipoprotein-cholesterol levels, HOMA-IR, and high-sensitivity CRP levels, but not BMI [58]. The association between human resistin and HF has not been studied as much as its association with CHD, but increasing evidence demonstrates that elevated circulating levels of resistin are closely associated with the risk of HF progression.

Resistin as a Biomarker

In a case-control study, Takeishi et al. first demonstrated that serum resistin levels were higher in patients with HF and increased with advancing NYHA functional class [59]. They also found that elevated resistin levels predicted a higher event rate and worse mortality in patients with HF. In this regard, Wu et al. recently confirmed that serum resistin levels were associated with higher mortality in patients with systolic HF after adjustment of clinical parameters [60]. As described in the section on leptin, Bobbert et al. found that both resistin and leptin are powerful predictors of HF progression since they regulate the production of pro-inflammatory cytokines [13].

Two large prospective cohort studies supported the correlation between elevated resistin levels and HF development. A study of 2,739 subjects in the Framingham Offspring Study followed up for 6 years found a 26 % increase in the risk of HF with each 7.45 ng/mL increment in serum resistin levels after adjustment for clinical risk factors including BMI, insulin resistance, and CRP and BNP levels [54]. However, serum adiponectin levels were not associated with HF. The other study was a prospective cohort study known as the Health, Aging, and Body Composition Study, in which 2,902 elderly persons without prevalent HF (average age, 74 years) were followed up for 9 years [61]. Resistin was strongly associated with the risk of incident HF after adjustment for known risk factors. However, neither leptin nor adiponectin was associated with the risk of HF. Moreover, the Heart and Soul Study on American veterans with preexisting CHD showed a significant higher risk of HF and all-cause mortality among those in the highest quartile of resistin levels after adjustment for age, sex, and BMI [62]. However, the apparent effect of resistin was not independent of traditional risk factors for HF, although these factors might be dependent on resistin.

Compared with the roles of leptin or adiponectin in patients with HF, resistin seems to play a distinct and detrimental role in the development of HF. Several in vitro studies investigated the effects of resistin on cardiomyocytes, but it has not been completely clarified yet whether human resistin has direct pathological effects on HF progression. This should be the focus of research in the future.

Apelin

Apelin is a novel peptide that is an endogenous ligand for the angiotensin-like 1 (APJ) receptor [63, 64]. Apelin-APJ genes are ubiquitously

expressed in various tissues and show similarities with the ang II-ang II type 1 receptor (AT1R) system. The gene for an APJ receptor was first identified in 1992. The APJ receptor is a 377-aa, 7-transmembrane domain, G-coupled receptor whose gene is located on the long arm of chromosome 11. Ang II is unable to activate the APJ receptor despite its similarities to the AT1R, and the APJ receptor was believed to be an orphan receptor until 1998 when apelin was isolated from bovine stomach extracts. Apelin is secreted as a 77-aa pre-proprotein, which is cleaved to form several active peptides denoted by their length as apelin-13, apelin-16, apelin-17, apelin-19, and apelin-36. It has been shown that shorter synthetic C-terminal peptides consisting of 10–13 aa exhibit stronger activity than apelin-36. The apelin-APJ system is expressed in the central nervous system and the periphery including AT. It plays a role in the regulation of fluid and glucose homeostasis, feeding behavior, vessel formation, cell proliferation, and immunity. In addition, evidence indicates that the cardiovascular system is the main target of the apelin-APJ system (Fig. 28.1). APJ receptors are expressed in the heart at a similar density as AT1Rs. The proposed cardiovascular effects of the apelin-APJ system are opposite to the effects of the renin-angiotensin system (RAS), which plays a vital role in the pathogenesis of HF. Therefore, the apelin-APJ axis might act as a compensatory mechanism initially, but become downregulated in end-stage HF.

Circulating apelin levels were found to be mildly elevated during the early stage of HF, but they reduced as the disease advanced [65, 66]. Plasma apelin levels were reduced in patients with chronic HF compared to normal controls [67]. In patients with severe HF, the improvement in NYHA class and LVEF following cardiac resynchronization therapy was associated with an increase in plasma apelin levels [68]. mRNA of apelin was significantly increased and that of the APJ receptor was decreased in the failing heart due to CHD and DCM [66]. In a heart for which successful reverse remodeling was achieved using VAD, the tissue concentration of apelin was increased, and the APJ gene was upregulated [65]. However, recent clinical investigations demonstrated lower and/or similar plasma levels of apelin in patients with HF compared to normal subjects and no significant differences between plasma apelin levels and functional classes or LVEF [69]. These findings suggest that apelin does not reliably predict acute decompensated HF and is not a prognostic marker of confirmed HF.

More recently, an animal experiment indicated that the APJ receptor is bifunctional for both mechanical stretch and endogenous apelin [70]. Thus, the role of the apelin-APJ system in the development of HF might be more complex than it seems.

Visfatin/NAMPT

Visfatin/NAMPT (nicotinamide phosphoribosyltransferase) was originally cloned in 1994 as a cytokine named pre-B cell colony-enhancing factor (PBEF) [71, 72]. PBEF is a 52-kDa secreted protein that has been found to be an important cofactor for serum cell factor- and IL-7-mediated B cell maturation. In 2001, other investigators identified the gene *nadV*, whose presence allows nicotinamide adenine dinucleotide (NAD)-independent growth of the gram-negative bacteria *Haemophilus influenzae* and *Actinobacillus pleuropneumoniae*. They found that NadV has significant sequence homology to PBEF. Indeed, the murine homolog of PBEF is an enzyme catalyzing the reaction between nicotinamide and 5-phosphoribosyl-1-pyrophosphate to yield nicotinamide mononucleotide, an intermediate in the biosynthesis of NAD. The crystal structure of dimeric PBEF is now known as NAMPT, and it is recognized as a key enzyme in NAD biosynthesis. Further, in 2005, NAMPT was identified as an adipokine-designated visfatin. It was found to be highly expressed in visceral AT compared with subcutaneous AT, and its plasma levels increased during the development of obesity. Both the extracellular (cytokine-like) and intracellular (enzymatic) functions of visfatin seem to be responsible for immunity, metabolism, and stress response in both physiological and pathophysiological

conditions, further underlining the complexity of this molecule.

Recently, visfatin has been implicated in the pathogenesis of various CVDs including HF because of its role in inflammation and matrix regulation (Fig. 28.1). Moreover, visfatin has been found to protect most cells from apoptosis. Since NAD is involved in multiple redox reactions as a cofactor, the role of visfatin as a key enzyme of NAD biosynthesis has gained importance. The most studied NAD-dependent proteins in regard to visfatin are sirtuins and poly (ADP-ribose) polymerases (PARPs), which probably play an important role in HF progression.

Only a few clinical investigations regarding the association between visfatin and HF have been conducted so far. Schulze et al. demonstrated that plasma visfatin levels increased in patients with chronic HF and further increased in those with acute decompensated HF [46]. In the latter group, plasma visfatin levels returned to those in patients with chronic HF after treatment, just as plasma adiponectin levels did. Wu et al. demonstrated that plasma visfatin levels were similar between survivors and non-survivors of acute decompensated HF, although plasma resistin levels were significantly associated with high mortality [60]. Further investigations are needed to determine the potential of visfatin as a biomarker of HF.

Lipocalin-2

Lipocalin-2 (neutrophil gelatinase-associated lipocalin) is a 25-kDa secreted glycoprotein expressed abundantly in AT and the liver [18]. Previous studies indicated a positive correlation between circulating lipocalin-2 levels and the levels of fasting glucose, HOMA-IR, and high-sensitivity CRP, suggesting that lipocalin-2 might be a risk factor and biomarker for insulin resistance, T2DM, and inflammation. Lipocalin-2 has been proposed as a potential link between obesity and obesity-related CVDs including HF. In addition, Yndestrad et al. reported that serum levels of lipocalin-2 increased in patients with HF and were associated with clinical and neurohormonal deterioration [73]. Elevated lipocalin-2 levels at the baseline were correlated with poor prognosis in patients with HF following acute MI. The expression levels of lipocalin-2 were reported to be increased in experimental models of autoimmune myocarditis and even in human myocarditis [74]. Enhanced systemic and myocardial lipocalin-2 expression in clinical and experimental HF suggests a role for this adipokine in the innate immune response in the pathogenesis of HF. Lipocalin-2 seems to act not only via conventional cell signaling pathways but also via the regulation of intracellular iron levels, which results in cardiomyocyte apoptosis (Fig. 28.1). It is interesting to note that lipocalin-2 has bacteriostatic properties and might play a role in linking infection, innate immunity, and CVD.

Other Novel Adipokines

Omentin (intelectin, intestinal lactoferrin receptor, or endothelial lectin HL-1) was initially identified in intestinal Paneth cells; it is associated with galactofuranose within the carbohydrate moieties of bacterial cell walls and has been implicated in gut defense mechanisms against pathogenic bacteria [75]. Although omentin 2 has been reported as a homolog of omentin, omentin 1 is the major circulating form. Recently, omentin has been reported to be preferentially produced and secreted by visceral AT (predominantly expressed in stromal cells) compared with subcutaneous AT. Omentin reportedly has insulin-sensitizing effects and anti-inflammatory properties. Thus, omentin might have beneficial effects toward metabolic syndrome and could be useful as a biomarker of CVDs including HF [76]. Chemerin (retinoic acid receptor responder 2) was found to be highly expressed in AT and the liver, as well as in innate immune cells [77]. Elevated serum chemerin levels were associated with the presence of CHD in patients with metabolic syndrome [78]. Vaspin (visceral adipose tissue-derived serpin, serpinA12) was originally identified as an adipokine, which is predominantly secreted from visceral AT in Otsuka Long-Evans Tokushima fatty (OLETF) rats [79]. Like the higher serum levels of vaspin,

high-vaspin mRNA expression in human AT was found to be correlated with obesity, insulin resistance, and T2DM [80]. The association between these novel adipokines and HF has not been evaluated yet and remains to be clarified in the future.

Summary

Among the various adipokines, which should be selected as biomarkers of HF? Table 28.1 presents a summary of previous reports in which, at least, 2 or more adipokines were simultaneously evaluated to clarify their significance as biomarkers of HF. Table 28.2 presents a summary of prospective cohort studies in which the role of a specific adipokine as a biomarker of incident HF was investigated. Accordingly, we recommend that the following 4 steps be taken while examining a specific adipokine for the purpose of managing patients with HF: choosing individuals at high risk for HF in the near future, helping to establish the diagnosis of HF, identifying patients at risk for adverse outcomes, and guiding therapy (Table 28.3).

Screening

Inferences drawn from previous prospective cohort studies strongly suggest that resistin is a promising biomarker for screening high-risk individuals for incident HF within an apparently healthy population. In contrast, the usefulness of leptin seems to be limited, although higher plasma levels of leptin do predict incident HF in individuals without preexisting CHD. We must pay attention while estimating plasma leptin levels because the association between the risk of HF and these levels seems to assume a J shape. A similar association has been proposed between plasma adiponectin levels and the risk of HF. Therefore, adiponectin is not an appropriate biomarker for screening high-risk individuals for incident HF within an apparently healthy population. We have not been able to estimate the value of other adipokines as screening biomarkers, since large-scale prospective cohort studies on these adipokines are yet to be conducted.

Table 28.1 Summary of previous reports in which 2 or more adipokines were simultaneously evaluated in patients with HF

Authors	Study type	Subjects	Circulating adipokine levels evaluated	Results
Bobbert et al. [13]	Case-control study	52 patients with DCM, 52 patients with inflammatory cardiomyopathy (DCMi), and 16 control subjects	Leptin, resistin	Both were elevated with patients with DCM and DCMi. Both were associated with prognosis
McManus et al. [30]	Cross-sectional study	2,615 asymptomatic healthy participants from the Framingham Offspring Study	Adiponectin, resistin	Adiponectin was associated with LV mass, whereas resistin was associated with fractional shortening
Yin et al. [44]	Cross-sectional study	96 patients with congestive HF	Leptin, adiponectin, resistin	Only adiponectin was associated with prognosis
Khan et al. [45]	Case-control study	36 patients with advanced HF before and after VAD and 10 control subjects	Leptin, adiponectin, resistin	All were elevated in patients with advanced HF. Only adiponectin decreased after VAD
Schulzu et al. [46]	Case-control study	44 patients with acute decompensated HF (ADHF), 26 patients with chronic stable HF (CSHF), and 21 control subjects	Leptin, adiponectin, resistin, visfatin	All were elevated in patients with CSHF and increased further in those with ADHF. Adiponectin and visfatin significantly decreased at the time of discharge in patient with ADHF
Wu et al. [60]	Cross-sectional study	108 patients with systolic HF	Leptin, adiponectin, resistin, visfatin	Only resistin was associated with prognosis

Table 28.2 Summary of prospective cohort studies in which the possibility of using a specific adipokine as a biomarker for incident HF was investigated

Authors	Subjects	Circulating adipokine levels evaluated	Results
Lieb et al. [8]	818 participants in the Framingham Study (average age, 79 years)	Leptin	Leptin was associated with high risk of CVD and HF, but did not provide incremental prognostic information beyond BMI. U-shaped relationship was observed between leptin and mortality
Wannamethee et al. [10]	4,080 men without prevalent HF (average age, 70 years)	Leptin	Leptin was associated with incident HF in men without preexisting CHD
Ingelsson et al. [53]	946 men without overt HF (average age, 70 years)	Adiponectin	Adiponectin was not associated with incident HF
Frankel et al. [54]	2,739 asymptomatic healthy participants in the Framingham Offspring Study (average age, 61 years)	Adiponectin, resistin	Resistin was associated with incident HF, but adiponectin was not
Butler et al. [61]	2,902 subjects without prevalent HF (average age, 74 years)	Leptin, adiponectin, resistin	Resistin was associated with incident HF, but neither leptin nor adiponectin was
Zhang et al. [62]	980 subjects with documented coronary heart disease (average age, 66 years)	Resistin	Resistin was associated with high risk of mortality and hospitalization for HF, but did not provide prognostic information beyond traditional cardiovascular risks

Table 28.3 Current situation regarding the usefulness of each adipokine as a biomarker of HF

Circulating levels	Screening biomarker	Diagnostic biomarker	Prognostic biomarker	Managing biomarker
Leptin	Δ useful in men without preexisting CHD	○	Δ in patients with DCM and DCMi	×
Adiponectin	×	○	○	○ attention should be paid in patients treated with β-blockers
Resistin	○	○	○	×
Apelin	?	×	×	Δ within limited data
Visfatin	× within limited data	○	× within limited data	○ within limited data
Lipolalin-2	?	○	○ within limited data	?

○, promising; Δ, limited usefulness; ×, not recommended; ?, not evaluated

Diagnosis

Increasing evidence demonstrates that plasma levels of most adipokines are generally increased in patients with HF. However, the value of each adipokine as a diagnostic biomarker is a secondary matter, and we should better utilize plasma adipokine levels in combination with each other, since the mechanisms by which plasma levels of each adipokine increase, although different, overlap partially.

Prognosis

This is the most likely use of plasma adipokine levels for patients with HF. Although the prognostic value of leptin remains indefinite, plasma levels of adiponectin and resistin would be useful to predict the prognosis of patients with HF. We could not estimate the value of other adipokines as prognostic biomarkers because the data available on these adipokines are currently limited.

Management

Recent findings suggest that plasma adipokine levels would decrease with the improvement of cardiac function and mechanical unloading. However, the pattern of changes in plasma adipokine levels after treatment seems to differ among adipokines. The levels of adiponectin and visfatin are reported to decrease rapidly, with the improvement of hemodynamics. However, the use of

β-blockers reportedly affects the association between plasma adiponectin levels and the prognosis of HF, so the significance of adiponectin in managing patients with HF remains indefinite. At present, we do not know whether the effect of β-blockers can be similarly observed for other adipokines.

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29 Aging-Related Changes in Cellular and Molecular Mechanisms of Postinfarction Remodeling: Implications for Heart Failure Therapy

Henry Han-Jen Shih and Andrew J. Boyle

The normal course of aging is well known to result in decreased cardiac function; decreased capacity to tolerate insults, such as myocardial infarction (MI); and a higher prevalence of pathological remodeling post-MI. Recent progress in aging biology has allowed investigators to understand the effect of aging from the molecular, organelle, and cellular levels that ultimately result in organ dysfunction. In this chapter, we will review the natural course of cellular and molecular changes in the heart that predispose an aging heart toward adverse remodeling, the age-related differences in the postinfarction remodeling process, the clinical implications of aging and postinfarction remodeling, and future targets for heart failure therapy in the aged population.

Cellular and Molecular Changes in the Aging Heart Predispose to Remodeling

For a long time, the cardiomyocyte was regarded as a cell type that lasts the life span of the organism, with no capability of cell renewal once the cell is lost. This concept of irreversible cell loss shaped the paradigm of our understanding and management of ischemic heart disease, and it may have contributed to therapeutic nihilism for elderly patients presenting with MI, as their loss of myocardium was thought to be irrecoverable.

However, recent research findings suggest that cardiomyocytes have the capacity to replace themselves, albeit at a very low rate. At any point in time in a young healthy heart, a small percentage of cardiomyocytes are committed to programmed cell death, and a similar percentage are formed, thus maintaining an equilibrium of cardiomyocyte cell number.

A recent study of a global-scale pulse-chase experiment has enabled the calculation of the rate of cardiomyocyte renewal. The pulse comes from the radiation exposure from repeated nuclear weapon testing during the cold war period, which resulted in incorporating a detectable level of radioactive carbon into newly generated cardiomyocytes during that period. On autopsy, the authors studied the proportion of cardiomyocytes that contained radioactive carbon, and using mathematical models, they estimated the renewal rate for cardiomyocyte at baseline to be 1 % per year in young adult hearts and 0.45 % per year in older adult hearts [1]. Additionally, even in the absence of clinical cardiac injury, the result of constant low-level cell death over time, in concert with the decreased rate of renewal with age, leads to a gradual decline in the number of cardiomyocytes over the span of a person's lifetime. The low rate of cell turnover in the heart is in

H.H.-J. Shih, MD
School of Medicine, Tufts University, 145 Harrison Avenue, Boston, MA 02111, USA
e-mail: henry.shih@tufts.edu

A.J. Boyle, MBBS, PhD (✉)
Department of Cardiology, University of Newcastle, John Hunter Hospital, 2 Lookout Road, New Lambton Heights, Newcastle, NSW 2305, Australia
e-mail: andrewboyle500@gmail.com

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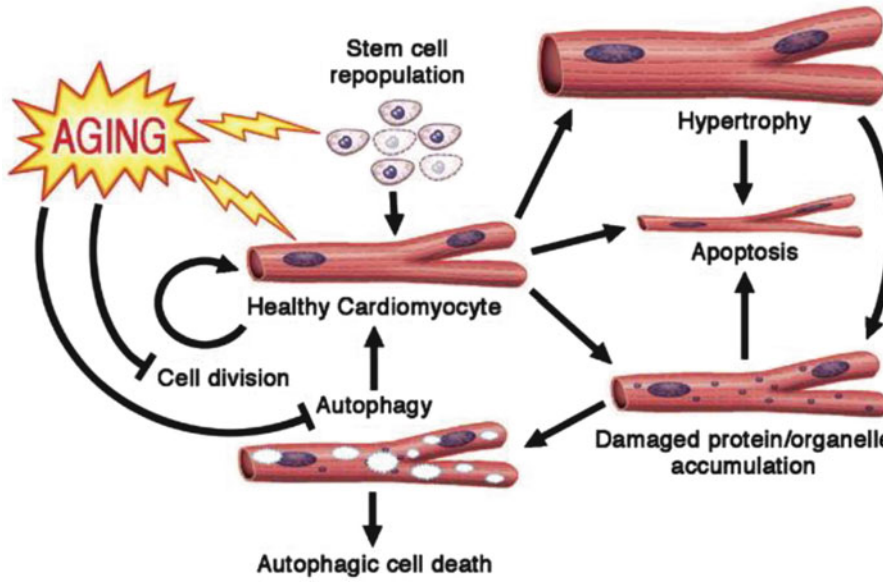

Fig. 29.1 *Aging of cardiomyocytes*. The aging cardiomyocyte has decreased renewal capacity from stem cell failure and possibly cardiomyocyte cell division failure. Aging cardiomyocytes also have a cellular biochemistry profile predisposing toward apoptosis. Neurohormonal signaling to compensate for reduced cardiac function causes cells to hypertrophy, thereby increasing the metabolic demand, and causes increased production of proteins and organelles subjected to oxidative damage. Lastly, accumulation of intracellular waste and insufficient autophagy result in cell death. *Regular arrows* = promotion/induction; *blocked arrows* = inhibition; lightning = detrimental effects of aging (reprinted from Shih H, Lee B, Lee RJ, Boyle AJ. The aging heart and post-infarction left ventricular remodeling. J. Am. Coll. Cardiol. 2011;57(1):9–17. With permission from Elsevier)

stark contrast to other organs known to have regenerative capacity, such as the liver, which can sustain 20 % of cells undergoing apoptosis in the setting of hepatitis and still regenerate until eventual functional recovery [2]. The altered balance between cell death and renewal that occurs in the aging heart sets the scene for worse outcomes in the setting of MI.

Cardiomyocyte Apoptosis and Autophagy

Aging is associated with a gradual loss of cardiomyocytes. Several mechanisms have been proposed that drive the chronic, progressive cardiomyocyte cell death. First, aging is associated with accumulation of cellular oxidative damage within cardiomyocytes. Cardiomyocytes consume a high amount of oxygen to meet their metabolic demand. Reactive oxygen species formed during oxidative metabolism are known apoptosis-inducing signals via increase in mitochondrial permeability and subsequent cytochrome C release [3]. Second, intracellular waste accumulates from random errors in protein synthesis, mechanical wear and tear from constant beating, and insults from extracellular causes such as ischemia, toxins, or inflammatory damage [4–6]. The resulting organelle and protein damage is usually cleared up via autophagy, a process of intracellular waste digestion. However, when the amount of waste cannot be effectively cleared up via autophagy, cellular function can be impaired and cell death cannot be avoided [7] (see Figs. 29.1 and 29.2).

It is known that aging cardiomyocytes have upregulation of autophagy [6]. Despite the increase in autophagic activity, aging cardiomyocytes are still left with an increased level of disrupted mitochondria, lipofuscin accumulation, damaged organelles, and disrupted cellular organization, suggesting an imbalance between accumulation and clearance of cellular waste [8].

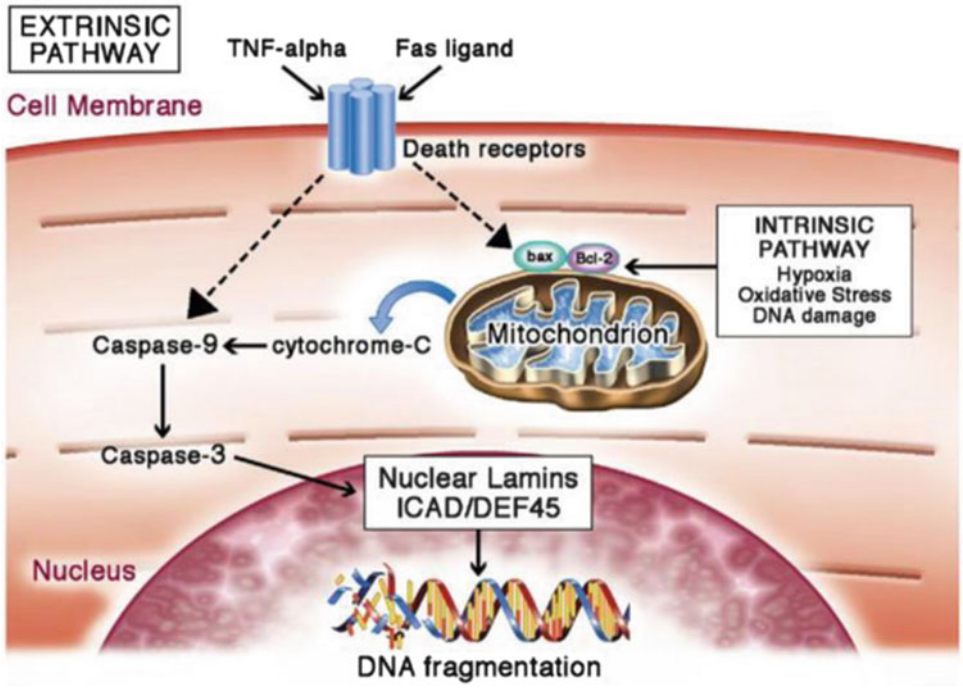

Fig. 29.2 *Cardiomyocyte apoptosis*. Cardiomyocyte apoptosis is mediated via both intrinsic and extrinsic pathways. Intrinsic pathway is activated via damage to the intracellular components from hypoxia, oxidative stress, or DNA damage. Bcl-2 family protein is activated by the stressor signals. Bcl-2 then increases mitochondrial outer membrane permeabilization complex, which releases cytochrome C and downstream apoptosis cascade. Extrinsically, death signals such as TNF-alpha and Fas ligand trigger apoptosis by directly activating the caspase cascade or indirectly via inducing mitochondria permeability change. The cascade cleaves nuclear lamins and breaks down nuclear structure. Caspase also cleaves and inactivates ICD/DEF45, a nuclease inhibitor. The result is DNase disinhibition and DNA breakdown (reprinted from Shih H, Lee B, Lee RJ, Boyle AJ. The aging heart and post-infarction left ventricular remodeling. J. Am. Coll. Cardiol. 2011; 57(1):9–17. With permission from Elsevier)

The accumulation of intracellular waste then leads to upregulation of pro-apoptotic and pro-autophagic gene expression, shifting the cell toward a pro-apoptotic state and eventually resulting in cell death. Overall, the gradual shift in cardiomyocyte state from pro-survival to pro-apoptosis over the course of an individual's lifetime results in a decrease of 30 % in the number of cardiomyocytes [9] (see Fig. 29.3).

Stem Cell Failure

The pool of cardiomyocytes is maintained in equilibrium, with a balance between formation of the new cells and death of the old cells. Besides the increased propensity toward cell death in the process of aging, the decreased rate of replenishing the pool of cell may contribute to the decline in overall cell number. New cells can come from cellular division from the existing cell or differentiation from stem cells or progenitor cells. It is known that most cardiomyocytes do not apoptose or divide. The basal rate of division is very low, estimated to be 14 cells per million, which makes the division rate quite similar to the apoptosis rate [10]. The overall decline in cell number in aging may be contributed to by the increased rate of cell death without a similarly increased rate of cell division [7].

Cardiac stem cells do not contribute much to the pool of cardiomyocytes in the absent of cardiac disease associated with massive cell death (i.e. necrosis induced by ischemia or infection). However, in such disease states, a significant amount of cardiac stem cell activation occurs. It is

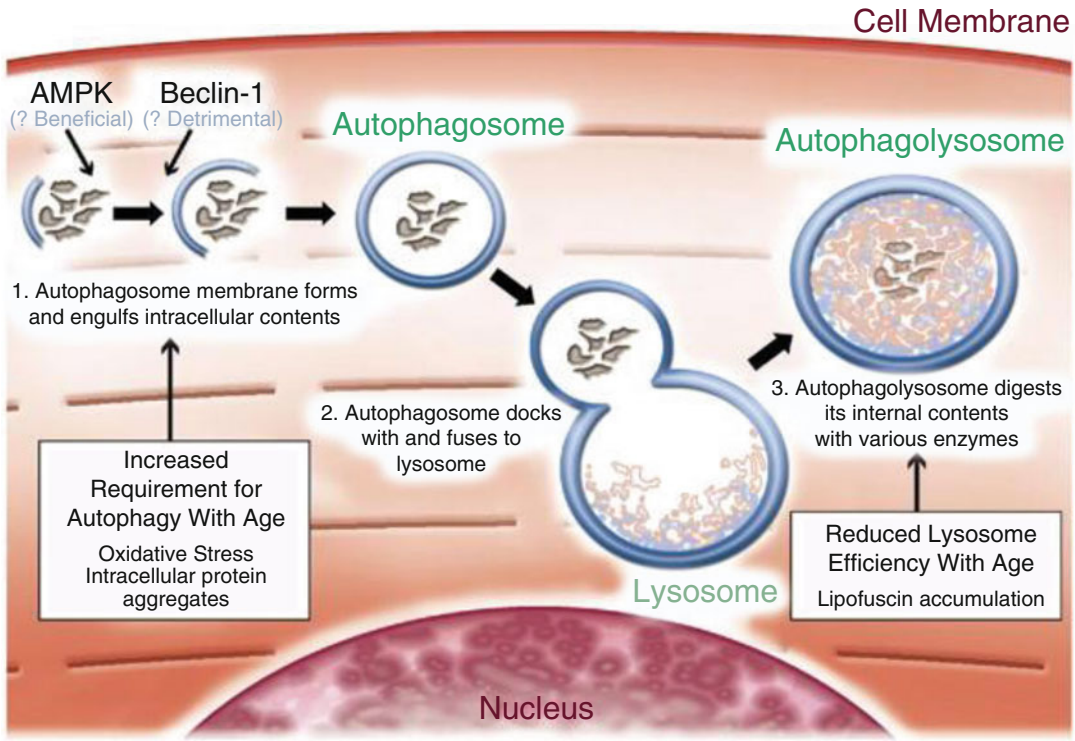

Fig. 29.3 *Cardiomyocyte autophagy*. The accumulation of intracellular waste and nutrient deprivation trigger autophagy signal that begins with formation of autophagosome, engulfment of intracellular waste, and vesicle fusion with lysosome to ultimately form autophagolysosome. Engulfed waste is digested in autophagolysosome, and the digested components are recycled to be used as cellular building block. In aging, the pathway of autophagy can be impaired by overwhelming the processing capacity due to increased waste production and reduced autophagy efficiency as the indigestible waste traps the autophagolysosome (reprinted from Shih H, Lee B, Lee RJ, Boyle AJ. The aging heart and post-infarction left ventricular remodeling. J. Am. Coll. Cardiol. 2011;57(1):9–17. With permission from Elsevier)

known that endogenous stem cells or progenitor cells have the capability to differentiate into cardiomyocytes and coronary vessels in response to myocardial disease, and the newly formed cells are structurally and functionally incorporated into the existing myocardium [10].

The effect of aging on cardiac stem cells plays a more significant role in disease state compared to the disease-free state. The worsening cardiac tolerance after insult and injury in aging studies can be at least in part attributed to cardiac stem cell aging [11]. It is ironic that stem cells, which are commonly considered to be the fountain of youth, cannot escape the fate of aging. Old stem cells that undergo senescence are less capable of self-replication or differentiation into functional tissues [12]. Stem cell senescence occurs via the following mechanisms: telomere arrest, DNA replication arrest, apoptosis, and autophagic cell death. Telomeres are the capping sequence on both ends of a DNA strand. The telomere sequences do not get fully synthesized in each cell cycle due to limitations of DNA polymerase. Upon reaching a critically short telomere length, cell cycle is arrested, and the stem cell loses its self-renewal property [13–15]. Another form of stem cell arrest comes from the stochastic errors in DNA replication. As the number of cell cycle (and therefore number of DNA replication cycles) increases during the journey of life, the errors of DNA replication accumulate. Upon reaching a certain threshold

of DNA errors beyond a repairable level, tumor suppression mechanisms activate to arrest cell cycle or induce apoptosis [16]. The accumulation of cellular waste contributes to stem cell failure as well, by triggering apoptosis and autophagic cell death mechanisms described previously. Lastly, the change in extracellular matrix (ECM) composition with increased fibrosis infiltration may constitute a hostile environment for stem cell engrafting [17].

Intracellular Remodeling-Protein Signaling and Hypertrophy

The number of cells that survive, die, or regenerate is only a part of the story of cardiac aging. Intracellular biochemical change, which can be termed "intracellular remodeling," in cardiomyocyte aging, can result in organ-level remodeling and heart failure. One example of intracellular remodeling involves changes in calcium handling. Calcium not only mediates the contraction of cardiomyocytes but is also involved in many intracellular signaling pathways. Intracellular calcium levels are usually low, and the cytoplasmic level is tightly regulated by precise coordination of voltage-gated channels on the cell membrane, sarcoplasmic reticulum, and sarcolemma [18].

Aging results in defective calcium cycling in cardiomyocytes. Proposed mechanisms for this abnormality include oxidative damage and dysfunctional protein synthesis, which result in lower density of calcium channel proteins, leaky channels, and less sensitive channel proteins. Ion channel proteins, which normally provide tight barriers and control calcium flux across the sarcolemma and sarcoplasmic reticulum, become defective with age. This results in abnormal release and ineffective reuptake of calcium between the organelles and cytoplasm, leading to intracellular calcium overload, and the downstream effect is inappropriate calcium-mediated myofibril contraction. Additionally, the sensitivity of myofibrils to calcium may be impaired due to age-related change in protein composition, reactive oxygen species damage, proteolysis, and reduced production. Together, the dysfunctional myofibril and dysfunctional calcium handling lead to worsened cardiomyocyte function. The aggregate of these dysfunctional cardiomyocyte cellular changes leads to organ-level myocardial dysfunction and heart failure [19].

Cardiomyocyte hypertrophy, which is associated with cardiac aging [20], is another example of intracellular remodeling. A likely explanation for the association is that in order to maintain adequate cardiac function, the aging heart compensates for the loss of cells via cellular hypertrophy and changes in ECM composition. Under the influence of hemodynamic load and neurohormonal and prohypertrophic signals, cardiomyocytes are capable of growing longitudinally and transversely, leading to a massive increase in cell size [21]. In old individuals and patients with cardiomyopathy, hypertrophy is thought to be a means to maintain short-term cardiac function but comes at the cost of deleterious pathological remodeling in the long term. A pathologically hypertrophied cell is more prone to cellular damage and cell death, which leads to a downstream spiral of more deleterious intracellular remodeling and eventual heart failure [22].

The mechanism of hypertrophy-related cell death can be partly explained by the altered protein synthesis/clearance balance. Hypertrophic signals from hemodynamic load, G protein pathways activated by extracellular signaling molecules, and peroxisome proliferation signaling in response to fatty acid oxidation all lead to increased protein synthesis that often occurs in the setting of increased oxidative stress. As a result, there is a simultaneous increase of both functional proteins and damaged proteins that overwhelms the waste-clearing autophagic system. Additionally, the chronic activation of intracellular Akt signal that promotes cardiomyocyte hypertrophy disrupts autophagy regulation [23, 24]. The inability to clear intracellular waste leads to reactive oxygen species causing additional protein and organelle damage, and cardiomyocyte contractility becomes impaired. The defective hypertrophied cells are more prone to cell death [3]. Moreover, defective hypertrophied cells affect the global cardiac function, which leads to

a persistently increased pathological neurohormonal signaling that promotes more cardiomyocyte hypertrophy, leading to a vicious cycle of hypertrophy begetting more hypertrophy (see Fig. 29.1).

Of note, the maladaptive hypertrophy of aging should be distinguished from the adaptive hypertrophy in young healthy heart exemplified in well-trained athlete. Athletic training activates distinct gene expression profile without the existing accumulation of oxidative intracellular waste or dysfunctional organelles. Physiological hypertrophy therefore leads to organized cardiomyocyte architecture and enhancement and preservation of long-term cellular function.

Extracellular Matrix Aging

Age-related changes affect not only cardiomyocytes but also the cardiac ECM. Matricellular proteins do not contribute to cardiac structure but influence the production and composition of ECM through cell-cell signaling and the senescence of matrix-producing cells. The cardiac remodeling of aging involves the activation of matricellular proteins to compensate for lost cells and sustain cardiac demand [25]. Matricellular protein activity and signaling lead to increased fibrosis and changes in the ECM profile. Specifically, there are more collagen, fibronectin, alpha-1 and alpha-5 integrin, and collagen cross-linking [26]. The end result is stiffened ventricular wall that impairs cardiac contraction, relaxation, and electrical conduction. When matrix-producing cells, including fibroblast, myofibroblasts, and inflammatory cells, undergo senescence, their collagen production becomes more variable, and their response to disease state becomes less effective.

Age-Related Differences in Experimental Post-MI Left Ventricular Remodeling

Aging is characterized by slow but progressive remodeling of the heart toward decreased cardiac function and decreased cardiac reserve to tolerate insults and injury, such as MI. Following MI, aging is associated with different effects on the cardiomyocyte and the ECM.

Immediately postinfarct, there is a robust inflammatory response, mediating dead tissue clearance, and wound healing. This includes the influx of inflammatory cells, the proliferation of fibroblasts, the appearance of myofibroblasts, and the elaboration of matrix proteins. This process appears to be less functional in the aging heart. In the canine heart subjected to experimental MI, aging is associated with a more robust upregulation of the inflammatory cytokines tumor necrosis factor alpha and interleukin (IL) 6, with an upregulation of the anti-inflammatory transforming growth factor beta-1 and with a more robust downregulation of the anti-inflammatory IL10, compared to younger animals. In addition, aging was associated with a more robust upregulation of ECM-modulating proteins, including matrix metalloproteinase (MMP) 9, MMP2, tissue inhibitor of MMP (TIMP) 3, secretory leukocyte protease inhibitor, secreted protein acidic and rich in cysteine, osteopontin, a disintegration and metalloproteinase (ADAM) 10, and ADAM 17, compared to young animals. These changes were associated with dysfunction at the organ level. Importantly, all these molecular changes, as well as the deterioration in LV function, could be effectively prevented in the elderly dogs with early administration of an angiotensin receptor blocker [27]. In addition to these inflammatory and matrix changes early post-MI, the aged myofibroblast, fibroblast, and inflammatory cells in old hearts have impaired responses to healing signals, impaired production of ECM for the process of healing, and delayed granulation tissue formation. This dysfunctional healing process slows scar formation, which may induce more wall stress in the surviving myocardium, which in turn contributes to the progression of adverse remodeling [28]. Furthermore, this may make the aging heart more prone to mechanical complications of MI.

At baseline, cardiomyocytes in the aging murine heart show increased expression of caspase-3, but a parallel increase in anti-apoptotic factors results in no difference in the rate of

Table 29.1 Effects of aging on the heart that predispose to adverse postinfarction remodeling

Cellular and molecular changes	Effect of aging	Clinical effects at baseline	Clinical effects after MI
Cardiomyocyte survival	↓	Impaired systolic function	LV dilation, eccentric remodeling, and systolic dysfunction
Cardiomyocyte proliferation	↓	Impaired systolic function	LV dilation, eccentric remodeling, and systolic dysfunction
Cardiac stem cell number	↓	Impaired systolic function	LV dilation, eccentric remodeling, and systolic dysfunction
Cardiomyocyte diameter	↑	LV hypertrophy	Increased wall stress, concentric remodeling
Myocardial fibrosis	↑	Diastolic dysfunction	Fibrosis of noninfarct zone, increased arrhythmias
Dysfunctional fibroblasts	↑	Diastolic dysfunction	Infarct expansion

cardiomyocyte apoptosis compared to young hearts [20]. However, after MI, there is greater increase in cardiomyocyte apoptosis in aging hearts than in young hearts, and this proceeds via multiple pathways, not just caspase-dependent pathways (our unpublished data), suggesting that the excess apoptosis with age is not due to exaggeration of the same apoptotic response seen in young mice, but is due to activation of different age-specific pathways to apoptosis. Identifying such age-specific pathways may result in new age-specific therapies for post-MI remodeling. In rats undergoing experimental MI, aged rats show a higher rate of cardiomyocyte apoptosis, and this is associated with worse cardiac function. Importantly, the aging rats responded to treatment, in this case with granulocyte colony-stimulating factor+stem cell factor, with a reduction in the number of apoptotic cardiomyocytes. But the lesser reduction in aged rats compared to young rats suggests that there need to be different doses, timing, or adjunctive therapies in the aged animals to achieve the same results as the young mice. Finally, the disruption from cardiac conduction system due to the loss of pacemaker cells and fibrous infiltration in ECM with aging also put elderly patient at increased risk of dying from arrhythmia and cardiac arrest [29] (see Table 29.1).

It is noteworthy that in these and other studies [30], remodeling following experimental MI can be prevented and/or treated in aged hearts, but the treatment is usually less successful than in young hearts.

Age-Related Differences in Patient Outcomes After MI

Elderly patients are more likely to die from their MI when compared to the younger patients. The mortality associated with MI increases by 6 % with each year of age [31]. On the organ and functional level, the reasons for increased post-MI mortality include higher rates of cardiac arrest and the tendency to develop mechanical complications of MI, such as papillary muscle rupture, ventricular free wall rupture, and ventricular septal defect [31–33]. This clinical phenomenon is likely a direct consequence of the ECM failure seen in experimental MI in aging animals, with delayed wound healing and scar formation. Among the MI survivors, elderly patients are more likely to develop heart failure as a consequence of MI than younger patients [34]. This is likely due to a combination of factors seen in experimental MI, including the loss of cardiomyocytes due to higher rates of apoptosis, less cardiomyocyte repletion due to stem cell failure, and stiffening of the heart from altered ECM responses. Even with optimal medical therapy for post-MI heart failure, elderly patients have significantly higher mortality and morbidity compared to the younger patients [35]. The cellular and molecular changes seen in experimental MI have very real implications for aging patients with MI.

The guidelines from American College of Cardiology and American Heart Association for

management of post-MI patients and prevention for progression toward heart failure do not distinguish between young and old patients. After an acute MI, patient should receive rapid restoration of cardiac perfusion via fibrinolysis, percutaneous cardiac intervention, or coronary artery bypass surgery regardless of age (Class 1 indication; level of evidence A). Moreover, the recommendation for post-MI maintenance therapy to prevent and treat LV remodeling, including the use of ACE inhibitor, beta-blockers, aldosterone antagonist, and cardiac rehabilitation, does not differ based on age [36].

The current principles of treatment for postinfarct remodeling chiefly involve stopping the offending causes and optimizing cardiac physiology to slow down the progression of adverse remodeling. Specifically, this entails providing sufficient oxygenation to the myocardium, reducing the afterload of the heart, and modifying the neurohormonal profile to minimize cardiac wall stress. There are no currently available therapies directed specifically toward the pathological processes occurring in the aging heart.

Potential Future Therapies for Post-MI Remodeling in Aging Patients

Stem Cell Therapy

Given that a major consequence of cardiac aging is the failure to renew diseased myocardium, one can theorize that an elderly post-MI patient would particularly benefit from cardiac regeneration. Stem cell therapy has the potential to repair damaged myocardium, and experimental studies are very encouraging. Early clinical trials, however, have yielded inconsistent results. A complete discussion of stem cell therapy is beyond the scope of this chapter, but there are particular challenges in translating stem cell therapy to the clinic in aging patients.

Current research indicates that the therapeutic effect of stem cell comes from both engraftment of stem cell and the paracrine effect exerted by the transplanted cell [37–39]. Differentiation of stem cells into functional cardiomyocytes may replace cells lost from the infarction and may help attenuate adverse remodeling. The paracrine effects of stem cells promote angiogenesis, decrease the rate of cardiomyocyte apoptosis, and may promote wound healing. These properties seem particularly appealing in the aging heart, because many of these functions address the exaggerated response of the aging heart to MI. Several issues confront the field of cell therapy as it applies to the aging heart. First, aging stem cells do not function as well as younger stem cells. Therefore, which cell type is optimal for cell therapy? Autologous cardiac stem cells may be effective therapy for younger hearts. However, in older hearts, these cells have clearly been shown to be dysfunctional. Perhaps allogeneic cell therapy is a better option in elderly patients. One possibility is using mesenchymal stem cells from young healthy donors, as these can escape immune recognition. Second, the optimal cell dose (i.e. number of stem cells) is not known. Age-specific studies need to be performed to assess this, as it is likely that older patients will need greater numbers of cells to achieve a similar result to younger patients.

Third, understanding the time course and regional changes in the post-MI remodeling with age is paramount to determining the optimal timing for cell therapy. For instance, it is thought that stem cells should be delivered at the peak of cardiomyocyte apoptosis to maximize their anti-apoptotic effect [3, 40]. However, there are distinct differences in the timing of the remodeling process in young and aging hearts, as described above. The slower time course of inflammation and granulation tissue formation with age will affect the success of cell engraftment and survival in aging hearts. Thus, more research is needed in defining the cell type and number as well as the optimal timing of cell therapy in aging hearts.

Paracrine Modulation

Paracrine signaling modulation has been proposed as a mechanism for the therapeutic effect of stem cell transplantation. It has been shown that

delivering the necessary factors, without needing the stem cells themselves, can exert cardioprotective benefits in young hearts following MI [38]. Paracrine effects can modulate endogenous stem cell activation and differentiation, promote cardiomyocyte survival, reduce pathological hypertrophy, and modulate the inflammatory milieu. Several targets of paracrine regulations are identified to have effective therapeutic effect. For instance, IGF-1 and TGF beta-1 act on cardiomyocyte to promote survival in aging hearts, whereas GSK-3beta expression induces cardiomyocyte differentiation and angiogenesis [41–43]. Age-specific research into paracrine signaling pathways is lacking and should be a focus of future studies.

Reverse Intracellular Remodeling

Several targets to reverse the process of intracellular remodeling have been proposed and experimented. Experimental models with overexpression of SER-CA2a-a calcium channel on sarcoplasmic reticulum improve cardiac function in aging animals [44]. Additionally, by amplifying the signal transduction in the calcium-dependent pathway via dexamethasone, contractility is also improved [45]. Because intracellular signaling is defective in aging cardiomyocytes, such treatments may be even more effective in older patients.

Gene Expression Therapy

The intracellular gene expression regulation via modulation of microRNA has recently appeared as a target point for intervention on cardiac remodeling. MicroRNAs are short RNA molecules that function as posttranscriptional modulators via repressing or degrading the existing pool of mRNA. In another words, microRNAs can act as fine-tuning controls to direct cells toward development, survival, or apoptosis [46]. Studies have found that in the post-MI state, expression of certain microRNAs leads to inhibition of cellular proliferation, alterations in the contractile function of cardiomyocytes, and promotion of apoptosis. Together, these cellular functional changes lead to pathological remodeling [47]. As a result, therapeutic control of the microRNAs via repressing maladaptive microRNAs and promoting pro-survival microRNAs may be an option for post-MI heart failure therapy in older patients.

In summary, the process of aging affects baseline cardiac function, cardiac reserve to tolerate MI, and the ventricular remodeling process after MI. The specific mechanisms of aging are starting to be understood at the molecular, cellular, and organ levels across different cardiac cell types, thereby opening a broad spectrum of possible targets for interventions to reverse the deleterious effect of aging on post-MI remodeling. Future research in modulating intracellular biochemistry, cell-to-cell signaling, and utility of stem cells may one day provide hope for the patients combating post-MI heart failure.

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30 Aging-Related Changes in Mitochondrial Function and Implication for Heart Failure Therapy

Satoaki Matoba, Atsushi Hoshino, and Hiroaki Matsubara

Introduction

Aging is a highly complex biological process associated with progressive accumulation of molecular, cellular, and organ damage, which leads to functional decline and increased susceptibility to disease and death [1, 2]. Mitochondrial dysfunction plays a critical role in aging [3]. There are three important roles of mitochondria: (1) energy production, (2) generation of reactive oxygen species (ROS), and (3) regulation of programmed cell death. Cellular homeostasis of all organisms is finely tuned by the function of mitochondria during aging. As the heart produces and consumes ATP most than other human organs, homeostatic control over the heart during aging is critically important.

In numerous aged tissues of many species, point mutations and deletions of mitochondrial DNA (mtDNA) accumulate [4]. These mitochondrial mutations lead to energy-generation defects, increased numbers of harmful reactive oxygen species, and subsequent decline of cellular homeostasis [5]. The causative role of mitochondrial compromise in the process of aging is confirmed by mice with mtDNA polymerase deficiency which show increased mtDNA mutations and subsequent premature aging. Indeed, preserving mitochondrial integrity delays age-dependent decline of organ function and extends life span in mice overexpressing catalase targeted to mitochondria [6].

In addition to antioxidant defense and protein quality control conducted by mitochondrial chaperones and proteases, mitochondrial integrity is maintained by the dynamic nature of the mitochondrial population in the cell. Membrane fusion and fission allow mitochondrial content mixing within a cell to keep up integrity, and severely damaged mitochondria are selectively removed by an autophagic process, termed mitophagy, to protect against apoptosis [6]. Preserving mitochondrial quality will be a therapeutic target to regulate the rate of organismal aging and the development of heart failure.

Energy Production and Generation of Reactive Oxygen Species

Cardiac mitochondria are the primary source of energy and maintain ATP levels through β-oxidation of fatty acid and by glycolysis. Decrease in energy production is reported in patients with heart failure [7]. In addition to the reduction in energetics, mitochondrial dysfunction

S. Matoba, MD, PhD (✉)
Department of Cardiovascular Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 kajii-chyo, Kamigyo-ku, Kyoto 602-8566, Japan
e-mail: matoba@koto.kpu-m.ac.jp

A. Hoshino, MD • H. Matsubara, MD, PhD
Department of Cardiovascular Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

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with oxygen consumption results in uncoupling of electron transport chain (ETC), and oxidative phosphorylation generates excess amount of reactive oxygen species (ROS). ROS are important signal in the cell, and mitochondria are the major source of intracellular ROS generation. It has been suggested that as much as 3–5 % of the oxygen consumed is ultimately diverted toward ROS production from isolated mitochondria [8]. Complex I and III of ETC are thought to be the major site of ROS production [9]. However, once ROS are generated, superoxide dismutates to hydrogen peroxide (H_2O_2) spontaneously. In the presence of nonprotein-bound redox cycling metals (i.e., copper and iron), H_2O_2 can be converted into the highly reactive hydroxyl radical ($^{\bullet}OH$) through the Fenton reaction. As the mitochondrial iron content increases with aging in the rodent myocardium, this reaction may extend the damage in aged heart [10]. Furthermore, mitochondrial DNA (mtDNA) is sensitive to oxidative damage because of its close location of ETC and the lack of histones. Indeed, the amount of ROS-induced base damage of mtDNA is much higher than that of nuclear DNA (nDNA) [11].

Higher level of ROS damage to mitochondrial proteins, lipids, and nucleic acids have also been detected in the old rodent myocardium [12]. Accumulation of mtDNA damage and subsequent mitochondrial dysfunction was characterized with the mice that express a proofreading-deficient mtDNA polymerase-γ (PolG). These mutants accumulate many mtDNA mutations and deletions [6, 13]. They showed reduced life span and premature onset of aging-related phenotypes including dilated heart. As these mice die of dilated cardiomyopathy, mice expressing cardiac-specific proofreading-deficient mtDNA showed the severe cardiomyopathy [14]. It is a remarkable discovery that overexpression of catalase targeted to the mitochondrial matrix (mCAT) rescued these mice [15]. To protect from ROS, mitochondria express several antioxidants, such as superoxide dismutase 2 (SOD2), catalase (CAT), peroxiredoxin 3, and peroxiredoxin 5. Regulating mitochondrial ROS with its scavenging system might be a strong tool for heart failure therapy; however, it requires more fundamental research on aging and mitochondrial dysfunction.

Recently, optimization of myocardial energy source is considered for the treatment of HF. Fatty acid oxidation is physiologically regulated by its concentration and several mitochondrial enzymes. As excess amount of lipid induces ROS and reduces the myocyte contraction (Fig. 30.1), regulating the balance of energy source will be beneficial for appropriate energy production and reduction of ROS damage [16].

Regulation of Programmed Cell Death

Myocardial infarction (MI) is one of the most causes of heart failure (HF) [17]. The causes of HF due to MI are a multifactorial process known as left ventricular remodeling. MI leads to irreversible death of cardiac myocytes within hours. MI also provokes neurohormonal changes which are attributable for compensation for impaired cardiac contraction caused by MI. At the organ level, LV remodeling consists of infarct expansion, myocardial hypertrophy, cardiac fibrosis, and ventricular dilatation. However, at the cellular level, the precise mechanism associated with LV remodeling has not been elucidated. Gould et al. have shown an age-dependent decrease in survival of following MI in mouse coronary ligation model [18]. In this model, although older animals live shorter than younger mice after MI, they have shown the possibility to improve the poor prognosis of aged mice with the pharmacological therapies.

To prevent myocyte cell death, reduction of apoptosis is extensively investigated [19]. Apoptosis is an evolutionarily conserved and highly regulated mechanism that results in the death and organized removal of useless cells. Morphologically, the process is characterized by chromatin condensation, DNA fragmentation, cellular shrinkage, and endocytosis of the dead cell by neighboring cells without inflammatory response. There are two major apoptotic signaling pathways: the "intrinsic" (mitochondrial) and "extrinsic" (death receptor-mediated) pathways. Apoptosis requires energy and activation of these biochemical steps. Under pathological conditions, these apoptotic programs can be triggered

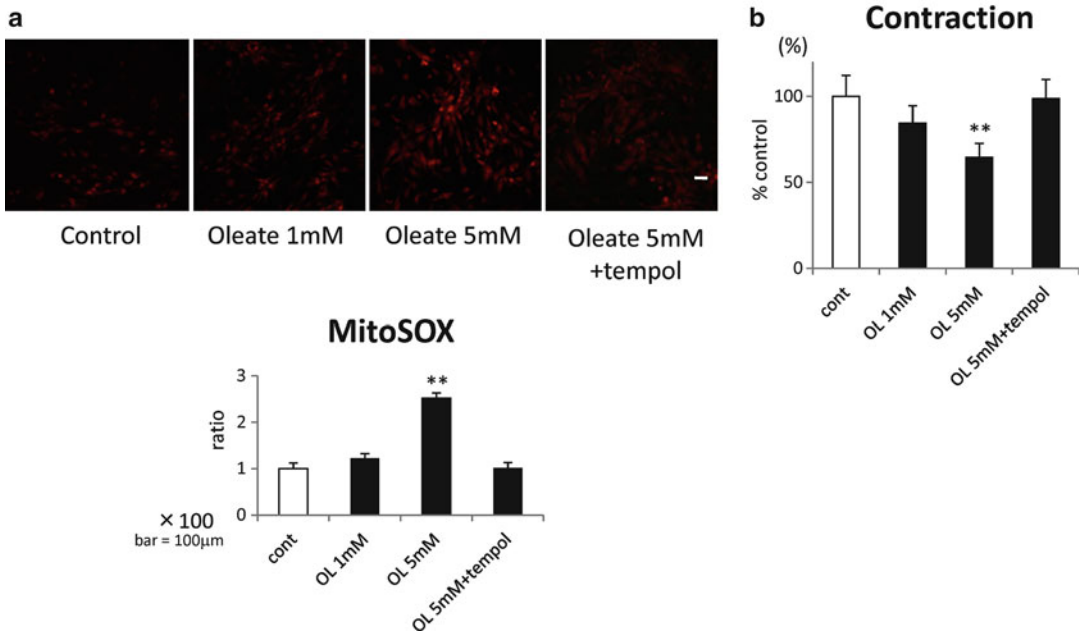

Fig. 30.1 *Fatty acid (oleate)-induced ROS generation reduced myocyte contraction*. (**a**) Incubation with oleate increased ROS generation detected by MitoSOX in myocytes. Treatment with tempol reduced ROS generation. (**b**) Contraction of electrically paced (3 Hz) myocytes was decreased by the administration of oleate (5 mM). Oleate-induced cell alteration was prevented by tempol. $^{**}P<0.01$ vs. control *OL* oleate (reprinted from Nakamura H, Matoba S, Iwai-Kanai E, Kimata M, Hoshino A, Nakaoka M, Katamura M, Okawa Y, Ariyoshi M, Mita Y, Ikeda K, Okigaki M, Adachi S, Tanaka H, Takamatsu T, Matsubara H.p53 promotes cardiac dysfunction in diabetic mellitus caused by excessive mitochondrial respiration-mediated reactive oxygen species generation and lipid accumulation. Circ Heart Fail. 2012;5:106-15. With permission from Wolter Kluwers Health)

inappropriately. Although cardiac myocyte apoptosis is a self-induced physiological cell death at 10 per 100,000 cells (0.01 %) at baseline, it increased to as much as 2 % in conditions such as dilated cardiomyopathy or ischemic cardiomyopathy [20].

In fact, aging myocytes are more susceptible to apoptosis. Cardiomyocytes are exposed to oxidative damage from high level of metabolic and mechanic stress. Oxidative damage on nDNA and mtDNA leads to increase of pro-apoptotic gene expression. In practice, senescent cardiomyocyte is defined by the expression of senescent markers p53, p21, and p16 and the presence of shorter telomeres [21]. Recently, Sahin et al. reported that telomere dysfunction repressed the master regulators of mitochondrial biogenesis, peroxisome proliferator-activated receptor gamma coactivator (PGC)-1α, and PGC-1β in the heart in a p53-dependent manner [22]. Although there are some differences in disease models [16, 23, 24], p53 is activated in heart failure [16, 23–25] and plays a significant role in the myocyte apoptosis of aged heart or diseased heart. Investigation of p53 and mitochondria has been receiving wide attention from cancer biologist to the investigators of aging. Research of their direct interaction and management against stress will provide important clues for cardiovascular investigators.

Control of Mitochondrial Biogenesis and Mitophagy

Fission/Fusion System

As the mitochondria are dynamic organelles that constantly divide and fuse to maintain their numbers, disruption of this process in the heart contributes to HF. Recent work has identified

changes in the new mitochondrial process such as mitochondrial fusion and fission and mitophagy as synergistic contributors to the development of HF [26]. Mitochondrial fusion mixes mitochondrial contents and enables to repair mtDNA and distribute metabolites equally. On the other hand, fission enables the segregation of mitochondria in two daughter organelles and increases the number of mitochondria.

Despite the variation in mitochondrial size and shape in the myocyte, dynamism of mitochondria in the adult heart is still unclear. In fact, dysregulation of mitochondrial turnover and fragmented mitochondria were reported in dilated cardiomyopathy [27].

These pathological changes in mitochondrial morphology are associated with a decrease in optic atrophy protein 1 (OPA1) levels and an increase in apoptosis [28]. The alteration of intramitochondrial structure was also observed in failing rat heart [29]. These researchers demonstrated that the disruption of mitochondrial dynamics and structure is the important process in the pathogenesis of HF. As many studies have been done in yeast and cultured mammalian cells, further work will be needed to define the role of mitochondrial fission/fusion in HF and to discover the way to regulate the fine balance of fission/fusion and mitochondrial function.

Mitochondrial Biogenesis

Mitochondrial biogenesis is regulated by the transcriptional level of nuclear-encoded coactivators and transcription factors. The first reported coactivator to regulate mitochondrial biogenesis and function was PGC1-α [30]. Next, PGC1-β and PGC-related coactivator (PRC) were identified [31, 32]. To activate the system of biogenesis, these three factors coordinated with other transcription factors such as nuclear respiratory factors 1 and 2 (NRF-1 and NRF-2), estrogen-related receptor-α (ERR-α), and PPAR [33]. Indeed, overexpression of PGC1-α induced mitochondrial biogenesis, which demonstrated increasing mitochondrial number and activation of oxygen consumption [34]. Recently, resveratrol treatment improved the survival of hypertensive model of heart failure [35].

Resveratrol treatment not only preserved mitochondrial biogenesis but also protected mitochondrial fatty acid oxidation. Increasing functional mitochondria physiologically will be a key to develop effective strategy to treat HF.

Mitophagy

Mitochondrial proteins can be degraded by Lon protease or AAA protease or proteasomes in the mitochondrial matrix, and some outer membrane proteins are eliminated via the proteasome [36]. However, mitochondrial degradation is mainly achieved by the autophagy-lysosome pathway. Selective autophagic degradation of damaged or unnecessary mitochondria is called mitophagy and plays an important role in mitochondrial homeostasis. Mitochondrial fission is essential for mitophagy; therefore, the impairment of fission disrupts the mitophagy, which induces the accumulation of dysfunctional mitochondria [37]. Loss of mitochondrial membrane potential is a major trigger for mitophagy. The selectivity of mitophagy is regulated by mitochondrial fusion/fission system and several key proteins Bnip3, Bnip3L/Nix, parkin, PTEN-induced kinase 1(PINK1), and p62/SQSTM1 [38, 39]. Bnip3 and Bnip3L/Nix are BH3-only proteins of the Bcl-2 family and known as the regulator of intrinsic mitochondrial pathway of apoptosis. However, recent studies demonstrated that they can also regulate autophagy [40, 41]. It is suggested that Bnip3 promotes degradation of proteins in ETC without activating apoptosis [42]; therefore, it is important for ROS mediator to reduce cardiac remodeling [40]. Parkin is an E3 ubiquitin ligase; dysregulation of parkin is linked to Parkinson disease. Parkin is highly expressed in many tissues, including the brain, heart, liver, and skeletal muscle. Mitochondrial stress translocates parkin from cytosol to mitochondria [41]. This translocation of parkin needs the activity of PINK1. The turnover of PINK1 by proteolysis is rapid, and the level of PINK1 is maintained at very low in healthy mitochondria. When mitochondria are damaged, proteolysis of PINK1 is inhibited,

which leads the accumulation of PINK1 only in damaged mitochondria and enables parkin to translocate to impaired mitochondria. Parkin also recruits the ubiquitin-binding deacetylase HDAC6 and p62/SQSTM1, which promotes the mitophagy.

Optimization of cardiac mitophagy might be a new therapeutic target for HF [39]. Recently, pharmacological inhibition of abnormal mitophagy ameliorated pressure overload-induced heart failure [43]. Furthermore, p53, tumor suppressor protein, is also focused on its function as a regulator of autophagy. There are multiple p53 target genes to stimulate autophagy. Damage-regulated autophagy modulator (DRAM) and Tp53-induced glycolysis and apoptosis regulator (TIGAR) are the candidates for cancer therapeutics [44–46]. Contrasting with this nuclear p53 function as a proautophagic function, Tasdemir et al. demonstrated that cytoplasmic pool of p53 inhibits autophagy [47]. In the ischemic heart, we reported for the first time that p53 inhibits ischemia-induced myocyte mitophagy and that TIGAR is upregulated in ischemic myocardium. TIGAR attenuated mitophagy to cause accumulation of damaged mitochondria, subsequent apoptotic myocyte death, and deterioration of cardiac remodeling (Figs. 30.2 and 30.3). These data suggested that p53/TIGAR-mediated dysregulation of

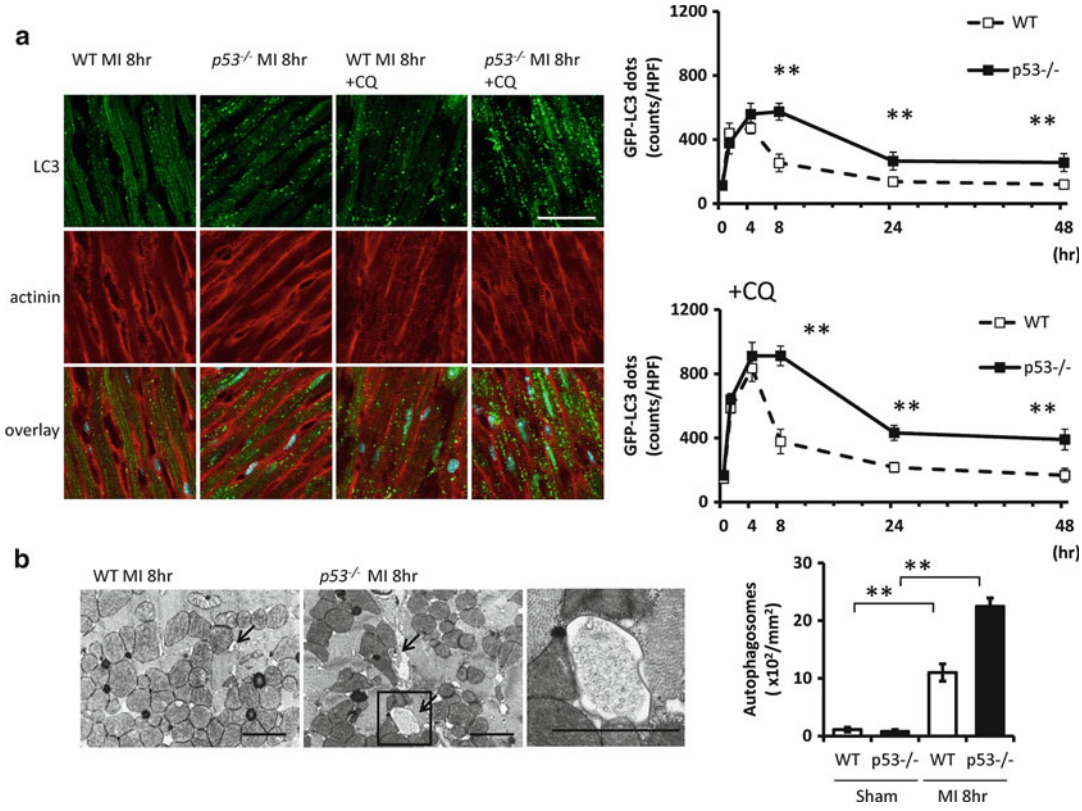

Fig. 30.2 *Sustained activation of autophagy after myocardial infarction in p53*$^{-/-}$ *heart*. Autophagic flux was assessed with intraperitoneal injection of chloroquine (CQ). (**a**) Representative images of GFP-LC3 dots in ischemic border zone of GFP-LC3 transgenic mice; *green*, GFP-LC3; *blue*, DAPI-stained nuclei; *red*, α-actinin-positive cardiac myocytes; original magnification ×600; scale bar, 40 μm. Time course analysis of GFP-LC3 dots in cardiac myocytes is shown in *right panels*. $^{**}P<0.01$ vs. WT. (**b**) Representative electron micrographs in ischemic border zone of WT and *p53*$^{-/-}$ mice 8 h after ligation. *Arrows* indicate autophagosomes; original magnification ×5,000 and ×10,000; scale bars, 2 μm. Quantitative analysis of autophagosomes is shown in *right panel*. $^{**}P<0.01$ (reprinted from Hoshino A, Matoba S, Iwai-Kanai E, Nakamura H, Kimata M, Nakaoka M, Katamura M, Okawa Y, Ariyoshi M, Mita Y, Ikeda K, Ueyama T, Okigaki M, Matsubara H. p53-TIGAR axis attenuates mitophagy to exacerbate cardiac damage after ischemia. J Mol Cell Cardiol. 2012;52:175-84. With permission from Elsevier)

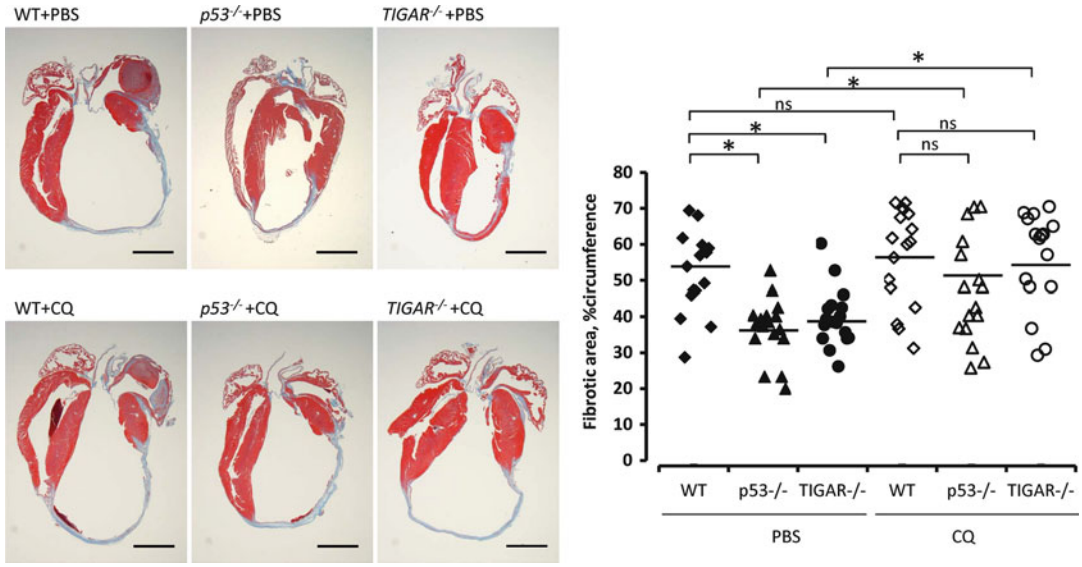

Fig. 30.3 *p53-TIGAR aggravates ischemic injury* via *inhibiting mitophagy*. Chloroquine (CQ) was intraperitoneally administered 4 h before coronary artery ligation and then once a day for 1 week. Representative images of Masson trichrome staining at 28 days after ligation. Percentage of fibrotic area in circumference is shown; scale bars, 2 mm. *$P<0.05$, **$P<0.01$ (reprinted from Hoshino A, Matoba S, Iwai-Kanai E, Nakamura H, Kimata M, Nakaoka M, Katamura M, Okawa Y, Ariyoshi M, Mita Y, Ikeda K, Ueyama T, Okigaki M, Matsubara H. p53-TIGAR axis attenuates mitophagy to exacerbate cardiac damage after ischemia. J Mol Cell Cardiol. 2012 ; 52:175-84. With permission from Elsevier)

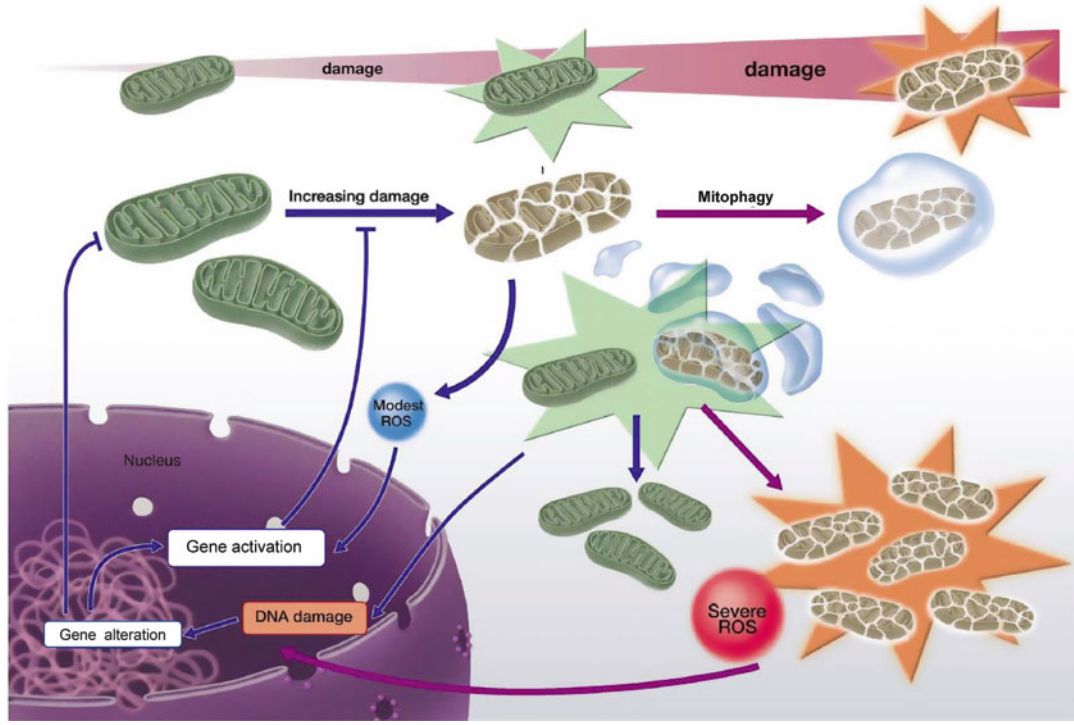

Fig. 30.4 *Damaged mitochondria without clearance deteriorate cellular homeostasis*. Increased generation of reactive oxygen species (ROS) from mitochondria promotes DNA damages (both mitochondrial and nuclear), if not scavenged effectively. Modest level of ROS is necessary for cell homeostasis. Mitochondrial quality control is regulated by its fusion/fission system and mitophagy

mitochondrial quality control could be involved in cardiac remodeling after myocardial infarction [40]. To elucidate the functions of p53 on mitophagy might be a key to protect aging-induced mitochondrial function because p53 plays a central role in stress management during the aging process of the heart and other tissues.

Conclusions

Mitochondria play central roles in cell survival by not only producing energy but also regulating apoptosis. In contrast, the destiny of mitochondria including fission/fusion and autophagic degradation is controlled by the host cell (Fig. 30.4). To understand the mechanism of aging of the heart, elucidating the relation between mitochondria and aging cell is essential. Many investigators paid their intensive attention to the mechanism of apoptosis and mitochondrial function; however, clinicians need more and clearer data to use their knowledge from bench to bedside. Current research focusing on mitochondrial biogenesis and mitophagy will be a promising avenue for learning how to restore mitochondrial function in aged heart.

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31 Regulation of SERCA Via Oxidative Modifications: Implications for the Pathophysiology of Diastolic Dysfunction in the Aging Heart

Fuzhong Qin, Richard A. Cohen, and Wilson S. Colucci

Cardiac Phenotype in Aging

Aging is associated with alterations in cardiac structure and function that are independent of hypertension, coronary artery disease, and diabetes [1–5]. The most prominent features of cardiac aging are increased left ventricular mass (i.e., LV hypertrophy or LVH), impaired diastolic function, and preservation of systolic function [6]. Systolic dysfunction, when present, is generally due to coronary artery disease and myocardial infarction. Likewise, experimental studies in animals, mainly rodents, show LVH and diastolic dysfunction with preserved systolic function [7]. Not surprisingly, the incidence of heart failure with preserved ejection fraction (i.e., HFpEF) increases dramatically with age, reflecting the dominant roles of LVH and diastolic dysfunction in the pathogenesis of heart failure in aging [8, 9].

LVH and diastolic dysfunction in aging are associated with characteristic cellular changes in the myocardium [3, 6] including an increase in the size of individual myocytes (i.e., myocyte hypertrophy) and an increase in the amount of matrix connective tissue (e.g., collagen) leading to interstitial fibrosis [9–11]. Myocyte hypertrophy is associated with a decrease in myocyte number that may reflect apoptosis.

In parallel with age-related changes in the myocardium, there is vascular remodeling which shares many features with that of the myocardium including vascular smooth muscle cell hypertrophy, collagen accumulation, and increased stiffness [6, 12]. Increased arterial stiffness leads to increases in systolic blood pressure and pulse pressure which are typical of aging. Increased vascular stiffness accelerates the rate of arterial pulse wave transmission (i.e., velocity) causing earlier reflection of the pulse wave during systole when the aortic valve is open, thereby resulting in increased LV afterload. Thus, age-related changes in arterial structure and function almost certainly contribute to the development of LVH [6, 9]. However, the cause-and-effect relationship between arterial and LV stiffening in aging is unclear: They may reflect a shared pathophysiological mechanism in the arteries and LV, and/or arterial stiffening may be causative, at least in part, of LV remodeling.

It is generally believed that age-related myocardial fibrosis leads to increased stiffness and reduced LV compliance, thereby resulting in impaired LV filling [4, 6, 9, 13]. It is less clear how LVH, which is due almost entirely to hypertrophy of cardiac myocytes, contributes to impaired diastolic function. While it is possible

F. Qin, MD, PhD
Cardiovascular Medicine Section,
Boston University Medical Center, Boston, MA, USA

R.A. Cohen, MD
Department of Medicine,
Boston University School of Medicine,
Boston, MA, USA

W.S. Colucci, MD (✉)
Boston University Medical Center,
88 East Newton Street, Boston, MA 02481, USA
e-mail: wilson.colucci@bmc.org

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that myocyte hypertrophy and increased LV wall thickness, per se, lead to impaired diastolic relaxation due to mechanical factors, it is more likely that the major consequence of LVH is due to associated alterations in myocyte function that affect calcium regulation and/or sarcomere function. An example of the latter might be changes in the amounts or isoforms of sarcomeric proteins such as titin. In this chapter, we will focus exclusively on a mechanism that may be implicated in causing abnormalities in cardiac myocyte calcium regulation and relaxation in aging [14, 15].

Calcium Dysregulation in Cardiac Aging

An extensive body of work suggests that calcium dysregulation contributes to impaired function of the cardiac myocyte in both heart failure and aging [3, 14, 16–21]. For example, several years ago, we observed in ventricular myocytes isolated from aging mice that there was prolongation of relaxation in association with abnormalities of the intracellular calcium transient characterized by slowing of calcium reuptake and elevation of diastolic calcium [22]. However, the precise mechanism responsible for calcium dysregulation in aging remains to be elucidated.

The intracellular calcium transient is regulated by a family of proteins including sarcoplasmic reticular (SR) calcium ATPase (SERCA), its inhibitory protein phospholamban (PLB), the calcium storage protein, calsequestrin, and the SR calcium release channel (CRC or ryanodine receptor) [15]. Intracellular calcium and/or SR calcium release is also regulated by calcium influx via sarcolemmal L-type calcium channels (dihydropyridine receptors) and the sodium/calcium exchanger [15, 19]. Molecular and functional changes in several of these calcium-handling/regulating proteins have been described in failing and aging hearts [15, 19].

SERCA plays a particularly important role in maintaining intracellular calcium homeostasis through its ability to pump cytosolic calcium into the SR during myocardial relaxation [19]. Several studies have shown that SERCA activity is decreased in the aging heart [15, 19]. In some cases this decrease in activity has been related to a decrease in SERCA protein level or a decrease in the ratio of SERCA to PLB [15]. Decreased SERCA activity may also reflect reduced phosphorylation of the SERCA-PLB complex as a result of lower protein kinase A-dependent phosphorylation of PLB [15]. Other studies have also demonstrated age-associated decreases in the amount of calcium/calmodulin-dependent protein kinase (CaMK, δ-isoform), endogenous CaMK-mediated phosphorylation of SERCA and PLB, and the phosphorylation-dependent stimulation of SR calcium sequestration [15].

Possible Role of ROS in Cardiac Aging

In addition to changes in the amounts and/or isoforms of calcium-regulating proteins that are expressed in the heart, growing evidence suggests that alterations in the function of at least one calcium-regulating protein, SERCA, can be regulated by means of oxidative posttranslational modifications (OPTM) [23, 24]. It is well known that reactive oxidative species (ROS) and oxidative stress are increased in aging myocardium [25–27]. One way that increased oxidative stress is reflected is by increases in the amounts of proteins with oxidative modifications (e.g., 3-nitrotyrosine) that can be visualized by immunohistochemistry or Western blotting.

While the presence of increased oxidative stress in the aging heart is well documented, the functional consequences are less clear. However, recent studies from two different groups, as well as our own unpublished findings, have demonstrated that many of the key features of cardiac aging can be prevented or substantially ameliorated by the use of transgenic mice that overexpress catalase. In one set of studies, Ren and his colleagues showed that cardiac myocyte-specific overexpression of cytosolic (i.e., peroxisomal) catalase improved intracellular calcium regulation and contraction/relaxation in cardiac myocytes [21, 28]. Likewise, in a separate set of studies, Rabinovitch and his colleagues showed

that the overexpression of catalase targeted to the mitochondria attenuated the age-related abnormalities of myocyte intracellular calcium handling and contraction/relaxation, as well as improved LV diastolic function [3, 8]. The ability of catalase to improve cardiac myocyte and LV diastolic function suggests that ROS may contribute to impaired myocyte relaxation and thereby contributes to LV diastolic dysfunction in aging. While these and other findings suggest that ROS may mediate calcium dysregulation and impaired myocyte relaxation, the precise mechanism and molecular target(s) remain to be elucidated.

SERCA OPTM: Activation Via Reversible S-Glutathiolation

It is now recognized that SERCA function can be regulated by OPTM. Over the last several years, Cohen and colleagues have shown that S-glutathiolation is an important OPTM of SERCA that results in increased enzyme activation. In their initial experiments, they showed that oxidants such as peroxynitrite ($ONOO^-$) at low concentrations (10–50 μM) increased both S-glutathiolation of SERCA and enzyme activity in both heart and aortic preparations [24].

Using in vitro systems, they further showed that the activation was due to S-glutathiolation of the thiol on cysteine 674 (C674). C674 is located in the hinge region of SERCA which is thought to be involved in regulating the passage of calcium into the SR and is located on the cytosolic aspect of the SR membrane [29]. In HEK293 cells, wild-type SERCA and a SERCA mutant were overexpressed in which C674 was changed to serine (C674S) and therefore could not be glutathiolated. Cells with the mutated C674 could not be activated by $ONOO^-$, thus implicating C674 as the key reactive residue [24, 30]. In a similar manner, in rat aortic smooth muscle cells, they showed that nitric oxide (NO) activated cells expressing wild-type SERCA, whereas overexpression of the C674S mutant prevented SERCA activation by NO [30, 31]. These observations were extended to intact arteries, where they showed that $ONOO^-$-induced S-glutathiolation of SERCA at C674 led to SERCA activation and a decrease in intracellular calcium and vascular smooth muscle relaxation [24].

SERCA Activation Via S-Glutathiolation in Cardiac Myocytes

Subsequently, we studied the effect of nitroxyl (HNO), the one-electron reduced and protonated form of NO, to regulate SERCA in vitro in cardiac myocytes [32]. HNO markedly increased SERCA activity and led to increased myocyte shortening and relaxation. This effect was associated with a reversible oxidative thiol modification as evidenced by a decrease in the amount of biotinylated iodoacetamide (BIAM) labeling of SERCA C674 thiols and was reversed by the reducing agent dithiothreitol (DTT), indicating that SERCA activation was mediated by a reversible oxidative thiol modification [32]. It was also shown that HNO activation of SERCA was associated with S-glutathiolation as visualized via immunoblotting and supported by the ability of overexpression of glutaredoxin-1, which reduces glutathione-protein mixed disulfides, to prevent both SERCA glutathiolation and activation. In myocytes overexpressing the C674S SERCA mutant, HNO did not increase glutathiolation or activation, thereby indicating that C674 is the key target of glutathiolation with HNO [32]. In unpublished studies in cardiac myocytes, we have also found that $ONOO^-$ at low concentrations (10–50 μM) increases SERCA activity via glutathiolation of C674. Thus, it appears that oxidative S-glutathiolation of SERCA at C674 is a common mechanism of SERCA activation. This mechanism is shared by cardiac and vascular smooth muscle cells and shown more recently to occur in endothelial cells as well [33].

SERCA OPTM: Inactivation Via Irreversible Oxidation

In a series of experiments in aorta, Cohen and colleagues showed that SERCA could also undergo irreversible oxidation at cysteine and tyrosine residues in association with reduced enzyme activity.

In atherosclerotic rabbit aorta, they found that there was irreversible oxidative sulfonation of reactive thiols on SERCA, in particular C674, which prevented its NO-mediated activation via S-glutathiolation [24]. In vitro, the oxidation of C674 likewise prevented NO-induced S-glutathiolation and activation of SERCA, and these effects were mimicked by overexpression of the C674S SERCA mutant [24]. Taken together, these findings led to the thesis that the reactive cysteine thiols responsible for the activation of SERCA by S-glutathiolation (e.g., C674) could be irreversibly oxidized in disease states associated with pathologic levels of oxidants, thereby rendering the SERCA unavailable for activation via glutathiolation. Oxidation of C674 in SERCA is also increased in the aorta of diabetic hyperlipidemic pig [34]. The pathophysiological relevance of this mechanism was further shown in studies in smooth muscle cells cultured in high-glucose media to mimic the diabetic state, where it could be shown that oxidation of SERCA C674 was associated with the failure of NO to inhibit migration [35].

SERCA may also undergo irreversible oxidation at tyrosines. In aortic smooth muscle cells isolated from the obese Zucker rat, a model of obesity and insulin resistance, there is nitration of SERCA at tyrosines 294/295, as well as oxidation of SERCA at C674, associated with failure of NO to inhibit serum-induced migration [31]. In this case, the source of oxidant appears to be the NADPH oxidase isoform, Nox4, since its knockdown prevents the oxidation and inactivation of SERCA [31]. Likewise, in the aortas of hypercholesterolemia rabbits, there was increased nitration of SERCA at tyrosines 294/295 that was associated with decreased SERCA activity and impaired acetylcholine- and NO-induced relaxation, both of which were restored by an antioxidant [36, 37]. Tyrosine-nitrated SERCA is also detected in the aorta of atherosclerotic humans [37].

Cysteine 674 Sulfonation in Cardiac Myocytes In Vitro

We have found that irreversible oxidation of SERCA also occurs in cardiac myocytes subjected to potent oxidants. Exposure of cardiac myocytes in vitro H_2O_2 caused oxidative cysteine modifications that were associated with impaired calcium handling and abnormal contraction/relaxation [38]. Using a site-specific antibody that recognizes SERCA sulfonated at C674 for immunoblotting, we have found that exposure to H_2O_2 causes sulfonation of SERCA at C674.

More recent unpublished studies in cardiac myocytes tested whether C674 oxidation is involved with inhibition of myocyte SERCA activity. Wild-type SERCA and the C674S SERCA mutant were overexpressed in cultured adult rat cardiac myocytes. Since the C674S SERCA mutant cannot be oxidized at C674, it provides an opportunity to test the functional consequence of C674 sulfonation. The ability of H_2O_2 to inhibit SERCA activity was attenuated by approximately half in myocytes overexpressing the C674S mutant, suggesting that oxidation of C674 accounts for approximately half of the decrease in activity caused by exposure to H_2O_2. The partial protection provided by the C674S mutant may reflect oxidation at other sites on SERCA, such as tyrosine 294/295, and/or other proteins that influence SERCA activity. Similar observations were made when a high concentration of $ONOO^-$ was used as the oxidant. Thus, it appears that in cardiac myocytes, as in the vasculature, potent oxidants can cause irreversible oxidation of SERCA at C674 leading to decreased calcium uptake activity.

Irreversible SERCA Oxidation in the Gαq Mouse

The Gαq-overexpressing mouse is a widely used model of systolic heart failure that is associated with increased oxidative stress in the myocardium [39]. Of note, this phenotype exhibits marked abnormalities of myocyte contractile function and calcium transients [23]. We found that the abnormalities in calcium handling are associated with a decrease in maximal calcium-stimulated SERCA [23]. However, the level of SERCA protein expression was not decreased, raising the possibility that decreased function reflects a posttranslational modification.

Consistent with this idea, we found evidence indicative of OPTM of SERCA. First, BIAM labeling to SERCA, which reflects the amount of free (i.e., reduced) thiols, was decreased. Second, immunohistochemistry with site-directed antibodies demonstrated increased levels of sulfonation at C674 and of nitration at tyrosine 294/295.

To further address the role of oxidants, the Gαq mice were crossbred with transgenic mice that express catalase in the cardiac myocyte. In these mice, overexpression of catalase decreased the OPTM of SERCA as measured by BIAM labeling and immunohistochemistry, restored SERCA activity, and improved myocyte calcium transients and contractile function [23]. These results thus suggest that OPTM of SERCA mediate, at least in part, myocyte contractile dysfunction in Gαq-induced cardiomyopathy. Of note, we have found evidence of SERCA sulfonation at C674 and nitration at tyrosine 294/295 in myocardium obtained from patients with severe heart failure (unpublished data).

Unifying Thesis for the Redox Regulation of SERCA

Our observations in cardiac myocytes in vitro and in diseased myocardium are consistent with a thesis of redox SERCA regulation first put forward by Cohen and colleagues based primarily on experiments performed in vascular tissue and cells [24] (Fig. 31.1). According to this thesis, oxidants in low, "physiologic" levels cause reversible S-glutathiolation of SERCA at C674 leading to activation. In contrast, higher levels of oxidants that may be associated with pathologic conditions lead to irreversible oxidation of SERCA at one or more sites, including sulfonation at C674. Irreversible oxidation of C674 may inhibit basal enzyme activity and further prevent activation via S-glutathiolation.

Does SERCA Oxidation Contribute to Cardiac Aging?

As noted, a hallmark of cardiac aging is impaired SR calcium cycling due to decreased SERCA activity [15]. Consistent with prior studies, in recent studies we have found that SERCA activity is decreased in the senescent heart [40]. Also as observed previously by ourselves [22] and others [21], we found that decreased SERCA activity is associated with impaired calcium reuptake and relaxation in myocytes isolated from the senescent heart. Some studies in the senescent heart have demonstrated a decrease in the level of SERCA protein expression [3, 41, 42] that may underlie the decrease in SERCA activity.

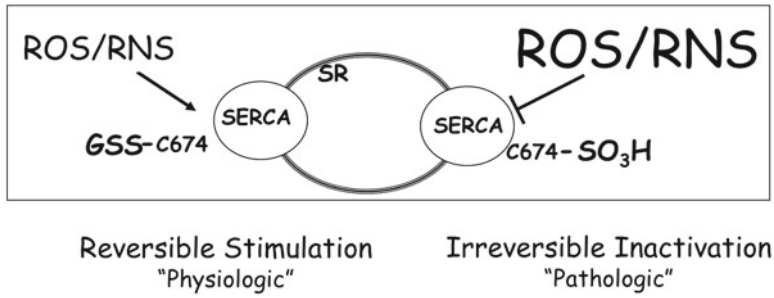

Fig. 31.1 Scheme showing theorized effects of ROS on SERCA function via OPTM. Under physiologic conditions, low concentrations of ROS cause reversible S-glutathiolation of SERCA C674 which results in an increase in SERCA activity, increased calcium reuptake into SR, and improved systolic and diastolic myocyte function. With pathologic levels of ROS, there is irreversible sulfonation of SERCA C674 which results in a decrease in SERCA activity, slowing of calcium reuptake into the SR, and impairment of myocyte function characterized by slowed relaxation and perhaps reduced contraction (modified from Adachi T, Weisbrod RM, Pimentel DR et al. S-Glutathiolation by peroxynitrite activates SERCA during arterial relaxation by nitric oxide. Nat Med 2004 November;10(11):1200-7. With permission from Nature Publishing Group)

On the other hand, several other studies in aging mice have shown no change in the expression of SERCA protein [15, 20, 43–45]. Thus, it appears that a decrease in SERCA protein, per se, is not necessary for decreased SERCA activity in the senescent heart. A decrease in SERCA activity may also result from an increase in phospholamban expression or activity or in the ratio of PLB to SERCA [15, 46]. However, this mechanism does not appear to explain the decrease in maximal SERCA activity that we observed in senescent hearts, since maximal SERCA activity is measured under conditions of excess calcium and ATP stimulation that are insensitive to modulation by PLB.

Another explanation for the observed decrease in SERCA in the senescent heart is that pathologic levels of ROS in the aging heart lead to irreversible OPTM of SERCA. In this regard, studies in skeletal and cardiac muscles have shown extensive age-related oxidation of SERCA cysteines [12] and nitration of tyrosines [47–49]. The ability of catalase overexpression to rescue SERCA activity and to preserve diastolic function in isolated myocytes and LV supports this thesis by indicating an important role for ROS. In this regard, we have observed that myocardial levels of 3-nitrotyrosine and 4-HNE are markedly increased in senescent hearts and that the increases are prevented in transgenic mice with catalase overexpression [40]. Furthermore, using a site-specific antibody that recognizes SERCA sulfonated at C674 [34], we found that cardiac aging is associated with sulfonation of SERCA at C674 and that this was prevented by catalase overexpression [40]. Thus, taken together with the demonstrated ability of C674 oxidation to inhibit SERCA activation, ROS-mediated SERCA OPTM may be an important mechanism leading to impaired diastolic function in the aging heart.

Implications

These studies indicate that ROS such as H_2O_2 lead to impaired diastolic function in cardiac aging, at least in part via oxidative modification of SERCA and, in particular, via sulfonation at C674. Strategies to target oxidant sources, decrease oxidant levels, and/or protect target proteins such as SERCA from irreversible oxidation may be of value in the amelioration of diastolic function in cardiac aging. It is likely that understanding the mechanisms and consequences of oxidative modification of SERCA will be of broad relevance to other conditions associated with diastolic dysfunction.

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SMP30 and Aging-Related Cardiac Remodeling and Heart Failure

32

Satoshi Suzuki and Yasuchika Takeishi

Identification of Senescence Marker Protein 30

Senescence marker protein 30 (SMP30) whose expression decreases with age was originally identified as a novel protein from rat liver by using proteomic analysis in 1991 [1]. Although many of the proteins that increase or decrease with age are affected by sexual hormone, especially androgen, decrease of SMP30 is androgen independent with age and is not affected by gender difference. In 1992, mRNA of SMP30 was isolated by northern hybridization, and genomic southern hybridization analysis demonstrated that SMP30 was widely conserved among numerous higher animal species including human [2]. Although SMP30 transcripts are detected in almost all organs, a large amount of SMP30 is expressed in liver and renal proximal tubular epithelium [2–4]. Analysis of the murine genomic clone revealed that SMP30 was organized by seven exons and six introns, and the amino acid sequence of mouse SMP30 showed 94 % similarity to rat SMP30 and 89 % to human SMP30 [5]. As with rat SMP30, the human SMP30 gene is present on the X chromosome. Human SMP30 consists of 299 amino acids just as rat and mouse, which is 88.6 % homologous to rat and has a molecular weight of almost 34 kDa [3].

A recent more detailed study reported that the full-length 34 kDa SMP30 protein undergoes intracellular processing to produce two additional forms of SMP30 with molecular sizes of 28 kDa and 24 kDa [6]. This author also suggested that the 28 kDa and 24 kDa forms tend to be associated with a particulate (mitochondria) fraction in cells, whereas the full-length 34 kDa SMP30 is equally distributed between the cytosolic and particulate fractions. The lower molecular weight 28 kDa and 24 kDa SMP30 forms were also detected in normal rat liver, suggesting that SMP30 does exist in multiple forms under physiological conditions [6].

Multiple Biological Function of SMP30

Although the functional domain of SMP30 was not recognized when it was first discovered, it has now been elucidated that SMP30 has multiple biological functions. Fujita et al. reported that SMP30 regulates the cytosolic-free Ca^{2+} concentration by modulating the Ca^{2+}-pumping activity using a large amount of SMP30-expressed HepG2 (human hepatocellular carcinoma) cell line after transfection with human SMP30 cDNA [7]. This effect of SMP30 is the same as regucalcin (RGN),

S. Suzuki, MD, PhD (✉)
Department of Advanced Cardiac Therapeutics, Fukushima Medical University,
1 Hikarigaoka, Fukushima, Japan
e-mail: ssatoshi@fmu.ac.jp

Y. Takeishi, MD, PhD
Department of Cardiology and Hematology, Fukushima Medical University, 1 Hikarigaoka, Fukushima, Japan

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which plays a role in the regulation of Ca^{2+} homeostasis by modulating the activity of Ca^{2+}-binding proteins, such as Ca^{2+}-ATPases/Ca^{2+} pumps, calpain, and Ca^{2+}-dependent protein kinases such as calmodulin kinase and protein kinase C [8]. Although RGN was discovered as a calcium-binding protein without the typical Ca^{2+}-binding EF motif in 1978, it became clear that RGN and SMP30 refer to the same protein [8–10]. Moreover, the aforementioned SMP30-transfected HepG2 (HepG2/SMP30) cells were shown to be covered by numerous microvilli on the cell surface and bile canaliculi, while possessing specialized adhesion contacts, such as tight junctions and desmosomes, at endoplasmic membranes [11]. In the same study, HepG2/SMP30 cells retarded cell growth when compared with control cells. Furthermore, reactive oxygen species (ROS) formation in the mitochondrial and post-mitochondrial fractions, superoxide dismutase (SOD) activity, and lipid peroxidation estimated by thiobarbituric acid reactive substances (TBARS) were suppressed in HepG2/SMP30 cells compared with the control cells, suggesting that SMP30 had strong antioxidant activity [12]. The group suggested that these effects of decreased ROS formation in HepG2/SMP30 cells might be associated to intracellular Ca^{2+} modulation by SMP30 overexpression. A recent study further revealed that RGN increased the mRNA and protein levels of sarco-/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) by using RGN overexpressing cells [13].

To examine the detailed function of SMP30 by in vivo study, Ishigami et al. generated SMP30 knockout (SMP30-KO) mice [14]. In this study, they demonstrated that the hepatocytes of the SMP30-KO mice were found to be more susceptible to apoptosis induced by tumor necrosis factor (TNF)-α plus actinomycin D (ActD) than hepatocytes in wild-type (WT) mice. In addition, the TNF-α-/ActD-induced caspase-8 activity in hepatocytes of the SMP30-KO mice was greater than that in hepatocytes of the WT mice, but nuclear factor-κB activation was not changed in both strains of mice [14]. Histological sections of liver damage, including apoptosis after administration of anti-Fas antibody, are shown in Fig. 32.1. Hemorrhagic lesions detected by hematoxylin staining and apoptosis by terminal dUTP nick-end labeling (TUNEL) staining indicated that the SMP30-KO mice are more susceptible to liver injury and apoptosis after anti-Fas antibody treatment. In intracellular signaling analysis, phosphorylation of Akt which acts as a survival factor in cells was augmented in HepG2/SMP30 cells compared to the control cells following TNF-α plus ActD treatment [15]. Furthermore, calmodulin inhibitor trifluoperazine attenuated Akt activation and the anti-apoptotic effect of SMP30. Matsuyama et al. therefore suggested that the interplay between calmodulin and SMP30 regulates Akt activity and thus acts as a survival factor in hepatocytes [15]. Liver injury by diisopropyl phosphorofluoridate (DFP), which is one of the chemical warfare nerve agents such as sarine, revealed that the hepatocytes of the SMP30-KO mice were far more susceptible to DFP-induced cytotoxicity than those of the WT mice [16]. Moreover, the livers from the WT mice contained readily detectable DFPase activity, whereas no such enzyme activity was found in the livers from the SMP30-KO mice. From these results, Kondo et al. suggest that SMP30 might be a unique DFP-hydrolyzing enzyme in the liver and have a detoxification effect on DFP [16].

SMP30 is also important in the vitamin C (ascorbic acid: AA) biosynthesis pathway. Gluconolactonase (GNL), which converts to L-glucurono-γ-lactone, the immediate precursor to AA, from L-gulonic acid, is an essential enzyme in this pathway. The SMP30-KO mice developed symptoms of scurvy such as bone fracture and rachitic rosary when fed a vitamin C-deficient diet [17]. Kondo et al. revealed that the AA levels in the SMP30-KO mice organs at the time of death were <1.6 % of those in the control WT mice, and no GNL activity was detectable in the liver [17]. They suggested that SMP30 had lactonase activity toward the same substrates as GNL with a requirement for Zn^{2+} and Mn^{2+} as a cofactor. In addition, they showed that the excretion of AA in urine was increased after administration of D-glucurono-γ-lactone and that

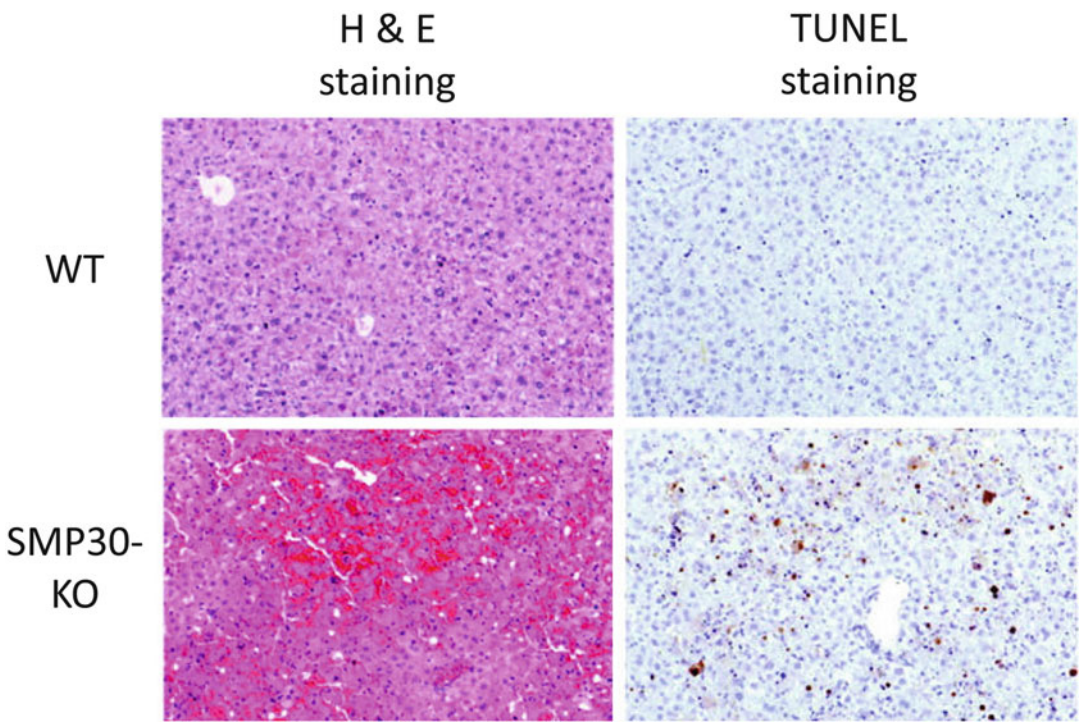

Fig. 32.1 Wild-type (WT) and SMP30 knockout (SMP30-KO) mice were injected via the tail vein with anti-Fas antibody (3 μg/25 g mouse body weight). The mice were sacrificed after a 6-h treatment with anti-Fas antibody. Histological examinations with hematoxylin–eosin (H&E) staining (*left side*) and terminal dUTP nick-end labeling (TUNEL) analysis (*right side*) of liver specimens (×100) (modified from Ishigami A, Fujita T, Handa S, Shirasawa T, Koseki H, Kitamura T, et al. Senescence marker protein-30 knockout mouse liver is highly susceptible to tumor necrosis factor-alpha- and Fas-mediated apoptosis. Am J Pathol. 2002;161:1273-1281. With permission from Elsevier)

there was an alternative pathway of AA synthesis without SMP30 although its pathway is fairly small (Fig. 32.2). From these results, they concluded that SMP30 is a unique GNL in the AA biosynthesis pathway of mammals [17].

On histological examination, the SMP30-KO mice showed abnormally enlarged mitochondria and lysosomes in the electron micrographs, and lipid droplet storage increased in the liver specimens with age compared to the WT mice [18]. At 12 months of age, the SMP30-KO mice had clearly visible deposits of lipofuscin and senescent-associated β-galactosidase (SA-β-GAL) in their renal tubular epithelia [19]. The SMP30-KO mice showed shorter lifespan than the control WT mice and definite malnutrition and emaciation [18]. These morphological features, which are the hallmarks of senescence, support the conclusion that SMP30-KO mice are a useful model of ordinal senescence. Moreover, phospholipids levels as well as total cholesterol and triglyceride levels were higher in the livers of the SMP30-KO mice than the WT mice [18]. This abnormal lipid metabolism might be attributable to short lifespan of SMP30-KO mice.

Many studies about the antioxidative stress effect of SMP30 in various organs have been reported. Although SMP30 expression levels were very low in the brain, generation of ROS and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity were augmented in the brains of SMP30-KO mice [20]. There was no change in antioxidant activities, including superoxide dismutase, catalase, and glutathione peroxidases, in the brain cortex between the

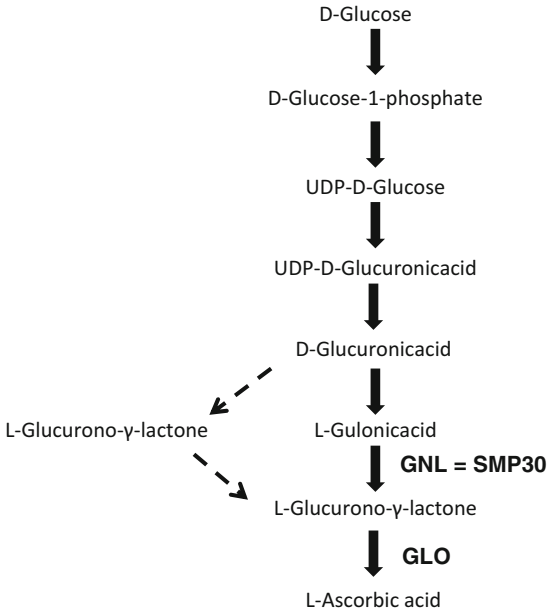

Fig. 32.2 The pathway of ascorbic acid biosynthesis from D-glucose to L-ascorbic acid. Senescence marker protein 30 (SMP30) acts as gluconolactonase (GNL), which catalyzes L-gulonic acid to L-gulono-γ-lactone. L-gulono-γ-lactone oxidase (GLO) is absent in humans according to mutation

SMP30-KO mice and WT mice, suggesting that SMP30 itself might have a role of antioxidant.

In a lung injury caused by chronic cigarette smoke exposure model in SMP30-KO mice, histological examination demonstrated marked airspace enlargement and peripheral alveolar wall destruction [21]. Moreover, this study revealed that lipid oxidative products, malondialdehyde levels in the lung, and glutathione content in bronchoalveolar lavage fluid specimens were upregulated in the SMP30-KO mice compared to those in the WT mice after chronic cigarette smoke exposure [21]. Because aging, as well as smoking, is considered to be a major contributing factor for the development of pulmonary emphysema, the protective effects against oxidative stress by chronic cigarette smoke exposure were considered to be effective for age-related lung diseases such as emphysema. An AA-free chow model of SMP30-KO mice, which leads to a complete lack of AA, showed the same results as the chronic smoke exposure mouse model [22]. Histological examination revealed the development of pulmonary emphysema and increased ROS production including TBARS in AA-free SMP30-KO mice compared to that of WT mice [22]. Interestingly, mRNA levels of type I collagen decreased by 82.2 % in the SMP30-KO AA-free mice compared to those of the WT AA-free mice; however, AA supplementation partially restored the collagen I mRNA level in the SMP30-KO mice to almost half of the level of those of the WT AA-free mice. This suggests that not only AA but also SMP30 plays an important role in collagen synthesis [22].

Hasegawa et al. reported the association of SMP30 and glucose homeostasis with the use of SMP30-KO mice [23]. Blood glucose levels were higher, and insulin levels were lower in the SMP30-KO mice than in the WT mice 30 min after intraperitoneal administration of glucose. However, insulin sensitivity evaluated using the intraperitoneal insulin tolerance test indicated a greater glucose lowering effect in the SMP30-KO mice than in the WT mice. Immunohistochemistry with 5-bromo-2-deoxyuridine (BrdU) showed no differences in the degree of high-fat diet-induced compensatory increase in islet β-cell proliferation. Insulin secretion in response to glucose and KCL was significantly decreased in isolated islet cells from the SMP30-KO mice compared to those of the WT mice without there being a difference of ATP content between the two groups. They concluded that an impairment in the early phase of insulin secretion underlies glucose intolerance in SMP30-KO mice [23].

Although SMP30 levels usually decrease with age, SMP30 protein expression in the liver and kidneys was enhanced by a calorie restriction (CR) diet, and downregulation of SMP30 was accompanied by increased generation of ROS [24]. It is well known that CR retards aging and extends lifespan in various animals including human beings, and one of the most important factors of this mechanism is the reduction of oxidative stress [25]. Therefore, understanding the association of oxidative stress and SMP30 leads to the elucidation of the association of SMP30 and age-related stress disease.

SMP30 and Cardiovascular Diseases

Aging is associated with a progressive increase in the prevalence of coronary disease and hypertension, resulting in the increased incidence of heart failure due to the ischemic and hypertensive cardiomyopathy. Increased activation of the renin–angiotensin–aldosterone system (RAAS) induces oxidative stress, and both RAAS and oxidative stress are associated with age-related cardiac remodeling [26]. Angiotensin II, a primary effector molecule of RAAS, contributes not only to vasoconstriction, cardiac hypertrophy, remodeling, and heart failure but also to the activation of NADPH oxidase. We examined the aforementioned antioxidative and antiapoptotic effects of SMP30 on aging-related angiotensin II-induced cardiac remodeling mouse model.

We used age-matched (12–16 weeks) SMP30-KO and WT mice (C57BL/6 background) which were fed with regular chow and drinking water containing AA (1.5 g/L) because the SMP30-KO mice were unable to synthesize AA [17–20]. A high dose of angiotensin II (800 ng/kg/min) and saline as control was continuously infused through a subcutaneously implanted osmotic minipump for 14 days.

Upon analysis of the gravimetric data, the heart weight (HW) and left ventricular weight (LVW) corrected by tibial length (TL) were similar between the control WT mice and the KO mice. Following angiotensin II infusion, the ratios of HW to TL and LVW to TL were significantly higher in the SMP30-KO mice than in the WT mice, regardless of the systolic blood pressure being similarly elevated in both the angiotensin II-infused WT mice and KO mice.

Histological examination showed that the angiotensin II-infused SMP30-KO mice had substantial left ventricular (LV) hypertrophy with LV dilatation compared with the angiotensin II-infused WT mice, which suggested eccentric hypertrophy in the angiotensin II-infused SMP30-KO mice in contrast with hypertrophy in the angiotensin II-infused WT mice. The cardiomyocyte cross-sectional area was significantly larger in the angiotensin II-infused SMP30-KO mice than in the angiotensin II-infused WT mice (Fig. 32.3, top). The degree of cardiac fibrosis was significantly higher in the angiotensin II-infused SMP30-KO mice than in the angiotensin II-infused WT mice (Fig. 32.3, bottom). These data revealed that the deficiency of SMP30 exacerbated angiotensin II-induced cardiac hypertrophy and fibrosis, independently of systemic blood pressure.

Echocardiography revealed that the LV end-diastolic diameter was enlarged, and fractional shortening was significantly reduced in the angiotensin II-infused SMP30-KO mice compared with the angiotensin II-infused WT mice at 14 days after angiotensin II infusion. Doppler examination of mitral inflow and tissue Doppler images of mitral annulus showed remarkable depression of LV systolic and diastolic functions in the SMP30 mice compared to those in the WT mice after angiotensin II infusion.

Dihydroethidium (DHE) staining was performed to check the generation of ROS. Although angiotensin II infusion dramatically increased the ROS generation in both WT mice and SMP30-KO mice, the ROS generation in the angiotensin II-infused SMP30-KO mice was significantly greater than in the angiotensin II-infused WT mice (Fig. 32.4). Angiotensin II stimulation increased $p67^{phox}$ expression of the NADPH oxidase subunit, and the expression levels of $p67^{phox}$ were significantly elevated in the angiotensin II-infused SMP30-KO mice compared to those of the angiotensin II-infused WT mice ($P < 0.01$). These data suggested that the deficiency of SMP30 increased angiotensin II-induced myocardial oxidative stress via upregulation of NADPH oxidase. Moreover, apoptotic cardiomyocytes after angiotensin II infusion detected by the terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) method were significantly higher in the SMP30-KO mice than in the WT mice.

We demonstrated the antioxidative and antiapoptotic effects of SMP30 in cardiac remodeling using angiotensin II-infused mouse model in this chapter. SMP30 could have a cardioprotective

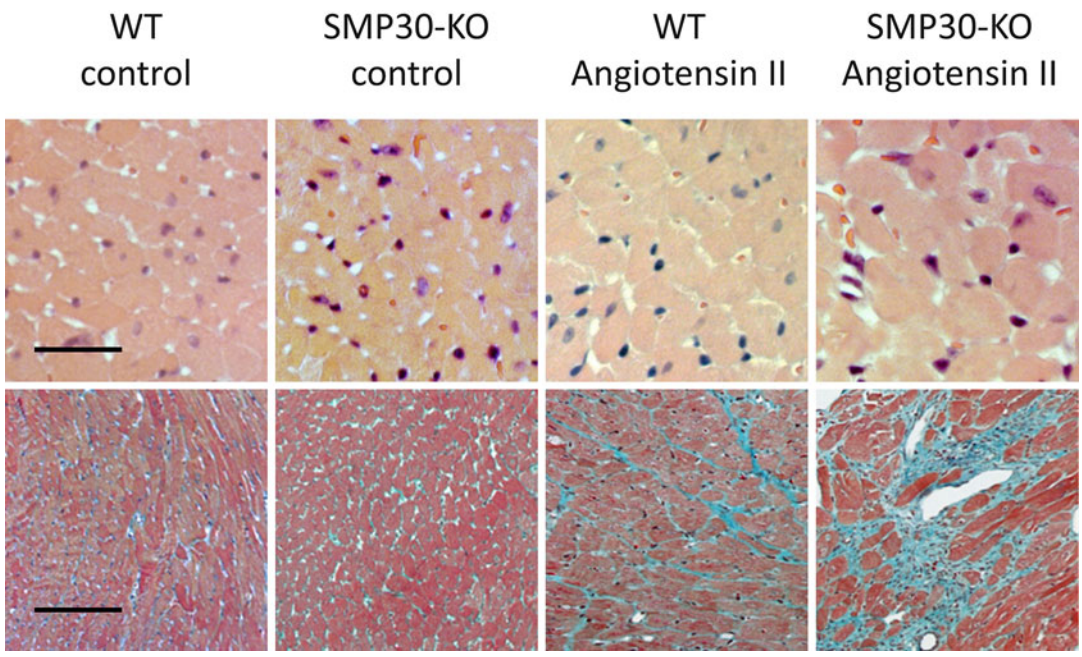

Fig. 32.3 (*Top*) Hematoxylin and eosin staining of myocardial cross sections in the WT and SMP30-KO mice with and without angiotensin II (bar = 50 μm). Cardiomyocyte cross-sectional area is significantly larger in the angiotensin II-infused SMP30-KO mice than in the angiotensin II-infused WT mice (372 ± 11 vs. 399 ± 17 μm [2], $P < 0.01$). (*Bottom*) Elastica-Masson staining of myocardial sections (bar = 100 μm). The degree of cardiac fibrosis is significantly higher in the angiotensin II-infused SMP30-KO mice than in the angiotensin II-infused WT mice (6.4 ± 0.8 vs. 7.5 ± 0.7 %, $P < 0.01$)

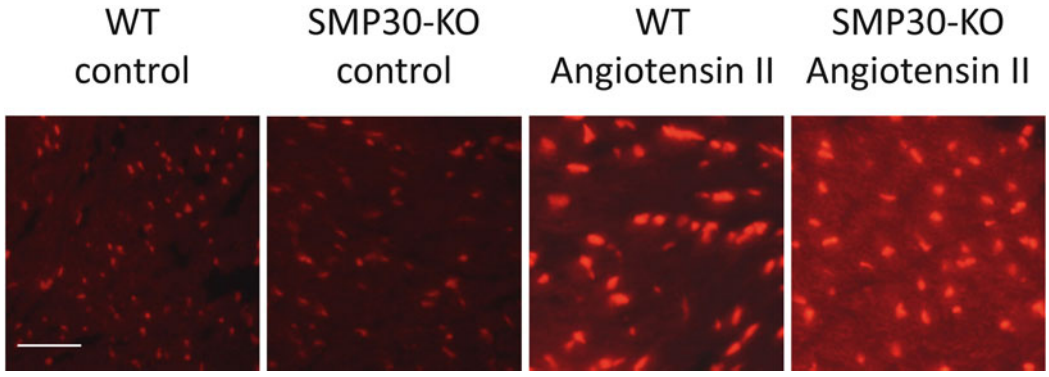

Fig. 32.4 Representative dihydroethidium (DHE) staining of frozen left ventricular tissues (bar = 50 μm). The superoxide generation in the angiotensin II-infused SMP30-KO mice is significantly greater than in the angiotensin II-infused WT mice ($P < 0.01$)

effect similar to that of the brain, lung, and liver. These results also suggest that SMP30 might be one of the key factors and therapeutic agents for cardiac remodeling accelerated by oxidative stress and aging.

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