Diastolic heart failure

By: Rebecca Gary and Leslie L. Davis

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Abstract:

Diastolic heart failure (DHF) is estimated to occur in 40% to 50% of patients with heart failure. Evidence suggests that DHF is primarily a cardiogeriatric syndrome that increases from approximately 1% at age 50 years to 10% or more at 80 years. DHF is also more likely to occur in older women who are hypertensive or diabetic. Although survival is better in patients with DHF compared with systolic heart failure, mortality rates for patients with DHF are four times higher than those for healthy, community-dwelling older adults. The increase in DHF is anticipated to continue during the next several decades largely because of the aging of the population; increase in risk factors associated with hypertension, diabetes, and obesity; and ongoing technologic advances in the treatment of cardiovascular disease. Few clinical trials have evaluated therapy in this population, so evidence about the effectiveness of treatment strategies for DHF is limited. Future research should target novel interventions that specifically target patients with DHF who are typically older and female, and experience exertional intolerance and have a considerably reduced quality of life.

Keywords: diastolic heart failure | aging | hypertension | diabetes | obesity | treatment strategies

Article:

Approximately 550,000 individuals in the United States are diagnosed with heart failure (HF) annually, and this number is anticipated to increase to 1.5 million by 2040, largely because of the aging of the population, positive lifestyle modifications, and technologic advances in the treatment of coronary artery disease.[1] HF is the leading reason for hospital admissions and death among older adults and is the most expensive Medicare expenditure, with costs estimated to be between 30 and 40 billion dollars annually.[2-8]Evidence indicates that diastolic heart failure (DHF) and systolic heart failure (SHF) are equally distributed in the population, and that they differ in pathologic mechanisms and in the gender and age of those affected.[9-13] However, despite the potential economic and clinical implications of DHF, few clinical trial data are available and treatment continues to remain largely empirical.[14]

Table I. Differences and similarities between systolic and diastolic heart failure

	Systolic heart failure present	**Diastolic heart failure present**
Signs and symptoms		
BNP	↑↑	↑
Exercise testing		
Duration	↓	↓
Systolic BP	↑	↑↑
Pulse pressure	↑	↑↑
VO_2	↓↓	↓
LV remodeling		
End-diastolic volume	↑↑	N
End-systolic volume	↑↑	↓
Myocardial mass	↑ (eccentric LVH)	↑ (concentric LVH)
Relative wall thickness	↓	↑↑
Cardiomyocyte	↑ length	↑ diameter
EC matrix (collagen)	↓	↑↑
LV systolic function		
Ejection fraction	↓↓	N-↑
Stroke volume	N-↓	N-↓
Myocardial contractility	↓↓	↓
LV diastolic function		
Chamber stiffness	N-↓	↑↑
Myocardial stiffness	N-↑	↑
Relaxation time-constant	↑	↑
Filling dynamics	abnormal	abnormal
End-diastolic pressure	↑↑	↑↑
Preload reserve	exhausted	limited
Morbidity	↑↑	↑↑
Survival	↓↓	↓

BNP, Brain natriuretic peptide; *BP*, blood pressure; *VO_2*, oxygen consumption; *LV*, left ventricular; *LVH*, left ventricular hypertrophy; *EC*, extracellular.
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HF, whether systolic or diastolic, is a complex syndrome characterized by dyspnea and fatigue secondary to structural and functional changes in the heart resulting from a variety of conditions that occur in conjunction with neurohormonal and cytokine activation. Diastolic dysfunction is caused by an abnormality of the mechanical properties (distensibility, filling, and relaxation) of the left ventricle (LV). Patients with diastolic dysfunction may experience HF symptoms, be asymptomatic, or have a normal or even low left ventricular ejection fraction (LVEF) when also associated with systolic impairment. Diastolic dysfunction is caused by factors that are intrinsic to the myocardium, such as those affecting the cardiomyocytes, extracellular matrix, or vascular

system, which has both similarities and differences to systolic dysfunction as shown in Table I.[15-21]

Patients with DHF exhibit classic HF symptoms (eg, dyspnea, fatigue, and evidence of pulmonary congestion on chest radiograph). In the majority of patients, the primary reason for DHF is diastolic dysfunction. However, systolic function is normal as evidenced by an LVEF of 50% or more.[8,16-20,22] Brain natriuretic peptide (BNP) has improved the ability to diagnose DHF and is useful for excluding other conditions, but does not differentiate DHF from SHF.[23,24]

Epidemiology

The Cardiovascular Health Study (CHS)[9,10] was the first large epidemiologic study (N = 4842) to examine cardiovascular disease risk in the elderly. HF was present in 425 subjects (8.8%) of the sample, whose mean age was 77 ± 5 years. This was most notable among women, in whom HF increased from 6.6% at age 65 to 69 years to 14% at age greater than 85 years. More than half (55%) of the women in the CHS exhibited a normal LVEF, and LVEF was only mildly reduced in 80% of the women.[10] DHF was more common in women than men (67% vs 42%; $P < .001$), which is consistent with findings from the Framingham study[5,7,25,26] and others.[13,27-29]

More recent findings from the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) trial,[30] consisting of three component studies comparing placebo with candesartan, support earlier epidemiologic findings of increased DHF among women. The proportion of women in CHARM-Preserved (LVEF ≥ 40%)[31] was 40%. This number was higher than the 32% of women reported in the CHARM-Alternative arm of the study (LVEF ≤ 40%, intolerant to angiotensin-converting enzyme inhibitors [ACEIs], and not previously taking angiotensin receptor blockers [ARBs])[32] and considerably more than the 21% of women who were enrolled in the CHARM-Added component (LVEF ≤ 40%, ACEIs, or placebo in addition to candesartan).[33] Patients in the CHARM-Preserved study were more often hypertensive than patients in the CHS or Framingham studies (64% vs 50% and 48%, respectively). Compared with previous trials, the CHARM-Preserved subjects were older, more likely to be women, more likely to have a history of hypertension, less likely to report a previous myocardial infarction, and more likely to have New York Heart Association (NYHA) class II.[31] Preliminary findings from the Irbesartan in Heart Failure with Preserved EF (I-Preserve trial),[34] the largest trial to evaluate an ARB in patients with DHF (N = 4100), revealed that 60% were women, hypertension was the primary cause, and most were aged more than 70 years.

Prognosis and Hospitalizations

Among community samples, the mortality rates for patients with SHF are 10% to 15% annually, higher than the 4% to 8% observed in patients with DHF.[2,10] However, the death rate among patients with DHF is approximately four to five times higher compared with adults with normal diastolic function, indicating its serious impact.[10] Short-term survival and hospital readmission rates are more favorable in younger patients with DHF (<65 years) than patients with SHF but are similar at age 75 years or more.[2,3,35-37] Evidence also suggests that elderly patients with DHF are less likely to receive optimal treatment with ACEIs and beta-blockers, which may contribute to the poor outcomes in this age group.[2,38]

The cause of DHF seems to play an important role in prognosis and mortality. Although coronary artery disease is common in both systolic and diastolic HF, an ischemic cause is associated with higher mortality rates in DHF.[39] In addition, if diastolic dysfunction is present in the early stages of an acute myocardial infarction, HF and death are more probable.[3,4,19] The number of hospitalization readmissions related to nonischemic causes of DHF, however, is not significantly different than SHF. African Americans with DHF may be particularly susceptible to poor clinical outcomes because diabetes, hypertension, and obesity, all known to cause and exacerbate DHF, are more prevalent, severe, and poorly controlled.[40] The influence of socioeconomic disparities and health care access on the incidence and prevalence of in DHF is warranted among medically underserved populations who are more likely to have poorly controlled hypertension, diabetes, and higher rates of obesity.[41]

Pathophysiology of Diastolic Heart Failure

Although much less is known about DHF than SHF, the pathogenesis in most cases seems to be associated with LV diastolic impairment and is the focus of this review. However, conditions such as right-sided HF, lung disease, and pericardial and valvular heart diseases are also acknowledged to contribute to the pathologic changes associated with DHF.[17-20]

Diastolic dysfunction is associated with delayed LV relaxation, reduced distensibility (increased diastolic pressure with no change in volume), and increased chamber stiffness (increased slope of the diastolic pressure/volume relationship).[17] In contrast with those with SHF, patients with DHF show an inability to increase stroke volume via the Frank-Starling mechanism, even with severe elevation in LV filling pressures. A relatively small increase in blood volume can result in a substantial increase diastolic pressure and lead to pulmonary congestion and edema as illustrated in Fig 1.[17,19,20] Moreover, atrial fibrillation is particularly detrimental in patients with DHF, who depend on the atrial “kick” or contraction to maintain both end-diastolic and stroke volumes.[17-20]

FIGURE 1 IS OMITTED FROM THIS FORMATTED DOCUMENT

Fig 1. Pressure-volume loops contrasting isolated diastolic heart failure (A) with systolic heart failure (B) and combined systolic and diastolic heart failure (C). A normal patient (solid line) is compared with a patient with heart failure before (dashed line) and after (dotted line) treatment. HF indicates heart failure. Reprinted with permission from: Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I. Circulation 2002;105(11):1387-1398.

Cardiac remodeling occurs in both diastolic and systolic HF, but there are structural differences. Patients with DHF develop concentric hypertrophy, which includes a normal or reduced cardiac cavity size, an increased wall thickness, and a high mass/cavity ratio. The end-systolic and diastolic volumes are normal in most patients with DHF, and LVEF is normal or elevated. In contrast, patients with SHF have increased cavity size (eccentric remodeling), decreased or unchanged wall thickness, normal or reduced mass/cavity ratio, elevated systolic and diastolic volumes, and lower LVEF.

LV wall stress, neurohormonal and cytokine activation, and abnormal calcium regulation occur in both systolic and diastolic HF. However, collagen metabolism seems to differ in SHF and DHF and may explain in part the disparate structural changes associated with remodeling. With DHF progression, there is evidence of greater fibrillar collagen, collagen cross-links, and fibrosis. In addition, patients with DHF exhibit a reduction in matrix metalloproteinases and increase in tissue inhibitors of metalloproteinases. These changes are associated with loss of the normal supporting interstitial structure. Other evidence of abnormal collagen metabolism includes an increase in the ratio of titin isoforms N2BA/N2B. In addition, myocyte diameter is reportedly higher among patients with DHF compared with patients with SHF. The processes related to myocyte hypertrophy, cytoskeletal alterations, and fibrosis are not fully understood. However, because reversing or slowing remodeling is an important therapeutic target, changing the underlying collagen metabolism and regulation may be an important therapeutic goal for DHF in the future.[17-20]

Aging

Because DHF primarily occurs in older adults, age-related physiologic and pathologic changes likely contribute to the development of DHF.[42] Hemodynamic changes include a decline in maximal heart rate, cardiac output, and maximal oxygen consumption (peak VO_2). Stroke volume stays relatively unchanged or may decrease, whereas systemic vascular resistance increases, which elevates blood pressure and afterload.[2,5,17,21,42] With aging there is also greater LV stiffness, reduced LV compliance, increased LV wall thickness, reduction in myocardial and vascular responsiveness to beta-adrenergic stimulation, and lower mitochondrial response to higher demand for adenosine triphosphate production.[42]

Hypertension

Evidence suggests hypertension plays a central role in the development of diastolic dysfunction and DHF. Animal evidence supports that diastolic dysfunction occurs early in hypertension and that LV relaxation is responsive to increased afterload. Further, epidemiologic studies consistently indicate hypertension increases the risk for DHF up to threefold compared with those who are normotensive.[7,9] For example, the Framingham study reported hypertension preceded DHF in 91% of cases, and hypertension was present in equal numbers among CHS participants.[43] In studies using Doppler echocardiography, up to 20% of persons experiencing borderline or mild hypertension demonstrated impaired diastolic filling.[44-46] These findings indicate echocardiography screening may be advantageous for those at high risk for hypertension or who have prehypertension to determine diastolic dysfunction at earlier stages and perhaps prevent progression to DHF.

Hypertension increases LV afterload, which results in delayed relaxation time, elevated LV filling pressure, and reduced end-diastolic volume.[16,17,44,47,48] These pathologic changes are associated with abnormal myocyte stretching, sympathetic nervous system activation, and progressive neurohormonal and cytokine release.[49] These changes are associated with myocardial apoptosis and ventricular remodeling, which contributes to increased LV mass and further loss of compliance.[50] The role of genetic predisposition is not well understood but

suggests that there may be substantial heritability for hypertension and increased LV mass associated with DHF and is an important area for future study.

Obesity

Obesity, defined as a body mass index >30 kg/m^2, is a growing epidemic; increasing evidence suggests it may play an important role in the development of diastolic dysfunction.[51] Echocardiography provides the opportunity to evaluate and compare cardiac structure and changes among varying degrees of obesity and normal weight, and between symptomatic and asymptomatic patients.[52] For example, Powell and colleagues[51]examined the relationship among body mass index, LV structure, and systolic and diastolic function in 4281 patients who did not have greater than 50% coronary stenosis via coronary angiography. Echocardiography measurements determined that a higher body mass index was associated with greater LV mass (r = .18; P < .001), LV wall thickness (r = .17; P < .001), and LV end-diastolic diameter (r = .07; P < .001). These findings are consistent with other reports supporting obesity as a contributing factor for ventricular remodeling, impaired LV relaxation, and higher LV filling pressures, which lead to diastolic dysfunction and DHF. Gender differences in obesity may also influence the development of DHF because overweight and obese women experience DHF at higher numbers compared with overweight and obese men.[53]

Diabetes

Several studies have shown that HF is two to five times more likely to occur among diabetic persons than nondiabetic persons.[54] Evidence suggests that diastolic dysfunction may be one of the first signs of diabetic cardiomyopathy. For example, one study showed among 86 patients (43% women) with diabetes that more than 40% had diastolic dysfunction, 26% had impaired relaxation, and 17% had pseudonormalization (defined below) on Doppler echocardiography.[55] These findings are important because the patients were young (mean age 43 years) and normotensive, and had well-controlled diabetes (mean hemoglobin A_{1c}, 6.5 g/dL). These findings are supported by the Strong Heart Study (N = 2411 Native Americans) that reported impaired LV relaxation among diabetic persons. In addition, those with diabetes and hypertension had even greater impairment in LV relaxation when compared with those with diabetes alone.[56] As suggested previously, echocardiography screening may be an important diagnostic strategy for identifying early diastolic impairment before it progresses to DHF.

Poor glycemic control and an elevated hemoglobin A_{1c} may be associated with impaired LV relaxation. Among 49,000 diabetic persons enrolled in a registry, poor glycemic control increased the risk for HF. For every 1% increase in hemoglobin A_{1c}, the incidence of HF risk increased by 8%.[51] In another study, microalbuminemia was identified as a risk factor for the development of diastolic dysfunction. Findings from the Strong Heart Study showed a direct correlation between increasing urinary albumin excreted and LV diastolic dysfunction.[56] An altered myocardial glucose and increased fatty acid metabolism related to diabetes may be associated with changes in myocardial structure. These changes include myocyte hypertrophy, increased collagen, interstitial fibrosis, and intramyocardial microangiopathy, all of which contribute to the development of diastolic dysfunction and DHF.[56] Because diabetes is an

important risk factor for DHF, management of diabetes mellitus should incorporate prevention and treatment of DHF, especially among those with comorbid hypertension.

Multiple comorbidities

Because patients with DHF are often older, the presence and management of multiple comorbidities are often a reality in the clinical setting. A recent study of Medicare beneficiaries showed that patients hospitalized with HF frequently have two to six comorbidities, whereas a substantial number have seven or more coexisting illnesses.[57,58]It is important that health care providers are aware that polypharmacy is common in many elderly patients with DHF and may have potential deleterious consequences. For example, arthritis is a common condition in many older women with DHF, and many are prescribed nonsteroidal anti-inflammatory medications for chronic pain relief. These agents are known to promote fluid retention, elevate blood pressure, interfere with the action of ACEIs, and possibly worsen renal function.[8,58] Poor renal function is increasingly associated with poor clinical outcomes in HF, both systolic and diastolic.

Clinical manifestations

The clinical signs and symptoms of DHF include exertional dyspnea and fatigue, orthopnea, paroxysmal nocturnal dyspnea, lower-extremity edema, and exercise intolerance. In addition, pulmonary congestion, peripheral edema, and abdominal bloating may occur as the result of hepatic congestion. Because many patients with DHF are older, it is important to consider atypical symptoms that may occur, including lethargy, malaise, loss of appetite, confusion, irritability, fatigue, and reduced physical activity level.[2,8,59,60]

Despite having a normal LVEF, patients with DHF often experience considerable exertional intolerance.[16,20,61,62] This is consistent with studies that show little relation between LVEF and level of exertional intolerance. Patients with SHF and low LVEF may have equal or better exercise tolerance than patients with DHF who have a high or normal LVEF.[61-63]Several factors explain the exertional intolerance observed in patients with DHF. First, dyspnea results from reduced lung compliance secondary to increased LV diastolic and pulmonary venous pressure. Second, a lower stroke volume and cardiac output occurs despite a normal LVEF. Third, failure of the Frank Starling mechanism limits preload reserve and prevents cardiac output from increasing proportionately to the increased demands of exercise.[20] Finally, because many patients with DHF are older and often sedentary, physical deconditioning is common, which hastens the peripheral musculoskeletal alterations and leads to greater symptom severity and functional status decline.[63]

Clinical Evaluation

Initially, clinical evaluation of DHF includes a medical history, physical examination, chest radiograph, serum BNP, and electrocardiogram. Symptom similarity with other medical conditions, such as asthma and chronic obstructive pulmonary disease, has increased serum BNP use in clinical settings. A detailed review of cardiac symptoms including ischemic heart disease, such as chest pain, history of angina, myocardial infarction, arrhythmias, especially tachyarrhythmias, or valvular disease, should be evaluated. Pulmonary symptoms, such as

dyspnea on exertion, paroxysmal nocturnal dyspnea, and orthopnea, which often occur in pulmonary or valvular disease, may mimic or cloud the ability to diagnose DHF. Less common conditions contributing to DHF that should be incorporated routinely in the history are thyroid diseases and anemia.[2,8,17,20]

A number of physical signs accompany DHF and include elevated jugular venous pressure, hepatojugular reflex, and an S_4 or S_3 gallop. However, an S_4 (atrial gallop) occurs with greater frequency in patients with DHF because it reflects reduced compliance of the LV or left ventricular hypertrophy (LVH). Chest radiograph remains an important preliminary diagnostic test and may reveal the presence of pulmonary congestion or pleural effusion. A baseline electrocardiogram may suggest findings consistent with LVH. BNP levels correlate well with LV end-diastolic pressure, pulmonary artery wedge pressures, LVH, and systolic/diastolic dysfunction, but they do not differentiate the type of HF. Higher BNP is closely correlated with NYHA class and mortality, with higher levels associated with poorer clinical outcomes.[8,59,60]

Diagnostic measures

A precise diagnosis of diastolic dysfunction is often difficult and requires invasive techniques to determine LV volume, relaxation, and compliance properties. An abnormal upward shift of the end-diastolic pressure-volume curve obtained during radionuclide ventriculography is characteristic of diastolic impairment. This includes increased LV end-diastolic pressure with normal LV volume and systolic function. Concurrent pressure, volume, and geometry measurements can be taken throughout the cardiac cycle during cardiac catheterization procedures. Deceleration (time from peak E-wave velocity to zero) and isovolumic relaxation time (time from systolic ventricular outflow to mitral valve opening) may be normal or shorter. The isovolumic relaxation time, percentage of diastolic time to LV filling, LV compliance, and LV wall strain during diastole are then used to quantify diastolic function. The position of the pressure-volume curve and the slope of the pressure-volume relationship must be known to comprehensively evaluate diastolic function.[64,65]However, given the numerous factors that may alter diastolic function, it is unlikely that any one index will be developed to adequately reflect diastolic function.

In most clinical settings, diastolic function is estimated using Doppler echocardiography. With this noninvasive procedure, an objective measure of flow velocities from the left atrium to the LV across the mitral valve indirectly estimates LV filling pressure and diastolic function. Doppler echocardiography evaluation of LV filling correlates well with cardiac catheterization findings of LV volume during diastole.[65]

Doppler echocardiography includes two biphasic components: the E wave, which reflects early diastolic filling, and the A wave in late diastole, which reflects atrial contraction. These findings are most often expressed as the E/A ratio and are normally greater than 1, indicating both short isovolumic relaxation and deceleration time.[64,65] Echocardiographic evaluation is advantageous clinically because it can rapidly rule out diagnoses such as acute mitral or aortic regurgitation and constrictive pericarditis, which are also associated with signs and symptoms of HF and a normal ejection fraction. However, patient characteristics (eg, age, gender, and heart rate) and physiologic variables (eg, preload, LV relaxation, left atrial pressure, and LV compliance) are

important obstacles that make interpretation of Doppler echocardiography findings more difficult.

Three abnormal diastolic filling patterns that describe the type and severity of diastolic dysfunction have been reported in a number of studies. Delayed relaxation occurs with normal aging, as well as LV ischemia and hypertrophy. In the delayed relaxation pattern, relaxation of the LV progressively slows with an accompanying reduction in the early diastolic pressure gradient. An increased compensatory atrial response to LV filling occurs, and as a result the E/A ratio reverses to less than 1. Patients in this group are often hypertensive, have LVH, and may develop DHF over time.

Pseudonormalization is the second pattern of abnormal LV filling; this refers to the "pseudonormal" E/A ratio greater than 1. An increased left atrial pressure to compensate for the slowed relaxation time is characteristic of this pattern. An increased left atrial pressure to compensate for the slowed relaxation time is characteristic of this pattern. In some patients, use of the Valsalva maneuver may result in an inversion of the E/A ratio and facilitate better recognition of this abnormal pattern. Patients with this type of pattern typically have structural changes and established cardiac disease.[64,65]

Restrictive filling is the third abnormal LV filling pattern. During diastole, ventricular pressures rapidly increase and LV filling is negligible, resulting in an increased E/A ratio, often greater than 2, accompanied by a short deceleration time and isovolumic relaxation time. A restrictive pattern that is not reversed by HF therapies denotes a poor prognosis. Patients' condition can deteriorate rapidly or improve if optimal pharmacologic strategies are introduced.[64]

Treatment Strategies

Although there is substantial evidence to guide therapy for patients with SHF, few trials have been conducted with patients with DHF; therefore, little is known about optimal treatment strategies for this population. The management of DHF has two major objectives: to reverse the consequences of diastolic dysfunction (eg, venous congestion and exercise intolerance) and to eliminate or reduce factors (eg, hypertension) responsible for the diastolic dysfunction.[5,8,14,66-68] Other important goals of therapy include reducing the number of hospitalizations, increasing exercise tolerance, and improving overall quality of life (QOL).[8]

The Heart Failure Society of America[69] has published comprehensive guidelines for the treatment of HF based on Level A (randomized controlled trials), Level B (cohort case-control studies), and Level C (expert opinion) data. Recommendations for DHF are primarily Level C, reflecting the lack of clinical trial data for this population. The only Level A data reported are from the CHARM-Preserved trial,[31] which included 3023 patients in NYHA class II to IV with an LVEF greater than 40% who received either candesartan (target dose 32 mg once daily) or a matching placebo and were followed for a median of 37 months. Although cardiovascular death did not differ in the treatment groups, fewer patients in the candesartan group were hospitalized for HF (P = .017). On the basis of these findings, treatment for DHF is recommended primarily for those who are symptomatic (NYHA class II–IV) because there is no evidence to indicate that treatment of asymptomatic patients with DHF is beneficial, other than controlling for

hypertension. Because hypertension is the most common modifiable risk factor for the development of LVH other than age, aggressively treating blood pressure may be an important preventative measure for future development of DHF. Systolic blood pressure should be less than 140 mm Hg in general and less than 130 mm Hg in persons with diabetes.[44]

Symptom Management

Initially, patients with DHF often have symptoms related to pulmonary congestion. Pulmonary congestion can be decreased by reducing LV volume, maintaining normal sinus rhythm (arteriovenous synchrony), and prolonging diastole (thereby decreasing heart rate and increasing coronary artery filling time). One of the most common interventions to reduce LV volume is reducing intravascular volume, either by diuretics or nonpharmacologic approaches such as fluid or sodium restriction. Other interventions to reduce LV volume include decreasing central blood volume (by nitrate use) or blocking neurohormonal activation, more specifically blocking activation of the renin-angiotensin-aldosterone system (RAAS) system. Treatments aimed at blocking activation of the RAAS include the use of RAAS antagonists, such as ACEIs, ARBs, and aldosterone antagonists.[8,14,66-70]

Pharmacologic Treatment of Diastolic Heart Failure

Neurohormonal activation contributes to reduced cardiac output and exertional intolerance in patients with DHF.[71] Specific therapeutic targets include reducing blood pressure; controlling hypertension, ischemia, and tachycardia; and maintaining a sinus rhythm. Beta-adrenergic receptor blockers decrease blood pressure and reduce ventricular remodeling by lowering the harmful neurohormonal and cytokine cascade. Reducing heart rate is also essential using beta-blockade to improve diastolic filling time and volume, thereby increasing cardiac output.[8,14,66,72]

Diuretics in DHF are used to reduce congestion and circulation volume. Diuretic dosages should be used judiciously in DHF to avoid hypotension, fatigue, and renal impairment. Hypotension is especially important with DHF because small changes in diastolic volume may cause large changes in pressure and cardiac output, especially in individuals with a steep diastolic pressure-volume curve. Long-acting nitrates may also be used to decrease circulation volume and thus reduce pulmonary congestion through LV volume reduction.[14,71,72]

ACEIs or ARBs that inhibit activation of the RAAS have also been used in the treatment of DHF. Clinical trials investigating the use of ACEIs or ARBs for treatment of DHF have been limited; however, the major predictors of DHF, namely, advanced age, hypertension, LVH, diabetes, and coronary heart disease, have shown improvement with ACEI or ARB use.[72,73] Warner et al[74] found that the use of Losartan improved exercise tolerance and QOL in 20 patients with DHF. These findings were supported by Little and colleagues,[75]who demonstrated that losartan and hydrochlorothiazide blunted hypertensive response to exercise in 40 patients with DHF, but only losartan also improved exercise tolerance and QOL. In addition, in the CHARM-Added substudy, the addition of candesartan for patients already taking an ACEI (N = 1276) significantly reduced the mortality and number of hospitalizations in patients with SHF, although this has not been comprehensively evaluated in patients with DHF.[33] In contrast, other studies have shown no clear benefit for ACEIs in patients with DHF.[14,80] Nevertheless, current

evidence suggests that ACEIs are preferable to ARBs based on clinical trial data showing reduced mortality, lower hospitalization rates, fewer side effects, and lower costs.[8,14,66,67] Aldosterone receptor antagonists have also shown positive results in patients with SHF, and they are recommended early for patients with SHF after an acute myocardial infarction in the absence of hyperkalemia or renal dysfunction.[76] Further studies, however, are needed in patients with DHF to determine which pharmacologic regimen offers the most benefit.

Positive inotropic agents, such as digoxin, should generally not be used on a long-term basis for treatment of patients with DHF. There seems to be little benefit when there is preserved systolic function, and these agents may worsen the pathophysiologic mechanisms that cause DHF. Caution should be used even in the short-term use of positive inotropes for patients with DHF. An ancillary study of 988 patients with a preserved LVEF in the Digitalis Investigation Group[77,78] found no significant differences from placebo in mortality rates or hospitalization. Specifically, the use of digoxin was associated with a trend toward a reduction in hospitalizations resulting from worsening HF (hazard ratio, .79; 95% confidence interval, .59–1.04; $P = .094$) but also a trend toward an increase in hospitalizations for unstable angina (hazard ratio, 1.37; 95% confidence interval, .99–1.91; $P = .061$). The potential beneficial effects of digoxin in DHF may be related to its favorable effects on neurohormonal activation, although further investigation is warranted.[77]

Nonpharmacologic Management

DHF and aging both lead to a reduced exercise capacity, in part because of the loss of muscle mass (sarcopenia) and alterations in skeletal muscle blood flow and metabolism. Exercise training can in part reverse the peripheral alteration, improve functional capacity, and improve the symptoms associated with DHF and is now recommended by the American Heart Association/American College of Cardiology guidelines[73,79] and Heart Failure Society of America[69] in stable patients with NYHA class I to III. However, patients with DHF are at a disadvantage because there is currently no Medicare reimbursement for cardiac rehabilitation programs for patients with a nonischemic HF cause. In addition, because patients with DHF are typically older and female, transportation, cost constraints, and care-taking responsibilities often interfere with participation in site-based cardiac rehabilitation programs, making a home-based approach a more practical alternative.[79-90]Several small trials have shown that home-based, low-intensity (40%) walking is associated with low risk and has been shown to improve physical function and QOL in some patients with DHF.[67,81] The ongoing Heart Failure—A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION) trial is expected to provide greater insight into the effects of exercise in patients with SHF; whether these data can be extrapolated to patients with DHF who may also benefit from different modes of exercise therapy is an area for further discussion.[79]

To encourage patients to exercise at home, they should be provided with a basic exercise prescription (frequency and duration of exercise) and know how to self-monitor symptoms.[82] Exercise intensity can be prescribed using Borg's rate of perceived exertion scale (Table II,)[82] which asks patients to rate their perceived exertion or how hard they feel they are exerting themselves physically on a scale from 6 to 20. Initially, patients are instructed to keep their exertion level at 11 or 12 initially, which corresponds to light exertion. Patients should be

instructed to progress slowly and to closely monitor their heart rate and dyspnea level. A good rule of thumb is to instruct the patient to exercise at a level that enables them to walk and talk simultaneously.

Table II. Borg's rate of perceived exertion scale

Exertion	**RPE**
No exertion at all	6
Extremely light	7
	8
Very light	9
	10
Light	11
	12
Somewhat hard	13
	14
Hard (heavy)	15
	16
Very hard	17
	18
Extremely hard	19
Maximal exertion	20

RPE, Rate of perceived exertion.
With permission from: Borg G. Borg's perceived exertion and pain scales. Human Kinetics; 1998.

Heart rate monitors and simple exercise logs can facilitate exercise self-efficacy[83] by enabling the patient to track their weekly progress. Improved exercise self-efficacy has been shown to positively influence exercise adherence and maintenance in patients with HF and women with DHF. Other essential equipment for a home-based exercise program includes blood pressure monitors and weight scales. Before beginning an exercise program, patients should be instructed to weigh daily because rapid weight gain may occur in some patients and require medication adjustments. Patients should also be told to monitor their heart rate carefully for a rapid increase, blood pressure elevation, and pulmonary congestion, which may exacerbate their symptoms and lead to greater diastolic dysfunction.[16,20]

Treatment of the underlying factors contributing to DHF, such as long-standing hypertension, remains the key to preventing disease progression. Trends in blood pressure over time, how self-monitoring of blood pressure is performed by the patient, and the response to blood pressure management are clinically important information that should be tracked in an organized fashion by clinicians. Whether adherence to hypertensive medication regimen is problematic because of socioeconomic reasons, cognitive issues, or other factors should be evaluated during routine clinic or office visits.[8]

The patient and family members should be educated and understand the rationale for HF self-management care, including self-monitoring of daily blood pressure and weight, dietary sodium restrictions, physical activity level, and medication adherence. Patients should have quick access to primary health care providers in the event of increasing blood pressure or weight gains. Patients provided with blood pressure, weight, and symptom telemonitoring[84,85] to document and track their daily responses and self-management decisions have been shown to reduce the number of hospital readmissions and costs associated with HF treatment.

Nonadherence to dietary sodium restrictions results in unnecessary hospitalizations and requires the nurse to reinforce sodium dietary restrictions during clinic visits or telephone follow-up. For example, determining whether patients or family members can read labels for sodium content or interpret various labels for portion size should be an essential component of self-management education.[86] Because patients with DHF are typically older, female, and widowed, and live alone, they may lack adequate social support or socioeconomic resources to purchase medications consistently, shop for appropriate low-sodium food, or participate in physical or social activities, all of which may place them at higher risk for poor clinical outcomes. During routine visits, evaluation of subtle changes in self-care abilities, such as loss of transportation, may indicate a need for additional resources to avoid illness exacerbations and hospital readmissions.[87,88]

Patients with DHF may also be at higher risk for depression because of age-related transitions, such as loss of spouse, relocation or change in living environment, and limitations in the ability to conduct physical activities of daily living.[81,89-91] The strong evidence supporting the relationship between lack of social support and depressive symptoms with negative cardiac outcomes and hospital readmission and death indicates a need for ongoing psychosocial evaluation.[91-93] Simple diagnostic tests that may be used in the clinical setting include the Brief Symptom Inventory[94] or simply asking the patient about his or her mood.

Multidisciplinary Management

The complex syndrome of DHF is often complicated by multiple comorbidities, advancing age, lack of resources, sensory deficits, mobility limitations, depression, nutritional concerns, social isolation, and end-of-life decisions. These factors contribute to poor outcomes, nonadherence to medical regimens, increased hospitalizations, and institutionalization. The complexity of issues surrounding many patients with DHF requires a multidisciplinary approach to ensure these issues are addressed to improve clinical outcomes. Although the findings are mixed, several recent studies have documented the effectiveness of HF disease-management programs in reducing the number of hospitalizations and medical costs, and improving QOL in older patients, who more commonly have DHF.[95,96]

Conclusions

Although there are few clinical trials to provide strong support for treatment options in DHF, the number of studies is increasing and evidence has steadily grown during the past decade, providing enthusiasm that future therapies will emerge. The most effective management is the prevention of DHF, which includes strategies aimed at aggressively treating the established risk factors, such as hypertension, diabetes, and obesity. In the meantime, nurses have an important

role to play in educating patients about a low-sodium diet, lifestyle modifications, and a medication regimen to reduce symptom severity, exacerbations, and hospitalizations. Moreover, the role of palliative care in reducing symptom severity and enhancing QOL in patients who are older and have advanced DHF is an area that has had little investigation. Finally, to address the increasing burden of DHF, research must be refocused to include older adults and especially women, whose underlying disease pathology is more often diastolic dysfunction.

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