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Diastolic Heart Failure in the Elderly

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There has been growing recognition over the past two decades that a substantial proportion of patients who have heart failure (HF), particularly the elderly, have preserved systolic left ventricular (LV) function. This condition has been presumptively termed diastolic heart failure (DHF). This article discusses the pathophysiology, diagnosis, prognosis, and therapy of this important disorder in older people.

Epidemiology

In the population-based Olmsted Community project, records were reviewed from all patients during a 1-year period in whom an assessment of LV ejection fraction (EF) was obtained within 3 weeks of a new diagnosis of congestive heart failure (CHF) [1]. A normal EF was found in 43% of patients and this phenomenon increased with age (Fig. 1) [1]. This population was recently reassessed and it was found that the prevalence of DHF had increased mildly to 47%, whereas the prevalence of systolic heart failure (SHF) had decreased slightly [2]. Other large population-based reports, including the Framingham Study [3], the Cardiovascular Health Study (CHS) [4,5], the Strong Heart Study of American Indians [6], the Helsinki Ageing Study [7], and large Medicare studies [8,9], have found the prevalence of normal EF among those who have HF to be even higher, well over 50% [3–9].

There is a remarkable sex-related difference in DHF. In the cross-sectional analysis of CHS, 67% of elderly women who had prevalent CHF had a normal EF, whereas this finding was present in only 42% of men (Fig. 2) [4]. During the longitudinal analysis of 6-year follow-up in CHS,

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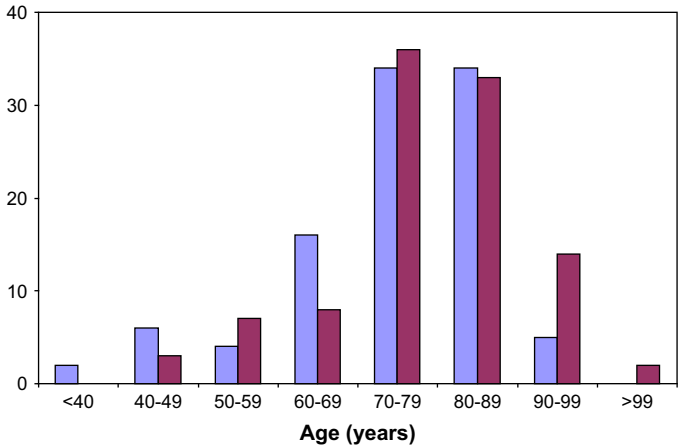

Fig. 1. Numbers of patients in Olmsted County, Minnesota hospitalized who had congestive heart failure in 1991 versus age with normal (*dark bars*) and reduced (*light bars*) ejection fraction. Note that CHF with a normal ejection fraction is absent in the youngest group (age <40 years) in contrast to the oldest group (age >99), where it comprises essentially all patients. (*Adapted from* Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation 1998;98:2282–89.)

more than 90% of women who developed HF had normal systolic function [10]. Because women significantly outnumber men in the older population, the population-attributable risk for HF with reduced systolic function was relatively small compared with those who had HF and normal systolic function [10]. As a result, the typical community-dwelling patient who has

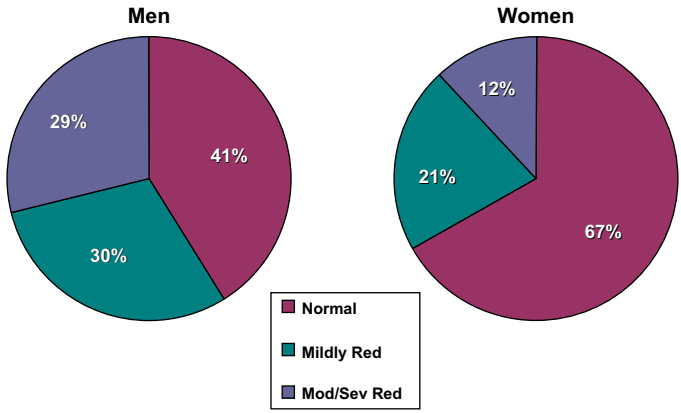

Fig. 2. LV ejection fraction by gender among community-dwelling elderly patients who have CHF in the Cardiovascular Health Study. (*Data from* Kitzman DW, Gardin JM, Gottdiener JS, et al. Importance of heart failure with preserved systolic function in patients ≥ 65 years of age. CHS Research Group. Cardiovascular Health Study. Am J Cardiol 2001;87:413–9.)

HF is an older woman who has normal systolic function and systolic hypertension. This profile contrasts sharply with the typical patients seen in referral HF clinics, who are middle-aged men who have severely reduced systolic function and ischemic heart disease. As one editorial declared, DHF is predominantly a disorder of older women [11].

Pathophysiology

Relatively few data are available regarding the pathophysiology of DHF. Both aging-related and sex-related differences in LV function may contribute. Among healthy normal subjects, older women tend to have higher left ventricular EFs, independent of their smaller chamber size, compared with men [12,13]. In addition, the female left ventricle in mammals has a distinctly different response to pressure load, such as is typical of systemic hypertension. In the HyperGen study, it was found that the deceleration time of early diastolic flow and isovolumic relaxation time were lengthened in women who had hypertension compared with men, independent of all other factors, indicating decreased myocardial relaxation [14]. In patients who had hypertension in the Framingham study the predominant pattern of hypertrophic remodeling in women was concentric, whereas in men it was eccentric, and this also has been reported in several other studies, including HyperGen [15] and LIFE.

Using aortic banding to create a model of chronic LV pressure overload in male and female rats, Douglas and colleagues [16] showed that male rats responded with LV dilation and modest wall thickening (eccentric hypertrophy) with resultant increased wall stress and decreased LV contractility. In contrast, the female rats increased their LV wall thickness and maintained a normal chamber size (concentric hypertrophy), and thereby enjoyed near-normal wall stress, and normal (even a trend toward supranormal) contractility. As a result, the female rats were able to continue to generate substantially higher systolic pressure, despite the excess afterload. Several other studies have shown similar overall results [17–19].

Large population-based studies have consistently shown that the strongest, most common risk factor for the development of HF is systolic hypertension. Combining this key point with the findings of the Douglas study provides a cohesive explanation for the divergent manifestations of HF in women versus men. The male LV is less able to tolerate pressure load, and in the presence of chronic systolic hypertension becomes dilated with thin walls and a depressed EF. The female LV is able to tolerate the pressure load better by developing concentric hypertrophy, allowing it to maintain normal LV size and EF. The long-term cost of this adaptation is impaired LV diastolic function. This phenomenon may help to explain the higher prevalence of DHF in women and why men tend to develop SHF whereas

women tend to develop DHF. The above interplay between LV remodeling and pressure load has been shown in rodent models to be influenced substantially by estrogen and androgen, and to be related to gender differences in cardiac angiotensin-converting enzyme (ACE) expression [20].

In addition to these sex-related changes, there are several normal age-related changes in cardiovascular structure and function that are likely relevant to the development of DHF. These include increased arterial and myocardial stiffness, decreased diastolic myocardial relaxation, increased LV mass, decreased peak contractility, reduced myocardial and vascular responsiveness to β-adrenergic stimulation, decreased coronary flow reserve, and decreased mitochondrial response to increased demand for ATP production [21]. Consequently, insults from acute myocardial ischemia or infarction, poorly controlled hypertension, atrial fibrillation, iatrogenic volume overload, and pneumonia, which would be tolerated in younger patients, can cause acute CHF in older persons [21].

These normal age-related changes result in decreased cardiovascular reserve, which confers an approximately 1% per year decline in maximal exercise oxygen consumption [22]. In addition, women also have been shown to have different cardiovascular physiologic responses to exercise than men, particularly in heart rate and stroke volume independent of age and body size [22–24].

Exercise intolerance, manifested as exertional dyspnea and fatigue, is the primary symptom in chronic HF. Although the pathophysiology of exercise intolerance in SHF as it presents in middle-aged men has been intensively examined, few studies have examined the pathophysiology of exercise intolerance in DHF. In a recent study, maximal exercise testing with expired gas was performed in three groups of older subjects: SHF, DHF, and age-matched controls [25]. It was found that in comparison to the normal controls, peak exercise oxygen consumption, an objective measure of exercise capacity, was severely reduced in the patients who had DHF and to a similar degree as those who had SHF (Fig. 3) [25]. In addition, submaximal exercise capacity, as measured by the ventilatory anaerobic threshold, was similarly reduced in patients who had DHF versus SHF, and this was accompanied by reduced health-related quality of life [25].

Our laboratory has completed several studies that have examined the central (cardiac) and peripheral (vascular) components of the exercise response to determine the mechanisms of the severely reduced exercise capacity in DHF. In the first, using invasive cardiopulmonary exercise testing, it was demonstrated that severe exercise intolerance was related to an inability to increase stroke volume by way of the Frank-Starling mechanism despite severely increased LV filling pressure, indicating diastolic dysfunction (Fig. 4) [26]. This dysfunction resulted in severely reduced exercise cardiac output and early lactate formation that appeared responsible for the severely reduced exercise capacity and associated chronic exertional symptoms.

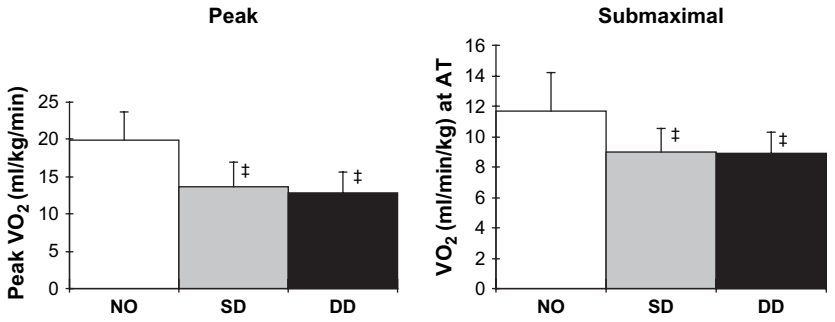

Fig. 3. Exercise oxygen consumption (VO_2) during peak exhaustive exercise (*left panel*) and during submaximal exercise at the ventilatory anaerobic threshold (*right panel*) in age-matched normal subjects (NO), elderly patients who have heart failure (HF) attributable to systolic dysfunction (SD), and elderly patients who have HF with normal systolic function, presumed diastolic dysfunction (DD). Exercise capacity is severely reduced in patients who have diastolic HF compared with normals ($P < .001$) and to a similar degree as in those who have systolic HF. (*Data from* Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiologic characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002;288:2144–50.)

A relatively simple but overlooked contributor to exercise intolerance in older patients who have HF is chronotropic incompetence. Using the most standard definition of chronotropic incompetence, we recently showed that this was present in 20% to 25% of older patients who had HF, that the prevalence was similar in DHF compared with SHF, that the presence of chronotropic incompetence was a significant contributor to the degree of exercise intolerance, measured as maximal oxygen consumption, and that this was independent of medications, including beta-adrenergic antagonists [27]. This finding has therapeutic significance because it could be potentially addressable with rate-responsive atrioventricular synchronous pacing.

Another study indicated that decreased aortic distensibility, likely attributable to the combined effects of aging- and hypertension-induced thickening and remodeling of the thoracic aortic wall, may be an important contributor to exercise intolerance in chronic DHF. Magnetic resonance imaging and maximal exercise testing with expired gas analysis were performed in a group of elderly patients who had isolated DHF and in age-matched healthy subjects. The patients who had DHF had increased pulse pressure and thoracic aortic wall thickness and markedly decreased aortic distensibility, which correlated closely with their severely decreased exercise capacity (Fig. 5) [28].

As discussed previously, several lines of evidence suggest that systemic hypertension plays an important role in the genesis of DHF. In animal models, diastolic dysfunction develops early in systemic hypertension, and LV diastolic relaxation is sensitive to increased afterload [29–34]. Increased afterload may impair relaxation, leading to increased LV filling pressures, decreased stroke volume, and symptoms of dyspnea and congestion [32].

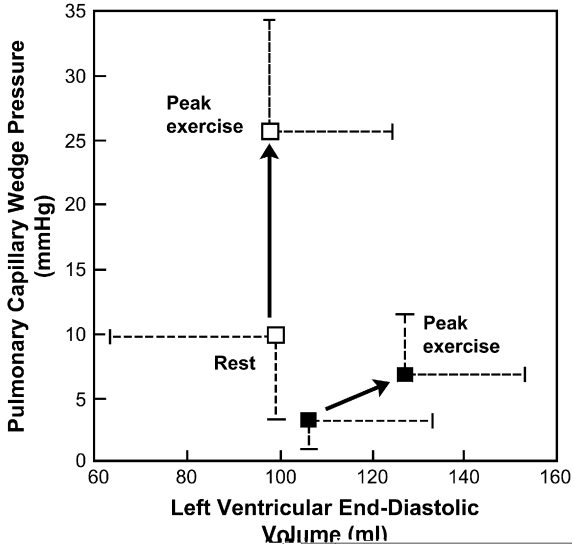

Fig. 4. LV diastolic function assessed by invasive cardiopulmonary exercise testing in patients who have heart failure and normal systolic function (*open boxes*) and age-matched normals (*closed boxes*). Pressure–volume relation was shifted upward and leftward at rest. In the patients with exercise, LV diastolic volume did not increase despite marked increase in diastolic (pulmonary wedge) pressure. Because of diastolic dysfunction, failure of the Frank-Starling mechanism resulted in severe exercise intolerance. (*From* Kitzman DW, Higginbotham MB, Cobb FR, et al. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Startling mechanism. J Am Coll Cardiol 1991;17:1065–72; with permission.)

Nearly all (88%) DHF patients have a history of chronic systemic hypertension [4,35,36]. In addition, severe systolic hypertension usually is present during acute exacerbations (pulmonary edema) [37–39].

The role of ischemia in DHF is uncertain. It would seem likely that it is a significant contributor in many cases. It had been hypothesized that patients found to have a normal EF following an episode of CHF may merely have had transiently reduced systolic function or ischemia at the time of the acute exacerbation. To address this question, an echocardiogram was performed at the time of presentation in 38 consecutive patients who had acute hypertensive pulmonary edema and was repeated again about 3 days later after resolution of pulmonary edema and control of hypertension [39]. The left ventricular EF and wall motion score index at follow-up were similar to those found during the acute echocardiogram. Furthermore, of those who had LV EF of 50% or greater at follow-up ($n = 18$), all but two had LV EF of 50% or greater acutely, and in those two cases the LV EF was greater than 40%, above the level that would be expected to cause acute HF because of primary systolic dysfunction (Fig. 6). These data suggest that marked transient systolic dysfunction and overt ischemia do not play primary roles

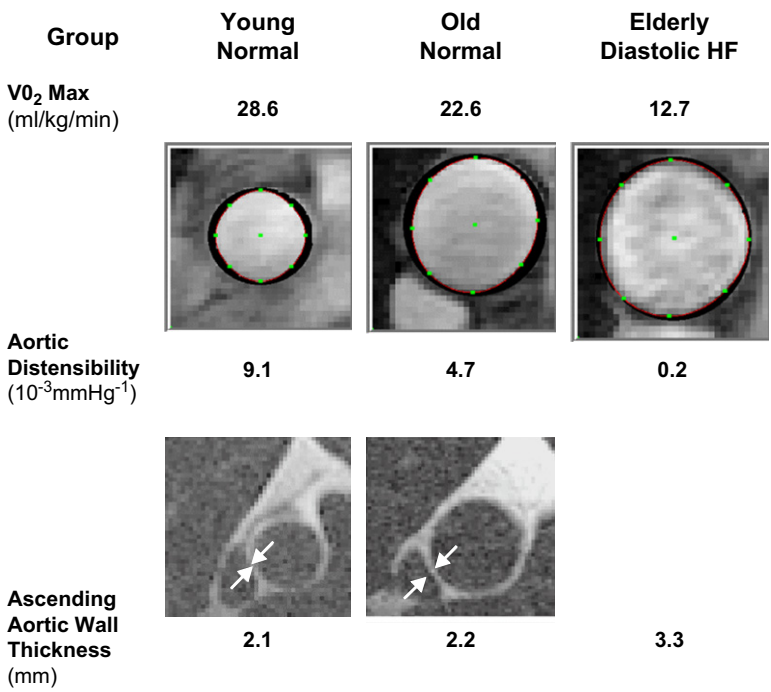

Fig. 5. Data and images from representative subjects from healthy young, healthy elderly, and elderly patients who have diastolic heart failure (DHF). Maximal exercise oxygen consumption (VO_2max), aortic distensibility at rest, and left ventricular mass:volume ratio. Patients who have DHF have severely reduced exercise tolerance (VO_2max) and aortic distensibility and increased aortic wall thickness. (*Adapted from* Hundley WG, Kitzman DW, Morgan TM, et al. Cardiac cycle dependent changes in aortic area and aortic distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. J Am Coll Cardiol 2001;38:796–802; with permission.)

in most patients who present with acute CHF in the presence of severe systolic hypertension and are subsequently found to have a normal EF [39]. Further, the data support the concept that acute pulmonary edema in these patients most likely is because of an exacerbation of diastolic dysfunction caused by severe systolic hypertension. The data also suggest that the EF measurement from an echocardiogram performed in follow-up accurately reflects that during an episode of acute pulmonary edema [39].

In a related study, 3-year follow-up was performed in 46 patients who initially presented with acute hypertensive pulmonary edema [38]. Most patients had a normal EF. Of those who were referred clinically for coronary angiography (n = 38), 33 had obstructive epicardial coronary artery disease and 19 underwent revascularization. Of these 19, by 6-month follow-up, 9 had been hospitalized with recurrent pulmonary edema and 1 had died. Severe systolic hypertension was nearly uniformly present at the time of recurrent pulmonary edema [38]. These two studies suggest that

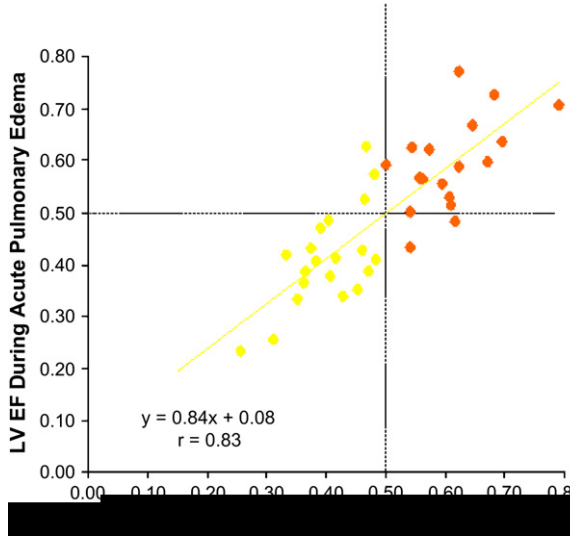

Fig. 6. Left ventricular ejection fraction (LVEF) measured during acute pulmonary edema and at follow-up, 1 to 3 days after treatment. Nearly all patients found to have normal EF (>50%) at follow-up also had normal EF during acute pulmonary edema. (*Adapted from* Gandhi SK, Powers JE, Fowle KM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 2000;344:17–22; with permission. Copyright © 2000 Massachusetts Medical Society. All rights reserved.)

severe systolic hypertension may play a pivotal role in the pathogenesis of acute exacerbations of DHF.

Neurohormonal activation likely plays an important role in the pathophysiology of DHF as it does in patients who have SHF. In a group of patients who have primary DHF, Clarkson and colleagues [40] showed that atrial natriuretic peptide and brain natriuretic peptide were substantially increased and there was an exaggerated response during exercise, a pattern similar to that described in patients who have SHF. In the study described earlier [25], it was found that brain natriuretic peptide was significantly increased in patients who had DHF compared with normal controls, but not so severely as in those who had SHF. Norepinephrine, however, was increased to a similar degree as in SHF.

The role of genetic predisposition in the genesis of DHF in the elderly is not known. Diastolic LV relaxation is significantly modulated by beta-adrenergic stimulation by way of phospholamban and, to a lesser extent, cardiac troponin-I, both of which are substantially under genetic control. Furthermore, data from the HyperGen study have shown significant heritability of hypertension [41], LV mass [42], and Doppler diastolic filling [43], all factors that likely play a role in DHF in the elderly. The genetic basis of familial hypertrophic cardiomyopathy, which has substantial phenotypic similarities to isolated DHF in the elderly, has been described [44,45]. It is

noteworthy that in that disorder the phenotype may not be expressed for 30 to 50 years.

Diagnosis and clinical features

The distinction between HF attributable to systolic dysfunction versus diastolic dysfunction usually cannot be made reliably at the bedside [46] and evaluation of new-onset HF in an elderly patient should include an imaging test, usually an echocardiogram [47]. This test not only assesses systolic function but also excludes unexpected but important diagnoses, such as aortic stenosis, severe valvular regurgitation, large pericardial effusion, hypertrophic obstructive cardiomyopathy, and cardiac amyloidosis. Unfortunately, a definitive noninvasive measure is not available for diastolic dysfunction. Doppler left ventricular diastolic filling indexes and particularly the newer tissue Doppler techniques [48] can provide helpful supplementary information, but their role in the clinical diagnosis of the DHF syndrome is unclear and their independent discriminatory power in unselected populations is not known.

Diagnostic criteria from the European Study Group on Diastolic Heart Failure [49] include: signs and symptoms of CHF, a normal or at most mildly reduced LV EF, and evidence of abnormal diastolic function. Subsequent work by Vasan [50] and Gandhi [39] suggest that DHF diagnosis usually can be made without the mandate for measurement of EF at the time of the acute event. Invasive measures of diastolic function are impractical and not feasible in most circumstances. Furthermore, two studies by Zile and coworkers [51,52] suggest that measures of diastolic function, invasive or otherwise, are not necessary for the diagnosis of DHF, because nearly all patients who meet the other criteria for DHF have diastolic dysfunction. The original European criteria thus have undergone substantial modification, primarily by simplification, as a result of the above progress in our understanding of the syndrome of DHF [53–55]. In addition to positive inclusion criteria, care should be taken to exclude other causes for the signs and symptoms suggesting HF [56]. Finally, patients who have HF, a normal EF, and no other explanation for their symptoms have the more pure diagnosis of isolated DHF. In CHS, this subgroup comprised 42% of the patients who had CHF and a normal EF [4]. Typical patients who have isolated DHF are women and often have high normal or super-normal EF (70% or more), normal or small left ventricular chamber size, thick walls with concentric hypertrophy, and no segmental wall motion abnormalities.

Because active myocardial ischemia can present as HF, particularly in the elderly, and has independent prognostic and therapeutic implications, a stress test is often indicated; in the case of concomitant severe or unstable angina, coronary angiography is indicated.

Rapid brain natriuretic peptide (BNP) assays can aid in the diagnosis of HF, particularly in the emergency setting, and may help in judging disease

severity and prognosis [19]. The role of BNP assays in the routine evaluation and management of chronic, stable DHF patients is not well defined, however [19]. It is notable that among healthy subjects, both sex and age significantly affect ranges of BNP [57,58]. Further, because BNP seems to be increased in DHF and systolic failure [40] it may not be helpful in discriminating between these two disorders [25].

Prognosis

The severity of exercise intolerance and the frequency of hospitalization appear to be similar in patients who have systolic versus diastolic HF [25,59–62]. This high rate of hospitalization is associated with poor quality of life and high health care costs [63,64]. The annual mortality rate for diastolic HF in the Framingham Study was 8.9% per year, a rate about twofold higher than nested case controls, although it was only half that reported for SHF (19.6%) [3]. Similar results were found in CHS [5]. In hospitalized patients, however, mortality is similar with diastolic and systolic HF (Fig. 7) [1,59,60,65,66]. This finding was recently confirmed in two large studies, which also showed that the mortality of DHF over the past 15 years is not decreasing [2,67,68]. An important observation in the Cardiovascular Health Study was that, given the higher prevalence among the elderly, the population-attributable mortality risk in patients who have DHF is actually higher than in those who have SHF, highlighting the public health implications of DHF in the elderly [5].

Predictors of prognosis are not as well defined in DHF as in SHF, but appear to include age, sex, and BNP levels [7,10,69].

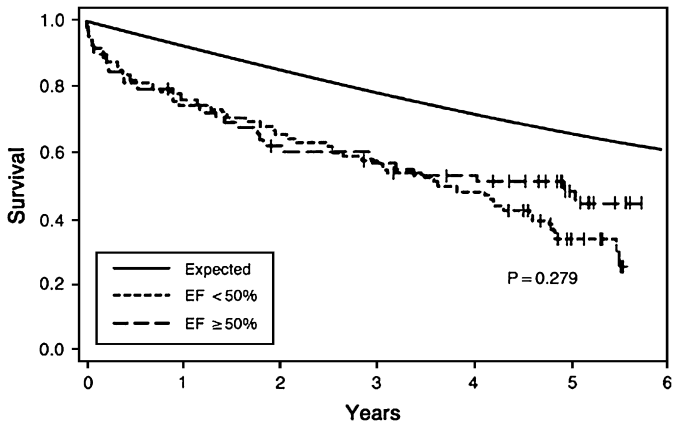

Fig. 7. Survival of patients admitted with congestive heart failure by ejection fraction. (*From* Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation 1998; 98:2282–89.)

Management

Our literature base regarding therapy of DHF is embarrassingly scant [55,70,71]. In contrast to SHF, for which numerous studies in many thousands of patients have generated a rich evidence base to direct therapy, there is essentially only one large, multicenter trial in DHF. This is remarkable given the high prevalence, substantial morbidity, and significant mortality of DHF [55,71–73]. This situation is particularly regrettable for older patients who bear the greatest burden of DHF.

Considering the surprising reversals and seemingly paradoxic outcomes during the circuitous journey to definitive, evidence-based therapy for SHF during the past 3 decades, one should not expect a clear, easy path toward establishing effective evidence-based therapy for DHF. Several large trials are now in progress.

The absence of specific evidence-based data to guide therapy is reflected in the brief discussion of DHF in the recent American College of Cardiology/American Heart Association 2005 Heart Failure Evaluation and Management Guidelines [74]. As discussed in the guidelines document, there are several empiric recommendations that can be provided [74].

General approach

The approach to the patient who has DHF should begin with a search for a primary cause. Most such patients are found to have hypertension as their main underlying condition [19]. Screening for ischemic heart disease with a noninvasive stress test or coronary angiography should be considered, especially in patients who have chest pain or flash pulmonary edema, to exclude severe coronary heart disease [19]. When found, manifest ischemia should be treated, including invasively if indicated [19], because ischemia is a therapeutic target in its own right and also strongly impairs diastolic relaxation. A small but important number of patients are found to have hypertrophic cardiomyopathy [75,76] with or without dynamic obstruction, undiagnosed valvular disease, or rarely amyloid heart disease [77].

Control of hypertension may be the single most important treatment strategy for DHF [78]. Chronic hypertension causes left ventricular hypertrophy and fibrosis, which impair diastolic chamber compliance. Acute hypertension significantly impairs diastolic relaxation. In addition, meta-analyses indicate that therapy for chronic, mild systolic hypertension in the elderly is a potent means of preventing the development of HF (Table 1), and it is likely that a major portion of cases prevented are attributable to DHF [78–82]. The ALLHAT study showed that the diuretic chlorthalidone was at least as effective for prevention of CHF as other antihypertensive medications [83].

Loss of atrial contraction is deleterious to LV filling, and atrial fibrillation with fast ventricular rate is a common precipitant to decompensated

Table 1
Effect of antihypertensive therapy on incident heart failure in the elderly

Trial	N	Age range (yrs)	Risk reduction (%)
European Working Party	840	>60	22
Coope and Warrender	884	60–79	32
Swedish Trial	1627	70–84	51
SHEP	4736	≥60	55
Syst-Eur	4695	≥60	36
STONE	1632	60–79	68

Adapted from Rich MW, Kitzman DW. Heart failure in octogenarians: a fundamentally different disease. Am J Geriatr Cardiol 2000;9(Suppl 5):97–111.

DHF. Sinus rhythm therefore should be maintained [19]. Achieving and maintaining sinus rhythm can be difficult in the elderly in whom the rate of atrial fibrillation is high. When sinus rhythm cannot be maintained, a more modest goal of rate control should be pursued.

Management goals in elders who have DHF include relief of symptoms, improvement in functional capacity and quality of life, prevention of acute exacerbations and related hospital admissions, and prolongation of survival. A systematic approach should comprise several elements: diagnosis and staging of disease, search for reversible cause, judicious use of medications, patient education, enhancement of self-management skills, coordination of care across disciplines, and effective follow-up. Every HF patient should have a scale, weigh regularly, and know what steps to take if weight increases beyond prespecified ranges. Diuretic adjustments can be performed by nurses over the telephone and in some cases by patients themselves. There must be easy access to health care providers so that problems can be addressed early to avoid decompensation with periodic telephone calls, frequent follow-up appointments, and monitoring programs using telephone and the internet [19,84].

There is now undisputed evidence of the efficacy of a multidisciplinary approach to care in reducing acute exacerbations leading to rehospitalization, improving quality of life, reducing total costs, and increasing survival [85–88]. Notably, many of these studies included significant numbers of patients who had normal EF [86]. Elders and women who have HF often have severe deconditioning and severe exercise intolerance and they should be encouraged to undertake regular moderate physical activity.

The association between alcohol intake and HF is controversial; one recent study suggested that moderate alcohol intake had a mild protective effect for HF in the elderly [89].

Pharmacologic therapy

Despite the fact that numerous randomized, controlled trials have shown a marked decrease in development of HF in patients treated for systolic hypertension (Table 1) [79–82], community surveys consistently show

undertreatment of hypertension. Adequate treatment of systemic hypertension is a potent means for prevention of DHF.

Diuretics

Diuretics are indispensable for rapid relief of pulmonary congestion and peripheral edema and are necessary in most patients who have moderate to severe HF to mitigate volume overload. They may accelerate activation of the renin-angiotensin system and cause renal insufficiency and electrolyte disturbances, however. The lowest dose capable of maintaining euvolemia should be used. Although some patients who have mild DHF can be treated effectively with a thiazide diuretic for some time, usually a loop diuretic is eventually required to maintain euvolemia.

Most patients who have HF have an intrinsic diuretic threshold below which minimal diuresis occurs, even when repeated doses are administered. Multiple daily doses thus are not usually necessary and are inconvenient particularly in older women in whom they can exacerbate urinary incontinence [56]. Usually, a single morning oral dose somewhat greater than the diuretic threshold provides effective control of salt and fluid retention. Nonsteroidal anti-inflammatory medications, frequently used in older patients, can cause relative diuretic resistance and should be discontinued if possible. During active diuresis, careful monitoring and replacement of electrolytes, particularly potassium and magnesium, are important; fluid restriction may be needed to avoid or alleviate hyponatremia [90].

Digoxin

Because most inotropes enhance early diastolic relaxation, digoxin might theoretically have a similar effect. In a recent report from the Digitalis Investigation Group Trial (DIG), in the large subset of ambulatory elderly patients who had mild to moderate symptomatic DHF and normal sinus rhythm, digoxin had no net positive or negative effect when assessed as either overall mortality or all-cause or cardiovascular hospitalizations (Fig. 8) [91]. Contrary to prior, small anecdotal reports, digoxin does not increase overall mortality and need not be avoided if indicated for other reasons in DHF patients.

Angiotensin-converting enzyme inhibitors

ACE inhibitors (ACEI) and angiotensin receptor blockers (ARBs) are attractive as therapy for patients who have DHF. They are the cornerstone of systolic HF therapy because they reduce mortality and hospital admissions and improve exercise tolerance and symptoms. As discussed previously, patients who have DHF also appear to have neuroendocrine activation, increased left ventricular filling pressure, and decreased stroke volume similar to those who have systolic failure [25,26,40]. ACE inhibition reduces blood pressure and LVH and improves left ventricular relaxation and aortic distensibility [92–96].

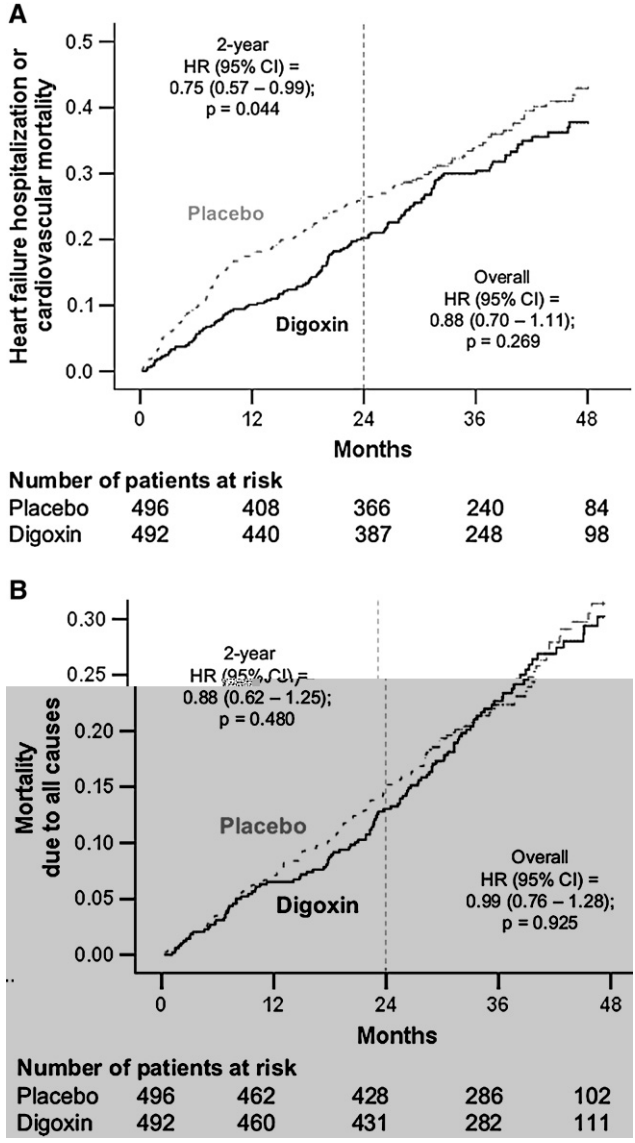

Fig. 8. Effect of digoxin on heart failure hospitalization and cardiovascular mortality (*A*) and all cause mortality (*B*) in patients who have heart failure and normal ejection fraction in the DIG trial. (*From* Ahmed A, Rich MW, Fleg JL, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure. The Ancillary Digitalis Investigation Group Trial. Circulation 2006;114:397–403; with permission.)

Aronow and colleagues [97] showed in a group of New York Heart Association class III HF patients who had presumed diastolic dysfunction (EF > 50%) that enalapril significantly improved functional class, exercise duration, EF, diastolic filling, and left ventricular mass. In an observational study of 1402 patients admitted to 10 community hospitals, ACEI use in DHF patients was associated with substantially reduced all-cause mortality (odds ratio 0.61) and CHF death (odds ratio 0.55) [98,99]. The European trial PEP-CHF is assessing the effect of the ACEI perindopril in elderly (age > 70 years) patients who have HF with an LV EF 40% or greater on death, HF admission, quality of life, and 6-minute walk distance [100].

Angiotensin receptor blockers

In a blinded, randomized, controlled, crossover trial of 20 elderly patients who had diastolic dysfunction and an exaggerated blood pressure response to exercise, the ARB losartan substantially improved exercise capacity and quality of life [101]. The CHARM-Preserved trial assessed the effect of candesartan on death and hospital admission in patients who had HF with EF > 40% [102]. This study included a substantial number of women and elderly. Over a median follow-up of 36 months, cardiovascular death did not differ from placebo; however, fewer patients in the candesartan group than in the placebo group (230 versus 279, $P = .017$) were admitted to the hospital for new episodes of CHF. The ongoing I-PRESERVE trial is assessing the effect of the ARB irbesartan compared with placebo, is recruiting a larger number of DHF patients, and is using more specific inclusion criteria.

Calcium channel antagonists

Calcium channel antagonists often have been suggested for DHF. In hypertrophic cardiomyopathy, a disorder in which diastolic dysfunction is common, verapamil seems to improve symptoms and objectively measured exercise capacity [103–106]. In laboratory animal models calcium antagonists, particularly dihydropyridines, prevent ischemia-induced increases in LV diastolic stiffness [107] and improve diastolic performance in pacing-induced HF [108–110]. Negative inotropic calcium antagonists significantly impair early relaxation, however [110–114], and in general have shown a tendency toward adverse outcome in patients who have systolic HF [110]. Setaro and coworkers [115] examined 22 men (mean age 65) who had clinical HF despite EF greater than 45% in a randomized, double-blind, placebo-controlled crossover trial of verapamil. There was a 33% improvement in exercise time and significant improvements in clinicoradiographic HF scoring and peak filling rate.

In a randomized, crossover, blinded trial, Little and colleagues [116] compared the calcium channel antagonist verapamil to the angiotensin receptor antagonist candesartan with the outcomes of peak exercise blood pressure, exercise time, and quality of life. Although both agents blunted the peak

systolic blood pressure response to exercise, only candesartan, and not verapamil, improved exercise time and quality of life (Fig. 9) [116].

Beta-adrenergic antagonists

Beta-adrenergic antagonists also have been successful as therapy for hypertrophic obstructive cardiomyopathy [117]. In addition, they substantially improve mortality in SHF patients. Furthermore, they reduce blood pressure, assist in the regression of ventricular hypertrophy, and increase the ischemic threshold, all of hypothetical importance in DHF [29,31,35,118,119].

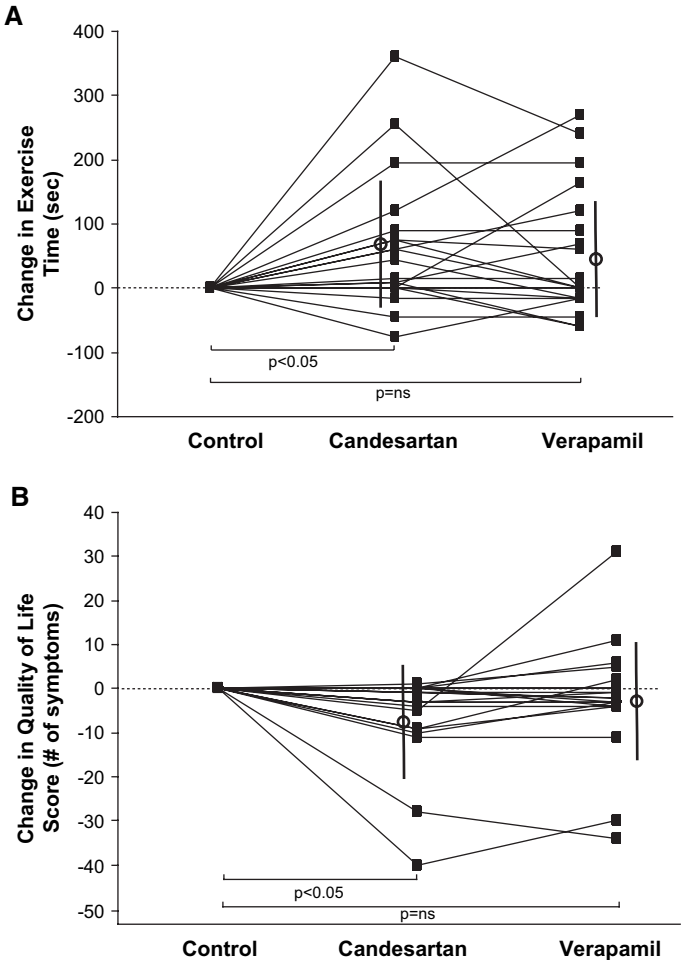

Fig. 9. Effect of candesartan angiotensin receptor antagonist compared with verapamil calcium channel blocker on exercise time (*A*) and quality of life (*B*) in patients who have diastolic dysfunction. (*From* Little WC, Wesley-Farrington DJ, Hoyle J et al. Effects of candesartan and verapamil on exercise tolerance in diastolic dysfunction. J Cardiovasc Pharmacol 2004;43(2):288–93; with permission.)

Cheng and coworkers and others have shown that early diastolic relaxation is impaired by beta-adrenergic blockade, however [120,121]. Delineating the role of beta-blockers in DHF will require large, well-designed clinical trials.

Aldosterone antagonists

The addition of low-dose spironolactone (12.5 to 50 mg daily) to standard therapy has been shown to reduce mortality 30% in patients who have severe SHF [122]. Aldosterone antagonism has numerous potential benefits in patients who have DHF, including LV remodeling, reversal of myocardial fibrosis, and improved LV diastolic function and vascular function [123–125]. Few data are presently available regarding aldosterone antagonism in DHF, however. In one small study, low-dose spironolactone was well tolerated and appeared to improve exercise capacity and quality of life in older women who had isolated DHF [126]. In another, spironolactone improved measures of myocardial function in hypertensive patients who had DHF [127]. Notably, spironolactone is much better tolerated in women, who have lower rates of mastodynia than men [122]. Spironolactone and eplerenone are contraindicated in patients who have advanced renal dysfunction or pre-existing hyperkalemia. Delineation of the role of this potentially promising strategy will need to await results of clinical trials [55]. The National Heart, Lung, and Blood Institute is sponsoring a large, multicenter, randomized, placebo-controlled trial of spironolactone in older patients who have DHF, which is in the process of launching at the time of this writing.

Novel agents

Glucose cross-links increase with aging and diabetes, and cause increased vascular and myocardial stiffness. Alagebrium, a novel cross-link breaker, improved vascular and LV stiffness in dogs. In a small, open-label, 4-month trial of this agent in elderly patients, LV mass, quality of life, and tissue Doppler diastolic function indexes improved, but there were no significant improvements in exercise capacity or aortic distensibility, the primary outcomes of the trial [128]. Various other agents and strategies currently are being evaluated or under consideration for this syndrome, including a selective endothelin antagonist.

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