Management of Diastolic Heart Failure

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A number of large randomized, placebo-controlled mortality trials provided evidence-based data to guide the treatment of patients with systolic heart failure, but, with one exception, similar trials in patients with diastolic heart failure (DHF) either are not yet completed or have not been conducted at all. However, randomized outcomes trials conducted in patients with hypertension with and without left ventricular hypertrophy and in patients with vascular diseases at high risk for cardiovascular events provide a strong rationale for long-term angiotensin-converting enzyme inhibition or angiotensin receptor blockade in patients with DHF. The treatment of patients with acutely decompensated DHF remains purely empirical. Thus, a pragmatic approach to the treatment of acutely decompensated DHF that includes the use of B-type natriuretic peptide is presented.
[Rev Cardiovasc Med. *2004;5(suppl 4):S37–S44*]

Key words: Systolic heart failure • Diastolic heart failure • Renin–angiotensin–aldosterone system • B-type natriuretic peptide • Nesiritide

In the absence of a convenient noninvasive technique to detect and quantify the severity of left ventricular (LV) diastolic dysfunction, the diagnosis of diastolic heart failure (DHF) is inferred when patients with objective evidence of heart failure have normal LV systolic function. The treatment of DHF can be viewed as empirical, because counterparts to the large placebo-controlled mortality trials that helped shape the treatment of systolic heart failure (SHF)

have not been conducted in patients with DHF, or their results are not yet available.[1] However, despite the lack of randomized, placebo-controlled trials directed specifically at DHF, the treatment of DHF can to a great extent be extrapolated from the evidence-based data acquired in large randomized trials that dealt with the treatment of comorbid conditions associated with or leading to DHF. In particular, therapy for DHF can be guided largely by the results of trials conducted in patients with hypertension, especially in those with LV hypertrophy (LVH) and in diabetic patients at high risk for vascular events.[2–4] Following a summary of the issues related to the diagnosis of DHF, this article presents a rational approach to the treatment of DHF by emphasizing the important role of comorbid conditions in the pathogenesis of the disease. Thereafter we discuss the rationale for reducing the activity of the renin–angiotensin–aldosterone system (RAAS) in patients with DHF and review a pragmatic approach to the treatment of acutely decompensated DHF.

The large placebo-controlled mortality trials that helped shape the treatment of SHF have not been conducted in patients with DHF, or their results are not yet available.

Diagnosis of Diastolic Heart Failure

The diagnosis of DHF is straightforward when patients are hospitalized for severe dyspnea and within 72 hours of presentation are found to have pulmonary vascular congestion on chest x-rays and a normal LV ejection fraction with increased LV mass on two-dimensional Doppler echocardiography. In such patients, elevated plasma levels of B-type natriuretic peptide (BNP) confirm the clinical diagnosis. Measurement of plasma BNP levels is most helpful in patients with known DHF and chronic obstructive pulmonary disease (COPD) who present with severe dyspnea. Marked elevation of plasma BNP levels in these patients reflects a state of decompensated DHF and the need for intravenous diuretic and vasoactive therapy. The left ventricle produces and releases BNP to a much greater extent than the right ventricle in response to an increase in filling pressure.[5] Thus, plasma BNP levels are substantially higher in patients hospitalized for decompensation of DHF than in patients hospitalized with right ventricular failure due to exacerbation of COPD. Plasma BNP levels averaged 647 pg/mL in the 7829 hospitalized patients with DHF enrolled in the Acute Decompensated Heart Failure National Registry (ADHERE) (Table 1),[6] whereas values below 200 pg/mL are typically reported in patients with right ventricular failure due to pulmonary artery hypertension.[7]

The diagnosis of DHF is less manifest in outpatient settings, where its presence is likely to be overlooked without overt evidence of pulmonary congestion and systemic evidence of fluid retention. In such a context, a history of progressive decrease in functional capacity in the absence of cardiac valvulopathy, COPD, anemia, and neuromuscular disease should orient the physician

Table 1
Characteristics of Patients Admitted With Acutely Decompensated Heart Failure in ADHERE

Characteristic	Heart Failure: Diastolic (n = 7829)	Heart Failure: Systolic (n = 8245)	*P*
Age (mean, y)	73.9	69.9	<.001
Female (%)	63	40	<.001
Medical history (%)			
Coronary disease	52	61	<.001
Myocardial infarction	47	61	<.001
Diabetes mellitus	45	41	<.001
Atrial fibrillation	21	17	<.001
LVEF by echocardiography (%)	48	27	<.001
Chronic medications (%)			
ACE inhibitors	38	49	<.001
Digoxin	22	36	<.001
Diuretics	65	65	
β-Blockers	46	46	
Clinical presentation (%)			
Rales	71	69	.002
Peripheral edema	70	64	<.001
Neurohormones			
BNP (mean, pg/mL)	647	918	<.001

ADHERE, the Acute Decompensated Heart Failure National Registry; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; BNP, B-type natriuretic peptide. Adapted from Yancy et al.[6]

toward a diagnosis of congestive heart failure. The remarkably uniform clinical profile of patients with DHF should alert the physician to a diagnosis of DHF in outpatient settings. Three quarters of patients treated for DHF in urban medical centers are elderly women (Table 2).[8,9] Nearly 80% of these women have a history of hypertension, and 50% are diabetic and overweight. The constellation of female gender, advanced age, hypertension, diabetes, and obesity should draw attention to coexistent abnormalities of LV diastolic function and thereby prompt the physician to request a two-dimensional Doppler echocardiogram.

The clinical profile of patients with DHF seems to be different in rural settings, where it is equally prevalent in men and women and where comorbid conditions, such as hypertension, diabetes, and obesity, are less prevalent than in patients with DHF treated in urban medical centers.[10] Theoretically, determination of plasma BNP levels should be most useful in helping with the diagnosis of DHF in outpatient settings, when symptoms and signs of fluid retention are less severe than in hospitalized patients.[11] However, at our institution, more than 50% of ambulatory patients with DHF and limited functional tolerance as evidenced by reduced peak aerobic capacity have plasma BNP levels within the normal range. This most probably reflects the modest elevation in LV filling pressure in ambulatory patients receiving diuretic therapy.

Although two-dimensional Doppler echocardiography does not currently provide a reliable index of LV diastolic function, echocardiography is the cornerstone for establishing the diagnosis of DHF.[12] First, echocardiography confirms that LV systolic function is normal by documenting an LV ejection fraction above 50%. Second, it excludes primary valvular, pericardial, or restrictive heart disease. Third, it strengthens the clinical diagnosis of DHF by demonstrating an increased LV mass in up to 85% of patients and moderate pulmonary artery hypertension in more than 50% of patients.[8] Imaging of mitral inflow and pulmonary venous flow is helpful for detecting the presence of LV diastolic dysfunction but does not permit accurate quantification of this dysfunction when cardiac loading conditions and especially left atrial pressure are unknown. Myocardial tissue Doppler data might provide a more accurate estimate of the severity of LV diastolic function because these measurements are load independent.[13]

Whether management of patients with DHF requires precise appraisal of the severity of LV diastolic dysfunction remains to be demonstrated. In patients with SHF, symptoms do not correlate with LV ejection fraction, and pharmacologic interventions are mostly administered to alleviate symptoms. Similarly in patients with DHF, symptoms correlate poorly with the severity of diastolic dysfunction, and therapeutic interventions are adjusted to alleviate symptoms.

Table 2
Clinical Characteristics and Comorbid Conditions in Hospitalized Heart Failure Patients From the New York Heart Failure Registry

	Total (N = 619) (100%)	Women (n = 449) (72.5%)	Men (n = 170) (27.5%)
Age (y)*	71.7 ± 14.1	72.8 ± 14.1	68.6 ± 13.8
History of hypertension	78.2	78.8	76.3
SBP (mm Hg, on presentation)	159.7 ± 35.5	158.8 ± 34.3	162.2 ± 38.5
DBP (mm Hg, on presentation)	83.9 ± 20.4	82.9 ± 19.7	86.3 ± 22.1
Diabetes mellitus	45.9	44.9	48.5
Coronary artery disease	43.1	42.3	45.1
History of COPD or asthma	24.5	25.1	22.9
Atrial fibrillation	23.4	22.7	25.3
Atrial flutter	2.1	1.3	4.1
Supraventricular tachycardia	0.8	0.5	1.8
Hypothyroidism	9.7	11.3	5.1
Hemoglobin (mg/dL)	11.8 ± 2.2	11.7 ± 2.0	12.2 ± 2.4
Glomerular filtration rate† (mL/min)	50.8 ± 28.5	50.1 ± 22.7	52.7 ± 22.8
Dialysis	4.5	3.6	7.1
Body mass index (n = 509)	30.6 ± 8.8	30.8 ± 8.9	30.2 ± 8.3
Body mass index >30 (n = 509)	46.2	46.9	44.4

Data are presented as percentages or mean ± standard deviation. COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; SBP, systolic blood pressure. Adapted with permission from Klapholz et al.[8]
*Difference between women and men, $P < .001$.
†Excluding patients on dialysis (n = 483).

Conditions Comorbid With DHF

The importance of the cause–effect relationship between hypertension and heart failure and especially DHF cannot be overstated.[14] Approximately 90% of people who develop heart failure are hypertensive or have a history of hypertension, according

to the Framingham Heart Study. The risk of developing heart failure is twofold greater in hypertensive men and threefold greater in hypertensive women. Because blood pressure is not controlled in 72% of the 50 million Americans with hypertension, it should not come as a surprise that the prevalence of hypertensive heart disease and especially of LVH leading to heart failure continues to increase.

Cardiac remodeling in hypertension includes hypertrophy of the myocardium and fibrosis of the interstitium. Although years of hypertension can clearly lead to LVH and thereby impair LV relaxation and increase LV stiffness, the substrate might be equally important in determining the risk of developing DHF in patients with or at risk for hypertension. Impairment of LV relaxation might precede the development of hypertension and certainly of LVH and increased LV mass in patients at risk for hypertension.[15] Whether myocardial ischemia resulting from an impaired coronary microcirculation contributes to impaired LV relaxation before the development of hypertension is unknown.

Impairment of LV relaxation might precede the development of hypertension and certainly of LVH and increased LV mass in patients at risk for hypertension.

Diabetes is the second most frequent comorbid condition in patients with DHF. The reported prevalence of diabetes in this population has ranged from a low of 23% in early reports to a high of 50% in current reports.[8,9,16] The prevalence of diabetes was 47% in the 7829 patients with DHF enrolled in the recently reported ADHERE.[6] Because the prevalence of diabetes is steadily increasing in the general population, it is also expected to increase in patients with DHF. Relative to age-matched nondiabetic subjects, the risk of developing heart failure is twofold greater in diabetic men and fivefold greater in diabetic women. This gender difference might in part account for the greater prevalence of DHF in women. Diabetes might increase the risk of developing DHF by multiple pathways. More than half of diabetic patients are hypertensive. Diabetes is an independent stimulus for LVH. Insulin resistance might alter cardiac metabolism and vascular function. Diabetes-induced impairment of endothelial function might further compromise vascular function in hypertensive patients, especially at the level of the microcirculation.

Diabetes-specific microvascular disease is related to a hyperglycemia-induced process of overproduction of superoxide by the mitochondrial electron-transport chain.[17] Activation of the receptor for advanced glycation end-products seems to be the final pathway leading to the cardiovascular complications of diabetes.[18]

Obesity as a comorbid condition of DHF is nearly as prevalent as diabetes. The association of hypertension, diabetes, and obesity in a significant number of patients with DHF suggests that the metabolic syndrome might be the initial disorder in some patients.[19] Alternatively, obesity might be unrelated to DHF but might exacerbate its effects: obesity requires that a large percentage of the cardiac output be distributed to tissues other than those of essential organs, thereby accelerating the progression of heart failure, especially when blood flow to the kidneys is compromised.

Evidence-Based Approach to the Treatment of Chronic DHF

The findings of therapeutic trials conducted in hypertensive patients with or without LVH and in patients with comorbid conditions similar to those accompanying DHF provide a strong rationale for reducing RAAS activity with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) in patients with DHF. As mentioned above, approximately 80% of patients with DHF have an increased LV mass and a history of hypertension. Overall, the clinical characteristics of patients with DHF are comparable to those of the high-risk vascular disease patients with normal LV ejection fraction who participated in the Heart Outcomes Prevention Evaluation (HOPE) study.[2] The HOPE study demonstrated that the rates of death, myocardial infarction, and stroke were substantially lower in high-risk vascular disease patients receiving ACE inhibition with ramipril than in those receiving placebo.[2] Of even greater relevance to the issue of DHF, the HOPE study unequivocally demonstrated the importance of LVH reduction, independent of blood pressure reduction, for the prevention of heart failure. Patients with new or persistent LVH develop heart failure at a significantly greater rate than patients in whom LVH regresses or is prevented altogether: 15.4% versus 9.3% ($P < .0001$).[20] These findings strongly underline that reversal of LVH, or at least prevention of LVH progression, is an important therapeutic goal for patients with DHF.

Among the pharmacologic inter-

ventions routinely used to lower blood pressure, ACE inhibition is clearly the most potent for reversing LVH.[21] Reducing the activity of RAAS with ARB rather than ACE inhibition has led to similar results. The Losartan Intervention for Endpoint Reduction (LIFE) study demonstrated that ARB with losartan is definitively more potent that β-adrenergic blockade (BAB) with atenolol in reversing LVH in hypertensive patients with LVH at baseline.[3] The superiority of ARB over BAB in reversing LVH was also demonstrated in the 1195 diabetic patients enrolled in the LIFE study.[22] As monitored by the Cornell voltage-duration product criteria, LVH regressed by 8% in patients randomized to ARB with losartan but changed negligibly in patients randomized to BAB with atenolol.[22]

In addition to their cardiac antiremodeling effects, ACE inhibition and ARB also exert a major antiremodeling effect on the coronary and systemic vasculature. Vascular alterations play a large role in the pathogenesis of end-organ damage in patients with hypertension. Small resistance arteries of patients with hypertension have a reduced lumen and external diameter, with increased media thickness and an increased media/lumen ratio.[23] Remodeling of the extracellular matrix mostly involves collagen deposition.[23] In patients with mild essential hypertension, ARB with losartan reduces blood pressure to the same extent as BAB with atenolol.[24] However, ARB with losartan corrects the altered structure (media/lumen ratio) and endothelial dysfunction in resistance arteries, whereas BAB with atenolol does not affect structure nor vascular endothelial function.[24] Chronic ARB with losartan reverses vascular endothelial dysfunction in patients with atherosclerosis by improving nitric oxide bioavailability, which in turn reduces oxidative stress in the arterial wall.[25] Thus, the vascular effects of ARB are multilayered. They include reversal of vascular remodeling and endothelial dysfunction and reduction in oxidative stress. These effects are most likely responsible for the beneficial effects of ARB on functional capacity in patients with DHF.[26] Calcium channel antagonism with verapamil and ARB with candesartan exert similar systemic hemodynamic effects in patients with DHF, but ARB with losartan improves exercise tolerance, whereas verapamil does not.[26] Overall, long-term ACE inhibition produces vascular effects very similar to those of ARB. The improvement in vascular endothelial function was clearly demonstrated with quinapril in the Trial on Reversing Endothelial Dysfunction (TREND).[27] Whereas large placebo-controlled mortality trials have been conducted with ACE inhibitors in patients with SHF, the effects of ACE inhibitors on clinical outcomes have never been evaluated in patients with DHF. Based on the findings of the HOPE and LIFE trials,[2,3] one can safely assume that patients with DHF who have similar clinical profiles to the patients enrolled in these trials will derive similar benefits from long-term ACE inhibition. It is, however, difficult from an ethical standpoint to justify a placebo-controlled trial of ACE inhibitors in patients with DHF, given that as many as 50% of these patients are presently being treated with ACE inhibitors.[8]

The results from a large randomized, placebo-controlled trial of ARB in patients with presumed DHF were recently reported.[28] The Candesartan in Heart Failure: Assessment of Reduction in Morbidity and Mortality (CHARM-Preserved) study did not find a significant reduction in cardiovascular events in patients randomized to candesartan when compared with placebo (relative risk reduction, 11%; $P = .11$). The clinical characteristics of patients with presumed DHF who were enrolled in CHARM-Preserved clearly differed from the clinical characteristics reported in many observational studies of patients with heart failure.[8,9] To what extent such differences explain the unimpressive results of CHARM-Preserved is unclear. A randomized, placebo-controlled trial of long-term ARB with irbesartan, I-PRESERVE (Irbesartan in Heart Failure with Preserved Systolic Function), is currently ongoing in patients with DHF.[29] Providing that the clinical characteristics of patients with DHF who are enrolled in I-PRESERVE match those reported in observational studies, the trial will provide the first evidence-based data to guide therapy of patients with DHF.

Based on the findings of the HOPE and LIFE trials, one can safely assume that patients with DHF will derive similar benefits from long-term ACE inhibition.

Aldosterone receptor blockade with spironolactone and eplerenone has beneficial effects on mortality rate and rate of hospitalization in severely symptomatic patients with SHF and in patients with LV systolic dysfunction or clinical heart failure after a recent myocardial infarction.[30,31] Of particular interest for the treatment of DHF, aldosterone receptor blockade inhibits collagen synthesis, thereby reducing cardiac fibrosis; improves vascular endothe-

lial function; promotes sodium excretion; and lowers systemic vascular resistance.[32] Aldosterone receptor blockade with eplerenone is as effective as ACE inhibition with enalapril in reducing LV mass in patients with hypertension and LVH.[33] Because the effects of eplerenone and enalapril on reducing LV mass are additive, combining aldosterone receptor blockade with ACE inhibition seems a very promising approach to the treatment of DHF. Unfortunately, such a combination is unlikely to be tested in a large randomized outcomes trial, because spironolactone is a generic drug, and the patent on eplerenone will expire in few years.

Because the effects of eplerenone and enalapril on reducing LV mass are additive, combining aldosterone receptor blockade with ACE inhibition seems a very promising approach to the treatment of DHF.

In summary, data acquired in large randomized clinical trials involving patients with comorbid conditions similar to those associated with the syndrome of DHF argue strongly in favor of reducing RAAS activity in patients with DHF. In most instances, DHF is the end result of years of hypertension. An obvious starting point in the treatment of DHF, therefore, is to do a much better job in treating patients with hypertension, especially those with LVH.[34]

Treatment of Acutely Decompensated Heart Failure

In the absence of any randomized, placebo-controlled therapeutic trials specifically involving patients with acutely decompensated DHF, physicians must use a pragmatic approach to the management of these patients. When patients present to an emergency department with acute shortness of breath and are found to have pulmonary vascular congestion on chest x-rays, they receive an intravenous loop diuretic. Failure of a patient to improve after intravenous administration of a loop diuretic should alert the physician to a misdiagnosis and lead to investigation of the cardiac mechanism behind the pulmonary congestion. It is impossible to differentiate clinically, with any degree of accuracy, acute SHF from acute DHF. Blood pressure tends to be higher in patients with DHF than in patients with SHF, and the converse is true for plasma BNP levels: 147/83 mm Hg versus 136/77 mm Hg ($P = .001$) and 918 pg/mL versus 647 pg/mL ($P < .001$), respectively, as reported in the ADHERE data.[6] However, such differences do not allow differentiation between DHF and SHF as the cause of pulmonary congestion.

When an echocardiogram cannot be immediately obtained and LV function is unknown, the next therapeutic intervention is intravenous administration of nesiritide (human recombinant BNP). The beneficial effects of nesiritide on clinical and hemodynamic parameters have been demonstrated in patients with acutely decompensated heart failure, whether due to systolic or diastolic dysfunction.[35,36] Although the therapeutic efficacy of nesiritide has been established more convincingly in patients with acute SHF than in patients with acute DHF, modulation of the loading conditions of the heart should be even more beneficial for patients with DHF than for those with SHF. Patients with acutely decompensated DHF often present with a marked elevation of systolic blood pressure that tends to reduce forward stroke volume and to increase functional mitral regurgitation. Patients with acutely decompensated DHF also present with a marked elevation of LV filling pressure that tends to decrease the coronary perfusion pressure gradient, thereby exposing patients with LVH to subendocardial ischemia that might impair LV relaxation and in turn might further increase LV filling pressure. Early administration of nesiritide can interrupt this vicious cycle by rapidly reducing LV filling pressure.

In addition to optimizing the loading conditions of the failing heart, nesiritide might provide renal protection and heighten urinary sodium excretion, thereby obviating the need for administration of loop diuretics, which can lead to a poor outcome.[37] Two contraindications are cardiogenic shock with systolic blood pressure below 90 mm Hg, and hypovolemia, especially when related to septic shock.

When an echocardiogram cannot be immediately obtained and LV function is unknown, the next therapeutic intervention is intravenous administration of nesiritide.

Conclusion

Although it has never been proved in a large randomized, placebo-controlled mortality trial, the impressive findings of several randomized outcomes trials involving patients with hypertension and patients with vascular disease at high risk for cardiovascular events provide a strong rationale for long-term ACE inhibition or ARB in patients with

compensated DHF. The management of these patients when they experience an episode of clinical decompensation is presently empirical. When intravenous loop diuretic therapy fails to return patients with DHF to a compensated state, nesiritide, a recombinant human BNP, seems to be the agent of choice, owing to its sustained vascular and renal actions. ■

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Main Points

- The diagnosis of diastolic heart failure (DHF) is straightforward when patients are hospitalized for severe dyspnea and within 72 hours of presentation are found to have pulmonary vascular congestion on chest x-rays and a normal left ventricular (LV) ejection fraction with increased LV mass on two-dimensional Doppler echocardiography.
- In patients with known DHF and chronic obstructive pulmonary disease who present with severe dyspnea, marked elevation of plasma B-type natriuretic peptide (BNP) levels reflects a state of decompensated DHF and the need for intravenous diuretic and vasoactive therapy.
- The importance of the cause–effect relationship between hypertension and heart failure and especially DHF cannot be overstated; according to the Framingham Heart Study, approximately 90% of people who develop heart failure are hypertensive or have a history of hypertension.
- Diabetes is the second most frequent comorbid condition in patients with DHF, with rates as high as 50% in current reports; obesity as a comorbid condition of DHF is nearly as prevalent as diabetes.
- Findings from several randomized outcomes trials involving patients with hypertension and patients with vascular disease who are at high risk for cardiovascular events provide a strong rationale for long-term angiotensin-converting enzyme inhibition or angiotensin II receptor blockade in patients with compensated DHF.
- When intravenous loop diuretic therapy fails to return patients with DHF to a compensated state, nesiritide, a recombinant human BNP, seems to be the agent of choice, owing to its sustained vascular and renal actions.

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