

THE ABC DIGEST OF **URBAN**
CARDIOLOGY

A PUBLICATION OF THE ASSOCIATION OF BLACK CARDIOLOGISTS, INC.



ABC Founder
Receives Lifetime
Achievement Award
from Harvard Medical
School (p. 12)

The Robert H. Ebert
Lecture (p. 13)

New Insights into
the Diagnosis and
Management of
Diastolic Heart Failure
in Hypertension
(p. 18)

Presorted Standard
US POSTAGE
PAID
Cleveland, Ohio
Permit 1702

VOLUME 30, NUMBER 4

JULY/AUGUST 2004

THE ABC DIGEST OF URBAN CARDIOLOGY

A PUBLICATION OF THE ASSOCIATION
OF BLACK CARDIOLOGISTS, INC.

6849 B-2 Peachtree Dunwoody Road
Atlanta, GA 30328

Urban Cardiology is a bimonthly publication of the Association of Black Cardiologists, Inc., a non-profit organization of medical professionals dedicated to the reduction of cardiovascular and related diseases in minority and underserved populations. The ideas and opinions expressed in this publication do not necessarily reflect those of the Association, editors, or publisher.

Correspondence should be addressed to:
URBAN CARDIOLOGY
Association of Black Cardiologists
6849-B2 Peachtree Dunwoody Rd., N.E.
Atlanta, GA, 34328

For advertising information, contact
Imquest, Inc.
590 S. Lenola Road, Suite 3121
Maple Shade, NJ 08052
856-489-7550

Publisher
Hilton M. Hudson, II, M.D., F.A.C.P

Editor in Chief
Elizabeth Ofili, M.D., M.P.H.

Editorial Staff
LaTrese Coyt, ABC
Debra Teague, Morehouse School of
Medicine
Yumekia Merckerson, Morehouse School of
Medicine

© Copyright The Association of Black
Cardiologists, Inc. 2004. All rights
reserved. No part of this publication in any
form may be reproduced or transmitted
without the expressed written permission
of the publisher. Library of Congress
ISSN# 1096-3863

Hilton Publishing, Inc.
P.O. Box 737
Roscoe, IL 61073

EDITORIAL BOARD

Editor in Chief: Elizabeth Ofili, M.D., M.P.H.
Morehouse School of Medicine
Atlanta, GA

Anekwe Onwuanyi, M.D., Assistant Editor
Morehouse School of Medicine
Atlanta, GA

Michelle Albert, M.D., M.P.H.
Brigham & Women's Hospital
Harvard Medical School
Boston, MA

Lawrence Burwell, M.D.
University of Virginia
Charlottesville, VA

Stephanie Kong, M.D.
MetroHealth Group of America
Atlanta, GA

Laurence Watkins, M.D.
Martin Memorial Health Systems
Stuart, FL

Deborah Williams, M.D.
Howard University Hospital
Washington, D.C.

Jackson Wright, Jr., M.D., Ph.D.
Case Western Reserve University
School of Medicine
Cleveland, OH

OUR EDITORIAL MISSION

The *ABC Digest of Urban Cardiology*, published bimonthly, is an official publication of the Association of Black Cardiologists, Inc. (ABC). The ABC is a non-profit organization of health professionals dedicated to the reduction of cardiovascular and related diseases, especially in minority populations, wherein lies a burden of excessive morbidity and mortality. This publication is provided as an educational service to all health professionals who share this dedication.

The mission of this publication is to assist such clinicians to deliver the best of care to patients with cardiovascular and related diseases and to do so in a culturally competent and demographically appropriate manner. We do so by providing—in a compact, easily comprehensive journalistic style—up-to-date information of immediate applicability to the unique clinical setting of urban medicine. This information consists of:

- Original, evidence-based, clinical and research main articles (including CME self-assessment).
- "Tidbits"—a regular column of useful clinical knowledge gleaned from recent clinical research trials and other information drawn from the medical literature.
- "Developments"—a regular column covering newsworthy recent events such as new drug and device market introductions, new controversies in medicine, new trends in health care, new scientific insights, and new demographic, economic, and governmental activity affecting the practice of medicine.
- Commentary from the president of ABC, the publication's editor in chief, and the publisher.

We strive continually to improve upon the execution of our editorial mission and therefore encourage and welcome your suggestions on how we can serve you, our reader, better.

In this issue you will observe product advertisements from AstraZeneca, Bristol-Myers Squibb Medical Imaging, Fujisawa Healthcare, GlaxoSmithKline, McNeil-PPC, Pfizer Pharmaceuticals and Schwarz Pharma. These pharmaceutical firms are providing educational grant support to the Association of Black Cardiologists, Inc. to enable us, among other things, to provide you with this publication without a subscription charge to you.

We encourage you—as you deem appropriate—to acknowledge and show appreciation for this support, as well as for these supporters' recognition of the special health challenges faced by minority and underserved populations and by the clinicians who treat them.

OUR PATIENTS, OURSELVES

Recently I received the sad news that Rev. Charles Williams, President of the Indiana Black Expo, lost his battle with prostate cancer. I've long admired Rev. Williams' indomitable spirit. After he received his diagnosis he didn't hang his head but instead acted to make sure other men didn't allow fear and ignorance to get in the way of getting tested and treated for prostate cancer. He penned *That Black Men Might Live* as a legacy to Black men everywhere in the hopes that they could learn from his example. The result: Thousands, of men have gotten tested for prostate cancer.

As I reflected on Rev. Williams' extraordinary life it made me wonder: why do patients sacrifice their health because of fear and lack of knowledge? What can we, as physicians, do to get patients to take charge of their health before tragedy occurs? While education and information are powerful weapons, they are useless if we can't connect with patients on a level that is comfortable and familiar to both of us. We have to do our part to break through the fear of the unknown, and remove the crippling panic some patients experience when they think of visiting a doctor on a regular basis. Because many of us come from the same communities as our patients, we are at a distinct advantage: we can relate to them directly. We too have felt helpless watching loved ones take the path of self-diagnosis. We understand that illnesses like high blood pressure, diabetes, and cardiovascular disease are directly related to cultural traditions that interfere with getting proper healthcare. We acknowledge that we sometimes have to meet people where they are and offer them ways to extend their lives that compliment their lifestyles without compromising medical certainties. We have to remind ourselves that we are treating both the patient and the disease, and that the faith and trust patients put in us is an awesome responsibility. We really are our brothers' keeper.

With Rev. William's legacy in mind, let's rededicate our efforts and realize that treating patients means treating ourselves; let's remember there is no greater feeling than knowing that when someone's life hangs in the balance, we not only make a difference, but we also encourage change.

From my heart to yours,
Hilton M Hudson II MD FACS, FCCP
Chief of Cardiothoracic Surgery, Reid Hospital, IN.
CEO, Hilton Publishing Co. Inc.

THE ABC DIGEST OF URBAN CARDIOLOGY

A PUBLICATION OF THE ASSOCIATION
OF BLACK CARDIOLOGISTS, INC.

VOL. 30, No. 4
JULY/AUGUST 2004

CONTENTS

Message from the CEO	8
Letter from the Editor	9
ABC Founder Receives Lifetime Achievement Award from Harvard Medical School	12
The Robert H. Ebert Lecture	13
New Insights into the Diagnosis and Management of Diastolic Heart Failure in Hypertension	18

Cover: Inset Illustration by Joel Gresham

The paintings used on the cover of the Digest of Urban Cardiology depict teachable moments between children and their grandparents. The dialogue here is:

Marcus: Hey Morgan, could you pass me a soda out of the cooler?

Morgan: Only if you cut me a piece of the watermelon.

Grand Ma Jackson: This family reunion is turning out to be one of the best ever. I have all my children and grand kids here. How could this get any better?

Aunt Cheryl: You are right Momma. It can't get any better than this.

Shawn: Hey Granny, tell me who this is on the family tree.

Grand Ma Jackson: I'll tell you all about everyone on the tree after we all sit down and eat.

Greg: Mommy, where's Grand Pa Ted?

Grand Pa Ted: Here I am Greg. I'm just trying to get some more sodas out of the truck.

Grand Ma Jackson: Hey everyone, lets sit down and eat some of this good cooking.

To "Talk Back" write to:
URBAN CARDIOLOGY

6849-B2 Peachtree Dunwoody Rd., N.E.
Atlanta, GA 34328
678-302-4222



WHERE DO WE GO FROM HERE? STEPS TOWARD A BOLD NEW FUTURE

“Where do we go from here?” is the title of the Annual Report delivered at the 11th Convention of the Southern Christian Leadership Conference on August 16, 1967. It was a question asked by perhaps one of the greatest orators of all time, Rev. Dr. Martin Luther King, Jr.. At the time the question was being asked, the Southern Christian Leadership Conference (SCLC) was both taking stock of its advances, and also the enormous challenge that still lay ahead. While Dr King was concerned with African Americans in every sphere of life, thirty-seven years later, regarding healthcare disparities, I am asking myself, “Where do we go from here?” As this summer draws to a close, and the ABC prepares to celebrate 30 years of progress, I can not help but be mindful of the challenges that lay ahead.

As a community we have always rooted our future in a deep and abiding knowledge of our past. This year, the Association of Black Cardiologists, Inc. (ABC) will commemorate thirty years of promoting the elimination of disparities in cardiovascular care and outcomes. This gala event, featuring a dinner and recognition ceremony, is planned for **Saturday, November 6, 2004** in New Orleans, just prior to the American Heart Association’s Scientific Sessions 2004. Dr. Richard Allen Williams, ABC founder serves as Chair of the 30th Anniversary Committee. We hope you are making plans to attend.

In the current installment of the Digest, we are proud to reproduce part of the address of Dr. Richard Allen Williams, given at Harvard

University’s Robert H Ebert Lecture. Dr. Williams, in his address, speaks to the disparities that have been recognized in the treatment of



African Americans for nearly 300 years. Looking back over the length and breath of his pioneering career, Dr. Williams chronicles his and others’ effort to integrate one of our Nation’s most prestigious medical institutions. Also in this issue, we are please to present a scientific review authored by two of our own, Dr. Elizabeth Ofili and Dr. Rigobert Lapu Bula.

The elimination of disparities in CVD research, treatment, and outcomes for African American patients, a vision we have shared for nearly 30 years, is about to become one step closer to being realized. Soon we will announce a campaign that will ultimately lead to a bold, unequivocal statement of our resolve to actualize our vision. Of course I am speaking of the ABC International Library, Research and Conference Center (ICC). Please visit our website (www.abccardio.org) for more details.

These are exciting times for the ABC, our members, our staff, and most importantly, the communities we serve! We are building on a solid foundation, and look forward to the new heights we will achieve. If you have any questions or are looking for a way to get involved, send us a note.

BRIDGING THE HEALTHCARE DIVIDE!

Dear Colleagues,

As I know that you have come to expect, this issue of the Digest brings you several fascinating features—The scientific review is a timely update titled “New insights into the Diagnosis and Management of Diastolic Heart Failure in Hypertension” by Rigobert Lapu Bula, MD, PhD. It highlights the growing burden, and common occurrence of diastolic heart failure in individuals with hypertensive heart disease, a major problem among African American patients.

“The Big Divide: Healthcare Across the Cultures” features excerpts from a courageous and inspiring speech by Richard Allen Williams, ABC founder, which he delivered during the Robert H. Ebert lecture at Harvard Medical School on April 24, 2004.

Recent epidemiologic and clinical data confirm the central role of hypertensive heart disease in the pathophysiology and disease progression.

Although diagnostic approaches, and treatment continue to evolve, Dr. Lapu Bula provides a template of the current strategies.

“The Big Divide: Healthcare Across the Cultures” features excerpts from a courageous and inspiring speech by Richard Allen Williams, ABC founder, which he delivered during the Robert H. Ebert lecture at Harvard Medical School on April 24, 2004.

The courageous stand that was taken by Dr. Williams and colleagues should inspire every one of us as we contemplate the daunting task of eliminating disparities.

Clearly the lessons of history tell us that a few good men and women make a difference in shaping humanity.

As clinicians, our opportunities to bridge the healthcare divide are clearly grounded in our duty to our patients, and shaped by active integration of such historic lessons as shared by Dr. Williams in his speech.

Happy Reading!

Best Regards,
Elizabeth Ofili, MD, MPH, FACC



ABC FOUNDER RECEIVES LIFETIME ACHIEVEMENT AWARD FROM HARVARD MEDICAL SCHOOL

Richard Allen Williams, M.D., the Founder of the Association of Black Cardiologists, was honored with Harvard Medical School's Lifetime Achievement Award during his presentation of the Ebert Lecture at that institution on April 23, 2004. The award was presented by Alvin F. Poussaint, M.D. in recognition of Dr. Williams' many contributions to the school's history and for his efforts to make it more diverse by helping to open the doors to the first African American interns, residents, fellows, and many medical students when he himself was a fellow and later a faculty member at the prestigious school in Boston. He also founded the Central Recruitment Council of Boston Hospitals, which established a process for recruiting minority doctors for all hospitals in Boston, a tradition which continues to this day.

In the lecture which he delivered in honor of the late Dean Robert H. Ebert, who responded positively to the campaign which Dr. Williams carried on at the medical school and in the city of Boston in the late 1960's to allow black and other minority doctors to train in the hospitals and medical schools there, Dr. Williams noted that he was the first African American to receive his postgraduate education at Harvard Medical School and that he decided to "rock the boat", at the risk of his fellowship, by protesting and circulating a petition for change. His successful efforts led to an increase in minority student enrollment from 1%, up to 18%, and the number of black house staff increased from zero to hundreds who have matriculated over the past 35 years. Harvard

Dr. Williams noted that he was the first African American to receive his postgraduate education at Harvard Medical School and that he decided to "rock the boat," at the risk of his fellowship, by protesting and circulating a petition for change.

Medical School now has a Dean for Diversity, Dr. Joan Reed, an Office of Recruitment and Multicultural Affairs, headed by Dr. Poussaint, and a full curriculum of cultural competence.

The speech that Dr. Williams gave began with the powerful statement from the demographer Hoffman who made an observation 200 years ago about the poor health status of blacks and predicted that they would be extinct by the year 2000. Dr. Williams linked this to his main theme of healthcare disparities and warned that unless some extremely profound changes are made in our healthcare delivery system, this prediction could still become true during this millennium. He gave many examples of how health care for blacks has been deficient and racist, and urged the audience of faculty, students, and staff to use their excellent training for the benefit of the poor, needy minorities. He stated that his own examples are the creation of the Association of Black Cardiologists and writing the Textbook of Black-Related Diseases, which are cited as his personal legacy.

THE ROBERT H. EBERT LECTURE

“THE BIG DIVIDE: HEALTHCARE ACROSS THE CULTURES”

Excerpt from speech given at Harvard Medical School

Richard Allen Williams, M.D.

Clinical Professor of Medicine

The David Geffen School of Medicine at UCLA

My Dear Colleagues in Science and Medicine:

It was my extreme pleasure to accept the invitation extended to me by Dr. Alvin Poussaint and your Committee on Recruitment and Multicultural Affairs to come back to Harvard Medical School, the scene of some of my most poignant memories. As Dr. Poussaint indicated in his introduction, I have been at Harvard in three capacities: as an undergraduate at Harvard College; as a postgraduate fellow in Cardiology; and as a member of the Cardiology faculty when I was Director of the EKG and Exercise Laboratories at the Brigham. This is my fourth visit to deliver a lecture since I left; I gave the Dr. William Augustus Hinton Lecture on two previous occasions, in 1994 and 1986, and the Black Health Association invited me to address them here in 1976. However, to be here to address you today is a signal honor, because I have the privilege of paying a special tribute to one of the greatest deans this institution has ever known.

I was privileged to have had a bit of contact with Dr. Robert H. Ebert, and I will begin this lecture by telling you about my personal recollections of the man for whom it is named.

I arrived at Harvard Medical School as a young, ambitious cardiology fellow at the Brigham and as an instructor in medicine working under the great Doctors Richard Gorlin and George Widmer Thorn. My selection for this coveted position was really quite contrived, unbeknownst to me at the time. I had the

opportunity to meet and be interviewed by Dr. Gorlin while I was finishing my internal medicine residency at USC. The year was 1968, and Dr. Martin Luther King, Jr. had just been assassinated. In the aftermath of his death, many people had a desire to do things of a compensatory nature as though to atone for this dastardly deed, and so I became a sort of unconscious beneficiary of Dr. King's murder. Of course, not knowing this, I assumed that I was chosen because of my academic prowess rather than for humanitarian reasons.

Upon reaching Boston, I was intercepted by Dr. Jack Norman, an African American cardiothoracic surgeon who had been trained at Harvard College and Harvard Medical School. I was surprised to learn that many people in the Harvard community had heard that I was coming, and he informed me of something which I did not know: that I was the first African American postgraduate trainee of any kind to be selected in Harvard Medical School's entire history, and that included interns, residents, and fellows. This meant that none of the twenty-odd hospitals such as Massachusetts General, the Brigham, Beth Israel, and the Deaconess had ever had a black house officer—ever—before I came. This included Jack Norman himself, who was very bitter about being passed over for postgraduate training in surgery despite a stellar academic career throughout eight years at Harvard. He had

continued on page 16

been forced to go to Texas to do his surgical training, and when he returned to Boston he was unable to secure a position at Harvard and had to settle for one at Boston University, where he became director of the Sears Surgical Laboratories. He refused, however, to consider himself a victim of discrimination.

Furthermore, I was told that I was an experiment, and that I should be quiet, be satisfied that I was chosen, and not to rock the boat. I was warned that if I did, people like Dr. Francis Moore, Dr. Clifford Barger and others on the HMS faculty would “burn my cremaster,” to use Dr. Norman’s expression. Doctors Chester Pierce and Harold Amos attempted to advise me about what they considered the proper approach to take.

Like a tiger who has been placed in a new cage, I became extremely curious about these new surroundings of mine, and I wanted to know more. I sought out Dr. Alvin Poussaint, and he gave me a blunt perspective of the way things had been at the medical school and on what he hoped the future would be in the period following King’s assassination. He urged me to focus on trying to increase the numbers of black students admitted to HMS, and I joined him and Dr. John Arredondo in organizing and directing the Harvard Health Careers Summer Program which groomed about 100 mostly black college students for medical school each year. I was startled to find that Harvard had admitted only 22 black students to the study of medicine in its long and illustrious history. As I dug deeper into Harvard’s medical history, I discovered that the first African American to study at Harvard Medical School, Martin Robison Delaney, had been expelled by Dean Oliver Wendell Holmes in 1850 for inciting displeasure among his white fellow students simply because they did not want to go to school with blacks. I also discovered that a

number of Harvard professors, including Doctors James Collins Warren, Louis Agassiz, Charles Meigs, and others, espoused the pseudoscience of phrenology which promoted the belief that the smaller skull size of Africans compared to Caucasians was an indicator of the intellectual inferiority of the Africans, and that blacks and whites were from separate species. As such, these Harvard luminaries joined those from other leading medical institutions in the North in providing scientific support for the practitioners and proponents of slavery.

Stimulated by the rather negative historical facts about Harvard that I had uncovered, I set about founding the Central Recruitment Council of Boston Hospitals and organizing a petition drive to force the medical school to recruit black and other minority house staff and for the medical school to accept more minorities; eventually the drive extended to Roxbury and incorporated politicians such as Boston City Councilman Mel King, organizations including the Black Muslims and the Black Panthers, local physicians, and many local residents. The majority of the Harvard Medical School faculty also signed the petition, including Doctors Edward Firshpan and David Potter, which was then presented to Dean Ebert, Dr. Thorn, and the Council of the Chiefs of Services of the Harvard-affiliated hospitals. A request was also made for Dean Ebert to come to a special town meeting in Roxbury, the black ghetto in Boston, to discuss the charges of discrimination.

Although I received clandestine warnings that I might be discharged from my fellowship for these actions, I was determined to see them through. The critical turning point came when Dean Ebert contacted me and agreed to come to the Roxbury meeting, which was hosted by the Nation of Islam and attended by the Panthers and other militants. I recall that he was cool and calm when he walked into that meeting, which amazed me and everyone else present. He was accompanied by Mark Goode,

his administrative aide, who was black, but was otherwise alone. He sat quietly while the grievances were detailed, and then he spoke. He admitted that Harvard had made mistakes and wanted to make some kind of restitution, which he said would be worked out with me and the Central Recruitment Council. With that, the meeting ended.

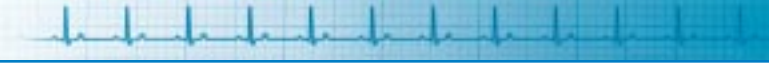
Several weeks later, I was summoned to a meeting of the Council of the Chiefs, presided over by Dr. George Thorn, the Hersey Professor of the Theory and Practice of Physic and Physician-in-Chief at Harvard Medical School. I went to the meeting accompanied by Dr. Vivian Pinn, who was an assistant professor of renal pathology at Tufts Medical School and is now the head of the Women's Health Division of NIH. We were asked to detail our grievances for the Chiefs and to list our requests. We asked for three things: funds for recruitment of minority house staff, with assistance from the Dean's Office; placement of myself on the Intern Selection Committee at the Brigham; and more help and support in our efforts to admit more black and other minority students to the medical school. They asked us to step outside, and twenty minutes later we were called back in. Surprisingly, they told us that on the recommendation of Dean Ebert, a consensus of the Chiefs had agreed to all of our requests and were going to provide \$25,000 for us to begin our recruitment efforts, effective immediately. So, on a cold, snowy day in Boston in 1969, we had won and the Central Recruitment Council of Boston Hospitals was officially launched. Within a few months we had visited the campuses of Howard and Meharry Medical Schools, the University of Puerto Rico, and several other institutions, and soon we were receiving applications for internships from minority aspirants. Although he was initially opposed to the recruitment plan, saying that he did not want to get "a big black thing started at HMS," Dr. Francis Moore, Surgeon-in-Chief at Harvard Medical School and the

pre-eminent surgeon in the world, accepted the first black house officer in Brigham history when he accepted Ron Brown from Meharry for a surgical internship. In addition, many more minority students were admitted to Harvard Medical School as well as to the other schools in Boston. Thus, the paradigm had shifted, and medical history was forever changed in Boston.

I will now provide some more general historical comments which will serve as a perspective for the current situation we face as a nation regarding healthcare disparities.

In the 18th century, the demographer and biostatistician Hoffmann predicted that, based on his studies, the black race would be extinct by the year 2000. This prediction was based on extremely terrible morbidity and mortality figures which he had collected, and the poor medical care which the slaves received. Was Hoffmann wrong? Obviously, black people are still around, more than 250 years after he made his prediction. Some might say that he may have been off his mark, and that the disappearance of blacks due to disease and poor health care was just a few years premature and may still happen. However, I think that the wisdom in his prediction was in alerting us to a danger which has been in progress since the slaves arrived; that we are enduring what Doctors W. Michael Byrd and Linda Clayton have called the "slave health deficit" and that we must correct the situation in order to deter the inevitable.

In order to focus on possible corrections, we need to acknowledge the facts that point to the deficit suffered by African Americans, and to ask why corrective actions were not made earlier. In this regard, we must ask a question about those in charge of healthcare delivery which is usually asked in the political arena: what did they know and when did they know it; and once they found out, why didn't they do anything about it?



NEW INSIGHTS INTO THE DIAGNOSIS AND MANAGEMENT OF DIASTOLIC HEART FAILURE IN HYPERTENSION

Rigobert Lapu-Bula, MD, PhD and Elizabeth Ofili, MD, MPH.

From the Divisions of Cardiology, Morehouse School of Medicine, Atlanta, GA

Abstract

It is now generally accepted that nearly 50% of patients with heart failure (HF) might have normal or preserved left ventricular (LV) systolic function. This increasingly common but often undiagnosed condition is referred to as a distinct type of HF caused by LV diastolic dysfunction and it often accompanies hypertensive heart disease. However, the clinicians caring for patients with diastolic HF do not fully understand its cause, how it progresses or how it could be appropriately diagnosed and treated. Because varying degrees of systolic and diastolic dysfunction might coexist in any individual patient and given the limitation of current diagnostic tools, the overall impact of isolated diastolic HF continue to evolve. Although this isolated diastolic HF is probably the dominant cause of symptoms and hospitalizations from HF in the elderly and in women, there is a paucity of clinical data to guide management of such patients. Ongoing large randomized clinical trials are testing new strategies for treatment of HF patients with preserved LV systolic function and early evidence indicates that AT-1 blockade may be beneficial.

Supported in part by the NIH Grant No. 5U54 RR14758 (CCRE), 5P20RR11104 (CRC) and NASA Grant No. NCC9-112.

Adapted with permission from the original paper by Lapu-Bula R and Ofili E. *Curr Hypertens Rep* 2004;6:164-170 [ref 1].

Introduction

Heart failure (HF) has long been considered to be a progressively debilitating syndrome characterized by frequent hospital admissions and high annual mortality rates. Coronary artery disease (CAD), hypertension (HTN) and aging are major risk factors for the development and progression of HF. For years, most of the attention has been focused on HF due to reduced left ventricular (LV) systolic function largely attributable to CAD. However, it is now generally accepted that nearly half of patients who present with symptoms of HF have relatively normal or preserved LV systolic function by currently available conventional methods [1-7]. In these patients, diastolic dysfunction has been implicated as main cause of HF [3,8] that often accompanies hypertensive heart disease [9].

Given the non-specificity of the symptoms in diagnosing HF and its wide spectrum of clinical presentations [10,11], some reports have questioned whether the apparently isolated diastolic HF may represent subclinical [12] or transient impairment in systolic function [13,14]. Others have observed that the patients' symptom of breathlessness can occur with many other non-cardiac conditions [15] or preventable causative factors leading to hospital admission [16,17]. Recognizing and understanding the progressive course of diastolic dysfunction underscores the growing need for new diagnostic criteria to define abnormalities of

ventricular relaxation and stiffness for early therapeutic interventions. Unfortunately, the current paucity of solid epidemiological data on the natural course of diastolic HF and ongoing disagreement/misconceptions over its relative independence from systolic HF [18,19,20] have led to delay in the development of such therapies; and perhaps most importantly preclude the screening efforts to detect the disease at its earlier stages [21]. This review provides a summary of the current concepts in the natural history of patients with diastolic HF in hypertensive heart disease (HHD), as well as a brief review of current treatment options.

The Growing Burden of Diastolic Heart Failure in Hypertension

Heart failure is a growing epidemic with the advancing age of the population [10,19]. It remains by far the most frequent cause of hospitalizations in patients aged 65 or older, accounting for over 6% of all hospital admissions. The incidence and prevalence of HF is increasing with 550,000 new cases being reported annually [22]. Epidemiological data indicate that as high as 40 to 60% of patients with clinical HF have normal systolic function [6,7,23,24]. The mortality rate of 8-17% [7,24,25], although half of that seen in patients with LV systolic dysfunction (15-30%), is nearly 3-fold higher than that of age-matched controls [7,26]. Furthermore, the high annual rate of hospital readmissions (40-50%) and length of stay make diastolic HF a costly condition in terms of morbidity, quality of life and economic burden to society [24-27]. In contrast to systolic HF, it is increasingly clear from population-based studies [6,28] that diastolic HF primarily affects the elderly, especially women [5,7,29]. There is also some evidence to suggest that blacks may be more susceptible to diastolic HF than non-blacks [19,30]. As recently discussed by Vasan et al. [19], the reason for this gender and racial variation in the prevalence of diastolic

HF is unclear, but could be related to differences in LV remodeling in response to pressure load and coexistent risk factors [19,31], such as aging, CAD, hypertension, obesity and diabetes.

Paradoxically there is increasing incidence of HF and related mortality and morbidity [32,33] at the time when death from CAD is stable or markedly declining. The burden of HF should not be growing if it was related chiefly to CAD, suggesting that other factors such as HTN might contribute to this growing burden. Of the nearly 50 million individuals affected with HTN in the United States, approximately 36 million (72.6%) are uncontrolled [34]. Such a failure to achieve HTN control is a universal problem with alarmingly low rates of BP control from 6-24% worldwide [35-38]. Furthermore, close to 18 million of these patients are not aware of having high BP and may already manifest symptoms of HHD or evidence of end-organ damage by the time of presentation/diagnosis. This underscores the need for rigorous screening for HTN as a first step toward offsetting the accompanying CV complications of the HHD. This late complication of chronic elevated BP or uncontrolled HTN, if not appropriately treated, may eventually culminate in end-stage HF by mechanisms that are not fully understood.

From the European Heart Failure Survey, among the 63% of patients with a record of LV ejection fraction (EF) reported by at least one imaging test (most often echocardiography), close to 50% have an EF above 40%" [11,39]. The surprisingly poor relationship between the degree of systolic dysfunction and the severity of symptoms [40], lend further support to the notion that abnormalities of LV diastolic filling is the key determinant of the functional and hemodynamic impairment in these patients [41]. In patients with a dilated cardiomyopathy and HF from ischemic or non-ischemic origin, abnormalities of LV filling provided additional independent prognostic information over that

continued on the next page

provided by LV systolic function, even in patients with markedly reduced EF [42].

Role of Hypertension in the Pathophysiology of Diastolic Dysfunction

Hypertension leads to alterations in cardiac structure and function either directly by increased hemodynamic load on the heart or indirectly via parallel vascular changes (**Figure 1**). Cardiac structural response to elevated BP (HTN) is characterized by early development of hypertrophy (LVH) and fibrosis of the ventricle [43,44]. This deleterious LV remodeling process may lead to two basic types of abnormalities in diastolic function and impaired filling of the ventricle that might manifest as delayed LV relaxation [18] and increased myocardial stiffness.

Using ultrasound imaging, we found that African Americans with high BP who have increased LV mass and altered LV geometry have abnormal vascular function, as measured by flow-mediated brachial artery reactivity or

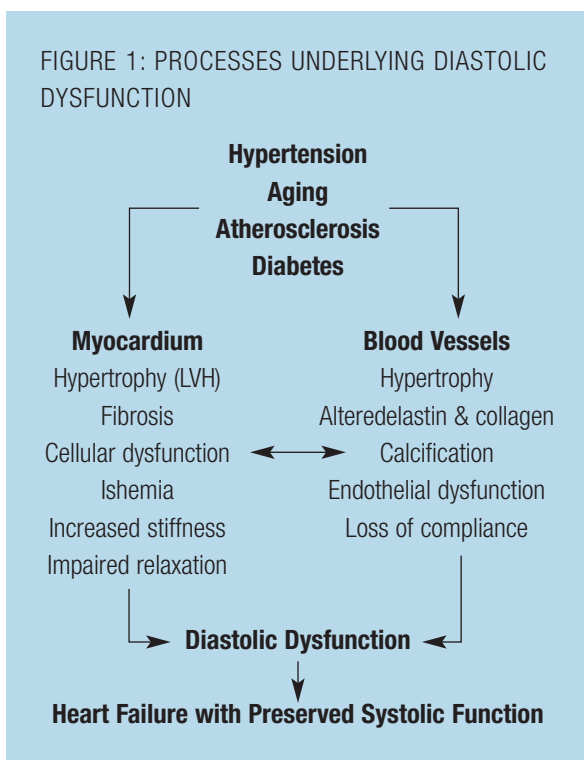
endothelial dysfunction [45]. Our studies suggest that hypertensive African-Americans with endothelial dysfunction are at high-risk for disease progression and cardiac end-organ damage, as measured by abnormal myocardial contrast perfusion [46]. This cardiac remodeling and vascular dysfunction as identified in these studies [45,46] may provide a clue as to why some African American hypertensives are at a greater risk for heart attacks and stroke, the leading causes of death in the United States [22].

During conditions of stress (including exercise, tachycardia) the hypertrophied heart is either unable to increase its end-diastolic volume due to decreased LV relaxation and compliance [47] or can do it at the expense of increased filling pressures. Thus causing an upward shift of the diastolic pressure-volume relationship with increased end-diastolic, left atrial and pulmonary capillary wedge pressures leading to symptoms of pulmonary congestion/edema. This may explain why hypertensive patients with limited compensatory preload reserve in response to stress, are susceptible to diastolic HF [19,20].

On the other hand, myocardial ischemia can contribute to impaired myocardial relaxation [2] and, hence diastolic dysfunction in HTN even in the absence of obstructive coronary arteries. In a preliminary study using Dipyridamole myocardial contrast echocardiography to evaluate the transmural distribution of myocardial blood flow (MBF), we found that subendocardial MBF reserve was blunted in hypertensive patients with LVH, suggesting the mechanism of LVH-induced myocardial ischemia in hypertensives [46].

Natural Course and Transition from Diastolic Dysfunction to Heart Failure

The mildest form of diastolic dysfunction occurring at the early stages of hypertensive LVH



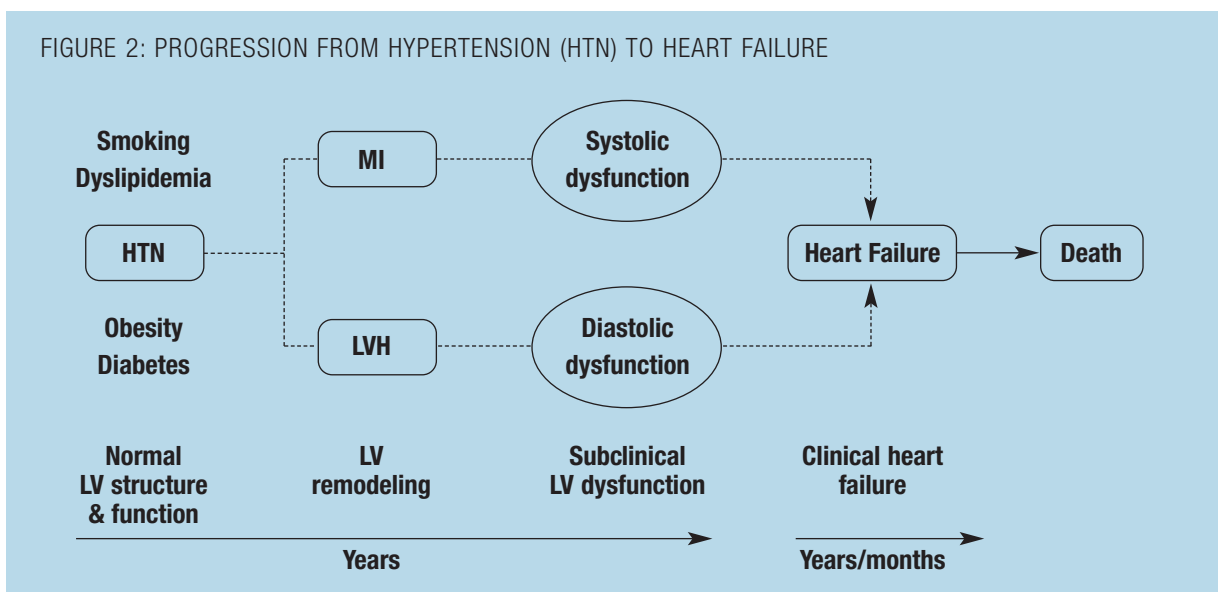
continued on page 23

can remain asymptomatic for years [2]. At the initial stage diastolic abnormalities are present with maintained diastolic and systolic function. As the heart continues to pump against increased afterload imposed by chronically elevated BP, LV systolic pump or diastolic filling begins to deteriorate. Overtime, congestive symptoms can develop due to progression and varying degrees of diastolic and systolic LV dysfunction that might coexist and eventually culminate in intractable end-stage congestive heart failure (HF) and cardiac death (**Figure 2**) [48] [49,50].

Using Doppler assessment of LV filling we were able to characterize patients by their level of exercise tolerance and symptoms of congestive HF during the four stages of the disease [40,42]. Briefly, stage 1 represents impaired relaxation or physiological pattern from increasing age of the patient; stage 2 is “pseudo” normalization and stage 3 is a restrictive-like filling pattern. In stage 4 there is atrial failure and the condition is irreversible. Patients might move between stages 1 and 3 with treatment or clinical deterioration. Delaying treatment until the irreversible stage 4 of the disease places the patient at a greater risk for CV events or need for transplantation [42].

Longitudinal studies suggest that alterations in diastolic function can occur as the sole manifestation very early in the course of HHD, well before the development of detectable HTN and may be independent or precede a significant increase in LV mass in subjects at risk of HTN [51]. These findings lend further support to previous cross-sectional observations in offsprings of hypertensive parents [52] and suggest that early identification of subjects with, or at risk for HTN and impaired diastolic function may help to stratify risk of disease progression, guide therapy and prevent target organ damage [51,53]. Most importantly, the clinical consequences of LVH regression on the development of congestive HF independent of BP reduction has been addressed with the ACE inhibitor Ramipril in the Heart Outcomes Prevention Evaluation Study (HOPE), which showed a high rate of HF in the group of patients who develop or have persistent LVH compared with those who have regression or prevention of LVH (15.4% vs. 9.3%, respectively, $P < 0.0001$) [54]. There is good reason for the benefit of ACE inhibition on diastolic HF, given the increase in levels of tissue ACE in models of cardiac hypertrophy [26,55].

continued on page 25



Diagnostic approach to Diastolic Heart Failure

Clinical Classification of Diastolic HF.

Diastolic HF is currently referred to as a clinical syndrome of HF with normal or preserved systolic function (HF-PSF). Clinicians caring for these patients still do not know how often isolated diastolic HF is the primary cause of HF, since many of these patients usually have lung disease or myocardial ischemia as alternative explanations for their symptoms [15]. In an attempt to resolve the ongoing controversy about the existence and importance of this clinical entity, many groups have provided guidelines for the assessment of LV diastolic function and the diagnosis of diastolic HF [56-58]. A definite diagnosis requires the unequivocal presence of the symptoms and signs of HF, the documentation of normal or near-normal/preserved LV ejection fraction (>0.50 or more) and direct evidence of increased diastolic filling pressure consistent with diastolic dysfunction [19,56,58]. Because these clinical features do not distinguish systolic from diastolic HF (**Table**), assessment of LV filling is necessary to

make this distinction [58] and to link the LV filling abnormality to the symptoms [15,16,59].

Recently, Vasan et al. [58] have provided standardized diagnostic criteria according to a hierarchy of evidence as definite, probable, or possible diastolic LV dysfunction at cardiac catheterization or echocardiography [58]. This classification recognizes the diagnostic uncertainty of DHF that has been in part validated by others in a prospective “echo-cath” study [3]. As suggested by these authors, the diagnosis of diastolic HF can be made without requiring objective measurements of diastolic function. Since the vast majority (>90%) of patients who met clinical definition of diastolic HF have objective evidence of diastolic dysfunction, including abnormal LV end-diastolic pressures, these specific indices of diastolic function should rather serve to confirm the diagnosis of diastolic HF.

It has been suggested that patients with suspected diastolic HF might have subtle or transient LV systolic dysfunction undetected by conventional methods [12]. In a small, but well performed, study including a series of 38 carefully selected consecutive patients who had acute pulmonary edema and marked systolic hypertension in the absence of pneumonia or MI, systolic

continued on the next page

TABLE: DIFFERENCES AND SIMILARITIES BETWEEN HF-PSF AND REDUCED EJECTION FRACTION HEART FAILURE

	DIFFERENCES	SIMILARITIES
Age	>65 or Older	—
Gender	More Women	—
Risk Factors and Comorbidities	Less CAD and MI	Obesity
	More Hypertension	Smoking
	—	Diabetes
	—	Dyslipidemia
	—	Atrial Fibrillation
Heart size/Wall thickness	Smaller/Thicker	—

Hf-PSF indicates heart failure with preserved systolic function; CAD, coronary artery disease; MI, myocardial infarction; HDL, high-density lipoprotein.

dysfunction or myocardial ischemia was unlikely to account for the occurrence of HF.

Furthermore, LVEF was unchanged during the acute episode of HF and on follow-up [19,20].

Methods of Diagnosing Diastolic HF. The gold standard for defining diastolic dysfunction is left heart catheterization with evaluation of the diastolic pressure-volume (PV) relations at rest and during exercise [59,60]. This invasive approach is not feasible in routine clinical practice [58], but is useful for serial evaluations of diastolic function following coronary interventions. The non-invasive imaging technique, especially echo-Doppler imaging of mitral inflow either alone or in combination with pulmonary venous flow, is helpful in the assessment of LV diastolic filling. The interpretation of the findings is largely dependent on the loading conditions, heart rate or the presence of atrial fibrillation. Newer measures presumed to be load-independent derived from either myocardial tissue-Doppler [19,61] or more recently cine magnetic resonance imaging [62] may improve the non-invasive assessment of LV diastolic function in the research setting. Whether these approaches are useful in clinical practice needs further evaluation.

The advent of biomarkers of neurohormonal activation, such as B-type natriuretic peptides [63] may be helpful in the care of patients with HF [19,64]; further studies are needed to determine whether these biomarkers could help to discriminate systolic from diastolic HF [64].

Approach to Treatment

Treating isolated diastolic HF is theoretically feasible but at present there is very limited data available to guide management of diastolic HF, since patients with this condition have been excluded from nearly all-large controlled trials in HF attributable to systolic dysfunction. While we await further evidence from ongoing treatment trials (see below), the implementation of the new therapeutic guidelines should be considered although data to support them are relatively incomplete. The goal of

treatment of diastolic HF is similar to systolic HF: relieve symptoms of volume overload, reduce hospitalizations, improve exercise capacity, quality of life and survival [5].

Acute Management includes the management of underlying pathology, such as myocardial ischemia and tachyarrhythmias as well as relief of volume overload.

Diuretics have a role in acute diastolic HF to reduce pulmonary congestion by shifting the pressure-volume relationship downward. It is important to avoid overdiuresis, because patients with diastolic dysfunction are sensitive to volume changes and an excessive volume reduction with diuretic might cause orthostatic hypotension or azotemia. Left atrial pressure (if hemodynamic monitoring is indicated) and blood urea nitrogen are useful for guiding diuretic therapy.

Beta-blockers help to control the heart rate in patients with atrial fibrillation and other supraventricular arrhythmias. They also have a role in diastolic HF precipitated by ischemia.

Calcium antagonists, such as Diltiazem is effective in controlling the heart rate.

Chronic Management generally focuses on improving LV relaxation and regression of LVH. Because HTN and its sequelae (LVH) are closely associated with diastolic HF, most of the drugs that are effective for managing systolic HF could also be logical treatment choices for controlling HTN and hence reducing the incidence of diastolic HF with regression of LVH.

ACE inhibitors and angiotensin receptor blockers (ARB). These agents inhibit the renin angiotensin aldosterone system, and are more effective in regression of LV hypertrophy compared with beta-blockers and calcium antagonists [65]. Additional myocardial relaxation effect may be seen via the bradykinin (NO) effect [66,67].

Aldosterone antagonists provide additional antifibrotic action [68]. In experimental model of arterial HTN, the competitive aldosterone receptor antagonist Spironolactone was able to prevent fibrosis in both ventricular irrespective of the development of LVH and HTN

[68]. These cardioprotective effects of spironolactone may help explain the prognostic value of antialdosterone therapy in patients with severe chronic HF evaluated in the RALES mortality trials [69]. Inhibition of fibroblasts and cardiac myocyte growth, as well as improvement of passive elastic properties of the myocardium, are mechanisms of action.

Calcium antagonists improve diastolic function by improving myocardial relaxation and enhancing diastolic filling. Additional benefits in hypertensive heart disease include reduced LV afterload, and decreased cytoplasmic calcium concentration [70]. By slowing the heart rhythm at a rate that optimizes diastolic filling time, calcium antagonist could also be useful in limiting tachycardia-induced ischemia that might cause further deterioration in diastolic function in these patients.

In summary, diastolic HF can be treated by focusing on achieving euvolemia and heart control in the acute stages. Treatment of the underlying condition particularly HTN and myocardial ischemia; nonpharmacologic measures such as control of dietary salt, weight management and increased physical activity have salutary effects, and should be actively integrated into the treatment strategy. There is no proven role for the use of digoxin in patients with diastolic HF and it is not indicated for this condition, except in those patients with atrial fibrillation” [2].

Ongoing Treatment Trials of DHF. As a result of the neurohormonal hypothesis, clinical trials [71,72] are currently investigating the role of ACE inhibitors, ARB and beta-blockers in patients with DHF or HF-PSF. Two separate placebo-controlled studies of angiotensin II receptor antagonists, the recently completed CHARM-diastolic arm/Preserved from the overall Programme (Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity) [72] and the ongoing I-PRESERVE (Irbesartan in Heart Failure with Preserved Systolic Function) are exploring new directions to advance our understanding of the pathophysiology of diastolic HF and the role of

treatment with ARB. Although the CHARM-Preserved trial has been very successful in demonstrating, albeit modestly, the impact of Candesartan on reducing future hospital readmissions for HF compared with placebo [72], these interesting results could not provide definitive answers as to the role of combination of ACE inhibitors and ARB's to treat diastolic dysfunction in the clinical setting. A relatively long-term follow-up of the CHARM study also left unanswered the potential effects of the drug on cardiovascular mortality over the 3-year follow-up. At the end of the 3-year follow-up, there was no difference in the rate of cardiovascular deaths between the Candesartan and placebo-treated patients. Although the ARB Candesartan did not decrease cardiovascular mortality, the advantage of reducing hospitalisations for HF may have major implications in the management of this common condition [72].

Unlike the recently completed CHARM-Preserved study with Candesartan, I-Preserved is the first and largest powerful ongoing clinical trial that is evaluating ARB Irbesartan, with or without ACE inhibitor background therapy, as a new reference treatment in this HF indication. It is enrolling exclusively symptomatic CHF patients aged 65 and older with EF >45% and recent hospitalization for CHF within the past 6 months or other findings consistent with diastolic dysfunction. This new trial will not only evaluate the promising treatment with ARB, but appears to be adequately powered and particularly rigorous in ensuring the diagnosis of HF with preserved systolic function that should advance our understanding of the syndrome.

Summary and Perspectives

Contrary to previously held belief, isolated/primary diastolic HF is the most commonly encountered type of HF in the elderly and is more common among women and patients with hypertension and LVH. Clinically, this syn-

continued on the next page

drome is defined when manifestations of HF are present with preserved LV systolic function.

Although invasive hemodynamic studies are the gold standard, their routine application in clinical practice is limited to a few patients. Echo-Doppler thus provides a useful tool for a comprehensive assessment of the underlying cause of diastolic HF and most importantly the differentiation of diastolic from systolic HF.

The therapeutic approach is generally to improve symptoms of congestion or volume overload, maintenance of sinus rhythm and atrial contraction and control of heart rate. Relief of myocardial ischemia, aggressive control of HTN to a target BP and regression of LVH are important goals of treating the underlying causative factors. The concept of neuro-hormonal modulation for reducing CV complications with ACE inhibitor or ARB is currently being evaluated in large clinical trials. Preliminary evidence indicates that AT-1 blockade may be beneficial.

Although these patients might have a more favorable prognosis than those with low EF, the rate of recurrent debilitating symptoms and hospital admissions underscores the need for implementing preventive strategies directed toward earlier and more aggressive control of the underlying structural heart disease. For this reason a change in the treatment paradigm should be considered with an emphasis on the early detection of LV remodeling. At the present time, further studies are needed to develop specific drugs aimed at improving abnormal relaxation/stiffness.

References

Lapu-Bula R and Ofili E. Diastolic heart failure: the forgotten manifestation of hypertensive heart disease. *Curr Hypertens Rep.* 2004;6:164-70.
Mandinov L, Eberli FR, Seiler C, Hess OM. Diastolic heart failure. *Cardiovasc Res* 2000;45:813-825.
Zile MR, Gaassh WH, Carroll JD, Feldman MD, Aurigemma GP, Schaer GL, Ghali JK, Liebson PR. Heart failure with a normal ejection fraction. Is the measurement of diastolic function necessary to make the diagnosis of diastolic heart failure? *Circulation* 2001;104:779-93.

Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA* 1996;275:1557-1562.
Vasan RS. Diastolic heart failure. The condition exists and needs to be recognized, prevented, and treated [editorial]. *BMJ* 2003;327:1181-2.
Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999;33:1948-55.
Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol* 1995;26:1565-74.
Bonow RO, Udelson JE. Left ventricular diastolic dysfunction as a cause of congestive heart failure: mechanisms and management. *An Intern Med* 1992;117:502-510.
Slama M, Susic D, Varagic J, Frohlich ED. Diastolic dysfunction in hypertension. *Curr Opin Cardiol* 2002;17:368-373.
Cleland JG, Khand A, Clark A. The heart failure epidemic: exactly how big is it? *Eur Heart J* 2001;22:623-6.
Cohen-Solal A. Diastolic heart failure: myth or reality? [editorial]. *Eur J Heart Fail* 2002;4:395-400.
Petrie MC, Caruana L, Berry C, McMurray JJV. "Diastolic heart failure" or heart failure caused by subtle left ventricular systolic dysfunction? *Heart* 2002;87:29-31.
Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction. Implications for systolic and diastolic reserve limitations. *Circulation* 2003;107:714-720.
Burkhoff D, Maurer MS, Packer M. Heart failure with a normal ejection fraction. Is it really a disorder of diastolic function? [editorial]. *Circulation* 2003;107:656-658.
Caruana L, Petrie MC, Davie AP, McMurray JJV. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or misdiagnosis? A prospective descriptive study *BMJ* 2000;321:215-9.
Michalsen A, Konig G, Thimme W. Preventable causative factors leading to hospital admission with decompensated heart failure *Heart* 1998;80:437-441.
Arques S, Ambrosi P, Gelisse R, Lucciono R, Habib G. Hypoalbuminemia in elderly patients with acute diastolic heart failure. *J Am Coll Cardiol* 2003;42:712-6.
de Simone G, Greco R, Mureddu GF, Romano C, Guida R, Celentano A, Contaldo F. Relation of left ventricular diastolic properties to systolic function in arterial hypertension. *Circulation* 2000;101:152-157.
Vasan RS, Levy D. Diastolic heart failure- No time to relax [editorial]. *N Engl J Med* 2001;344:56-59.

- Gandhi SK, Powers JC, Nomeir AM, Fowle K, Kitzman DW, Rankin KM, Little WC. The pathogenesis of acute pulmonary edema associated with hypertension. *N Engl J Med* 2001;344:17-22.
- van Kraaij DJW, van Pol PEJ, Ruiters AW, de Swart JBRM, Lips DJ, Lencer N, Doevendans PAFM. Diagnosing diastolic heart failure. *Eur J Heart Fail* 2002;4:419-430.
- American Heart Association. 2000 Heart and stroke statistical update. Dallas: American Heart Association 2000.
- Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, Redfield MM. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation* 1998;98:2282-2289.
- Philbin EF, Rocco TA, Lindenmuth NW, Ulrich K, Jenkins PL. Systolic versus diastolic heart failure in community practice: clinical features, outcomes, and the use of angiotensin-converting enzyme inhibitors. *Am J Med* 2000;109:605-613.
- Cohn JN, Johnson G. Heart failure with normal ejection fraction. The V-HeFT Study. Veterans Administration Cooperative Study Group. *Circulation* 1990;81(2 suppl):III48-III53.
- Sweitzer NK, Stevenson LW. Diastolic heart failure: miles to go before we sleep [editorial]. *Am J Med* 2000;109:683-685.
- Dauterman KW, Massie BM, Gheorghiadu M. Heart failure associated with preserved systolic function: a common and costly clinical entity. *Am Heart J* 1998;135:S310-9.
- Diller PM, Smucker DR, David B, Graham RJ. Congestive heart failure due to diastolic or systolic dysfunction: Frequency and patient characteristics in an ambulatory setting. *Arch Fam Med* 1999;8:414-420.
- Cohen-Solal A, Desnos M, Delahaye F, Emariou JP, Hanania G. A national survey of heart failure in French hospitals. *Eur Heart J* 2000;21:763-9.
- Topol EJ, Traill TA, Fortuin NJ. Hypertensive hypertrophic cardiomyopathy of the elderly. *N Engl J Med* 1985;312:277-83.
- Weinberg EO, Thienelt CD, Katz SE, Bartunek J, Tajima M, Rohrbach S, Douglas PS, Lorell BH. Gender differences in molecular remodeling in pressure overload hypertrophy. *J Am Coll Cardiol* 1999;34:264-73.
- Kannel WB, Ho K, Thom T. Changing epidemiological features of cardiac failure. *Br Heart J* 1994;72 (2 suppl):S3-9.
- Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol* 1992;20:301-6.
- The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997;157:2413-2446.
- Colhoun HM, Dong W, Poulter NR. Blood pressure screening, management and control in England: results from the health survey for England 1994. *J Hypertens* 1998;16:747-52.
- Marques-Vidal P, Tuomilehto J. Hypertension awareness, treatment and control in the community: is the 'rule of halves' still valid? *J Hum Hypertens* 1997;11:213-20.
- Joffres MR, Ghadirian P, Fodor JG, Petrasovits A, Chockalingam A, Hamet P. Awareness, treatment and control of hypertension in Canada. *Am J Hypertens* 1997;10:1097-102.
- Chamontin B, Poggi L, Lang T, Menard J, Chevalier H, Gallois H, Cremier O. Prevalence, treatment, and control of hypertension in the French population: data from a survey on high blood pressure in general practice, 1994. *Am J Hypertens* 1998;11:759-62.
- Cleland JGF, Swedberg K, Follath F et al. The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 1: Patient characteristics and diagnosis. *Eur Heart J* 2003;24:442-463.
- Lapu-Bula R, Robert A, De Kock M, D'Hondt A-M, Detry J-M, Melin JA, Vanoverschelde J-L. Relation of exercise capacity to left ventricular systolic function and diastolic filling in idiopathic or ischemia dilated cardiomyopathy. *Am J Cardiol* 1999;83:728-734.
- Vanoverschelde JLJ, Raphael DA, Robert A, Cosyns JR. Left ventricular filling in dilated cardiomyopathy: relation to functional class and hemodynamics. *J Am Coll Cardiol* 1990; 15:1288-1295.
- Lapu-Bula R, Robert A, De Kock M, D' Hondt A-M, Detry JM, Melin JA, Vanoverschelde JL. Risk stratification in patients with dilated cardiomyopathy: Contribution of Doppler-derived left ventricular diastolic filling. *Am J Cardiol* 1998; 82:779-785.
- Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling-concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. *J Am Coll Cardiol*. 2000;35:569-582.
- Weber KT, Brilla GG, Janicki JS, Reddy HK, Campbell SE. Myocardial fibrosis: role of ventricular systolic pressure, arterial hypertension, and circulating hormones. *Basic Res Cardiol* 1991;86(suppl 3):25-31.
- Lapu-Bula R, Ofili E, Oduwole A, Lankford B, Pack C, St Vrain J, Morgan J, Nkemdiche S, Li R. Left ventricular structural and geometric relations to endothelium-dependent vasodilatory function: A clue to the hypertensive phenotype in African Americans ?(abstr) *J Am Soc Echocardiogr* 2001; 14:P5-492.
- Lapu-Bula R, Ofili E, St Vrain J, Oduwole A, Lankford B, Pack C, Li R, Sklenar J, Kaul S. Differential characterization of transmural distribution of myocardial blood flow and its relation to left ven-

continued on the next page

- tricular structure in hypertensive patients: insights from dipyridamole contrast echocardiography. *Circulation* 2001;104(suppl):II-1954.
- Cuocolo A, Sax FL, Brush JE, Maron BJ, Bacharach SL, Bonow RO. Left ventricular hypertrophy and impaired diastolic filling in essential hypertension: diastolic mechanisms for systolic dysfunction during exercise. *Circulation* 1990;81:978-86.
- Vasan RS, Levy D. The role of hypertension in the pathogenesis of heart failure. A clinical mechanistic overview. *Arch Intern Med* 1996;156:1789-96.
- Jessup M, Brozena S. Heart failure. *N Engl J Med* 2003;348:2007-2018.
- Gaasch WH. Diagnosis and treatment of heart failure based on left ventricular systolic or diastolic dysfunction. *JAMA* 1994;271:1276-1280.
- Aeschbacher BC, Hutter D, Fuhrer J, Weidmann P, Delacretaz E, Allemann Y. Diastolic dysfunction precedes myocardial hypertrophy in the development of hypertension. *Am J Hypertens* 2001;14:106-113.
- Mo R, Nordrehaug JE, Omvik P, Lung-Johansen P. The Bergen Blood Pressure study: prehypertensive changes in cardiac structure and function in offspring of hypertensive families. *Blood Press* 1995;4:16-22.
- Sinaiko AR. Hypertension in children. *N Engl J Med* 1996;335:1968-1973.
- Mathew J, Sleight P, Lonn E, Johnstone D, Pogue J, Yi Q, Bosch J, Sussex B, Probstfield J, Yusuf S; for the Heart Outcomes Prevention Evaluation (HOPE) Investigators. *Circulation* 2001;104:1615-1621.
- Lorell BH, Grossman W. Cardiac hypertrophy: the consequences for diastole. *J Am Coll Cardiol* 1987; 9:1189-1193.
- European Study Group on diastolic heart failure. How to diagnose diastolic heart failure *Eur Heart J* 1998;19:990-1003.
- Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I diagnosis, prognosis, and measurements of diastolic function. *Circulation* 2002;105:1387-1393.
- Vasan RS, Levy D. Defining diastolic heart failure: A call for standardized diagnostic criteria. *Circulation* 2000;101:2118-21.
- Banerjee P, Banerjee T, Khand A, Clark AL, Cleland JGF. Diastolic heart failure: neglected or misdiagnosed? *J Am Coll Cardiol* 2002;39:138-41.
- Little WC, Downes TR, Applegate RJ. Invasive evaluation of left ventricular diastolic performance. *Herz* 1990;15:362-76.
- Ommen SR, Nishimura RA. A clinical approach to the assessment of left ventricular diastolic function by Doppler echocardiography: Update 2003. *Heart* 2003;89(Suppl III):iii18-iii23.
- Kudelka AM, Turner DA, Liebson PR, Macioch JE, Wang JZ, Barron JT. Comparison of cine magnetic resonance imaging and Doppler echocardiography for evaluation of left ventricular diastolic function. *Am J Cardiol* 1997;80:384-6.
- Cingolani OH, Yang XP, Cavaasin MA, Carretero OA. Increased systolic performance with diastolic dysfunction in adult spontaneously hypertensive rats. *Hypertension* 2003;41:249-254.
- Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, Gardetto N, Wanner E, Maisel AS. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. *Circulation* 2002;105:595-601.
- Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359:995-1003.
- Mitsunami K, Inoue S, Maeda K, Endoh S, Takahashi M, Okada M, Sugihara H, Kinoshita M. Three-month effects of candesartan cilexetil, an angiotensin II type 1 (AT1) receptor antagonist, on left ventricular mass and hemodynamics in patients with essential hypertension. *Cardiovasc Drugs Ther* 1998;12:469-74.
- Angomachalelis N, Hourzamanis AI, Sideri S, Serasli E, Vamvalis C. Improvement of left ventricular diastolic dysfunction in hypertensive patients 1 month after ACE inhibition therapy: evaluation by ultrasonic automated boundary detection. *Heart Vessels* 1996;11:303-9.
- Brilla CG. Aldosterone and myocardial fibrosis in heart failure. *Herz* 2000; 25:299-306.
- Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J; for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709-17.
- Betocchi S, Chiariello M. Effects of calcium antagonists on left ventricular structure and function. *J Hypertens Suppl* 1993; 11:S33-7.
- Cleland JGF, Tendera M, Adamus J, Freemantle N, Gray CS, Lye M, O'Mahony D, Polonski L, Taylor J. Peridopril for elderly people with chronic heart failure: the PEP-CHF study. *Eur J Heart Fail* 1999;1:211-17.
- Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson E, Olofsson B, Ostergren J. Effects of Candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003; 362:777-81.