

## Current Concepts in Diastolic Heart Failure

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Heart failure is a highly prevalent condition, particularly among elderly adults and women. In diastolic heart failure—or heart failure with normal ejection fraction—left ventricular systolic function is preserved. Although diastolic heart failure is clinically and radiographically indistinguishable from systolic heart failure, echocardiography can reveal a preserved ejection fraction with abnormal diastolic function. The present article reviews current medical concepts related to diastolic heart failure for medical practitioners, particularly primary care physicians, who play a vital role in the care of patients with heart failure. Treatment options, focusing on calcium channel blockers and angiotensin receptor blockers, are discussed. With early diagnosis and proper management, the prognosis of diastolic heart failure can be more favorable than that of systolic heart failure.

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Increasingly, left ventricular (LV) diastolic dysfunction is being recognized as a pathophysiologic entity which predisposes certain patients to a distinct form of heart failure called *diastolic heart failure* (DHF)—or heart failure with normal ejection fraction (HFNEF). The term *diastolic dysfunction* indicates abnormal diastolic distensibility, filling, or LV relaxation, regardless of whether the ejection fraction is preserved or abnormal or whether the patient is symptomatic or asymptomatic. Thus, diastolic dysfunction refers to abnormal mechanical (diastolic) properties of the left ventricle and is present in virtually all patients with heart failure. The terms DHF and HFNEF are used to describe patients with the signs and symptoms of heart failure, a preserved ejection fraction, and LV diastolic dysfunction.<sup>1</sup>

Diastolic heart failure is most common in elderly patients and women with a history of essential hypertension, ventricular hypertrophy, diabetes, and cardiac ischemia.<sup>2</sup> As a result

of the condition, mortality, morbidity, and healthcare costs are high.<sup>3</sup> Although DHF typically has a lower in-hospital mortality rate than systolic heart failure, hospitalization frequency for both conditions is comparable.<sup>4,5</sup>

For the current article, the authors searched Elsevier's EMBASE and MD Consult databases as well as the US National Library of Medicine's PubMed database through February 2007 for articles that focus on diastolic dysfunction. Key words and phrases searched consisted of "left ventricular diastolic dysfunction," "heart failure," and "heart failure with normal ejection fraction." The authors present a review of several aspects of DHF and provide recommendations and guidelines for the diagnosis, treatment, and prognosis of this condition.

### Epidemiology

Epidemiologic studies have suggested that 30% to 50% of patients with active congestive heart failure (CHF) have adequate LV systolic function.<sup>6-10</sup> Kitzman et al<sup>10</sup> found that 8% of patients older than 65 years have heart failure, 55% of whom have a preserved LV ejection fraction (LVEF). In addition, diastolic dysfunction has been shown to affect elderly women more than any other population subgroup.<sup>6,7,11</sup> Patients who have diastolic dysfunction are twice as likely to have diabetes mellitus.<sup>10</sup> Other commonly associated conditions include hypertension, renal dysfunction, myocardial ischemia, and ventricular hypertrophy.<sup>12</sup>

### Pathophysiology

#### Pressure-Volume Relationships

Studies related to pressure and volume changes during ventricular function provide unique insights into the diastolic, systolic, and overall pumping characteristics of the heart. Although a detailed discussion of such pressure and volume changes is beyond the scope of this article, a brief review of common principles is helpful.

Patients with DHF have a preserved ejection fraction despite increased LV diastolic pressure and pulmonary venous pressure. These patients have both increased passive stiffness and abnormal active relaxation of the left ventricle, which may work independently to cause abnormal diastolic physiology.<sup>13</sup> This effect has been suggested by showing that even after correction for slow relaxation, increased passive stiffness was found to be an important factor in LV diastolic dysfunction and DHF.<sup>13</sup> Under such conditions, the left ventricle typ-

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ically cannot fill to the minimal volume without elevating diastolic pressures, eventually leading to pulmonary congestion, which in turn leads to DHF.<sup>14-16</sup>

Ventricular relaxation, as an energy-dependent process, may be impaired by decreased availability of adenosine triphosphate (ATP) and changes in calcium metabolism.<sup>14,17</sup> Removal of calcium from the cytosol may be delayed by a decrease in the activity of sarco/endoplasmic reticulum calcium adenosine triphosphatase (SERCA) or an increase in the level of activity of phospholamban, which is a SERCA-inhibitory protein.<sup>14,18,19</sup> Pathologic ventricular hypertrophy, secondary to hypertension or aortic stenosis, with impaired relaxation of the ventricular muscle leads to a decrease in SERCA levels. Similar changes are seen in the myocardium of patients with hypertrophic or dilated cardiomyopathy. One animal study<sup>20</sup> showed that the calcium pump rate in the sarcoplasmic reticulum is diminished in the hearts of senescent rats compared with younger rats. Levels of SERCA are also known to decrease with age. Older hearts have degenerative changes in the myocardium and reduced  $\beta$ -adrenergic tone.<sup>21</sup> These changes might explain the disorder's prevalence in elderly patients.

However, despite these studies, some evidence suggests that the estimated end-diastolic pressure-volume relationship in a subgroup of hypertensive patients who have DHF with seemingly small hearts is normal and not consistent with the DHF paradigm as discussed in the preceding paragraphs.<sup>22</sup>

### **Myocardial Ischemia**

One of the most common cardiac diseases associated with abnormal LV diastolic function is myocardial ischemia. The slowing or failure of myocyte relaxation causes a fraction of actin-myosin crossbridges to continue to generate tension throughout diastole—especially in early diastole—creating a state of “partial persistent systole.” Two kinds of ischemia can alter diastolic function: (1) demand ischemia, created by an increase in energy use and oxygen demand that outweighs the necessary myocardial supply, and (2) supply ischemia, caused by a decrease in myocardial blood flow and oxygen demand without a change in energy use.

During demand ischemia, diastolic dysfunction may be related to myocardial ATP depletion with a concomitant increase in adenosine diphosphate, resulting in rigor bond formation.<sup>23</sup> Consequently, LV pressure decay is impaired and the left ventricle is stiffer than normal during diastole. Although ischemia is also associated with persistence of an increased intracellular calcium concentration during diastole, it is not clear if elevated calcium levels contribute directly to diastolic dysfunction.<sup>23</sup>

Supply ischemia results from a marked reduction in coronary flow. The net effect is inadequate coronary perfusion even in the resting state. Acute supply ischemia causes an initial transient downward and rightward shift of the diastolic pressure-volume curve such that end-diastolic volume

increases relative to end-diastolic pressure, creating a “paradoxical” increase in diastolic compliance.<sup>24</sup> By contrast, diastolic compliance substantially falls during demand ischemia.<sup>25,26</sup>

These opposite initial compliance changes with demand and supply ischemia may be explained by differences in pressure and volume within the coronary vasculature, by the mechanical effects of the normal myocardium adjacent to the ischemic region, and by tissue metabolic factors. However, the differences between supply and demand ischemia are transient: after more than 30 minutes of sustained ischemia, both types of ischemia result in decreased diastolic compliance.<sup>25,26</sup>

### **Renin-Angiotensin-Aldosterone System**

Activation of the renin-angiotensin-aldosterone system is a key factor in the eventual development of myocardial fibrosis and wall stiffness. Besides stimulating vasoconstriction and salt and water retention, angiotensin II increases collagen deposition.<sup>27</sup> Types I and III collagen are the major types present in the myocardium in both normal and diseased myocardial tissue. Fibrillar collagens within the myocardium are important substrates for matrix metalloproteinases (MMPs). The actual activity of MMP, a tightly regulated process, depends on the rate of synthesis, activation, and balance between active enzymes and inhibitors. Angiotensin II stimulates collagen synthesis and regulates collagen degradation by attenuating interstitial metalloproteinase 1 (MMP-1) activity and by enhancing production of the tissue inhibitor of MMP-1 in endothelial cells.<sup>28-30</sup> However, excessive deposition of collagen may be responsible for abnormal tissue stiffness and altered cardiac function during hypertrophy—particularly the chronic phase—and heart failure.

When establishing the pathophysiology during the chronic phase of hypertrophy and heart failure, the quality of the collagen is more important than the quantity of collagen. Collagen quality, which is determined by the type I/type III ratio of collagen, can help predict heart muscle stiffness.<sup>31</sup> Based on experiments performed on isolated fibroblasts, angiotensin II can directly activate collagen synthesis, while endothelin-1 increases both collagen synthesis and cardiac fibroblast proliferation and reduces collagenolytic activity.<sup>32,33</sup> Aldosterone, a mineralocorticoid, stimulates collagen deposition and sodium retention.<sup>27</sup> All of these changes in the extracellular matrix, particularly in fibrillar collagen, contribute to ventricular hypertrophy, diastolic stiffness, and eventually DHF.<sup>14</sup>

### **Pulmonary Diseases**

In patients who have lung diseases with respiratory failure—most notably patients with chronic obstructive pulmonary disease (COPD)—pulmonary hypertension and right ventricular dysfunction can develop. Such development has been attributed to increased right ventricular afterload because of pulmonary hypertension.<sup>34,35</sup> However, patients who have

COPD and respiratory failure may also have LV diastolic dysfunction.<sup>36</sup> For example, a right ventricular pressure overload may cause a leftward displacement of the interventricular septum, which in turn may cause LV diastolic dysfunction.<sup>37</sup> However, in a dog model with pulmonary emphysema and hypoxia, LV diastolic dysfunction was present without septum bowing.<sup>38</sup> This finding suggests that intrinsic mechanisms in the LV myocardium participate in LV diastolic dysfunction.<sup>38</sup>

There are many other causes of alveolar hypoxia that are responsible for right ventricular failure and LV diastolic dysfunction, such as obstructive sleep apnea (OSA) with or without obesity hypoventilation. Many obese patients with OSA also have essential hypertension and diabetes, placing them at increased risk for DHF. Currently, the pathophysiologic mechanisms linking OSA with diastolic dysfunction and DHF are not clearly understood. One explanation is that elevations in nocturnal blood pressure and sympathetic nervous system activity in patients who have OSA create ventricular pressure overload.<sup>39,40</sup> It is speculated that, as DHF occurs in patients who have other diseases, such as chronic hypertension and aortic stenosis, increased pressure overload at the cellular level results in decreased levels of SERCA and increased levels of phospholamban.<sup>41</sup> As stated earlier, increased pressure slows the removal of calcium from the cytosol, leading to impaired ventricular relaxation. In an experimental study,<sup>42</sup> ventricular pressure overload impaired myocardial relaxation. Concurrently, pressure overload causes activation of multiple cellular signals that create myocardial tissue hypertrophy and interstitial fibrosis, both of which increase passive stiffness.<sup>43</sup> In addition, impaired coronary flow reserve, which causes silent ischemia, worsens ventricular active relaxation when LV diastolic pressure begins to rise.

Another possible mechanism to explain the presence of diastolic dysfunction in patients who have pulmonary diseases relates to futile inspiratory efforts. Such efforts result in elevated negative intrathoracic pressure, leading to an increase in LV transmural pressure and enhanced ventricular afterload without an increase in systemic arterial pressure.<sup>44</sup> All of the aforementioned effects of enhanced negative intrathoracic pressure have been demonstrated to affect LV filling.<sup>44,45</sup> Abnormalities in diastolic function, substantially related to repetitive OSA events during sleep, are very common in patients with OSA. These alterations could be reversed, at least in part, with continuous positive airway pressure therapy.<sup>46</sup>

Patients with a variety of diseases and DHF have different pressure-volume mechanisms involved in their pathology. At one end of the spectrum are patients who have heart failure on the basis of diastolic dysfunction, and at the other end are patients with arterial hypertension. In the latter group, hearts appear to be very mildly dilated, with little or no detectable abnormality of systolic or diastolic pressure-volume relationships, and subtle changes in total body volume may induce DHF.<sup>47</sup> Another scenario involves ischemic heart dis-

ease with or without minor myocardial infarction where mild systolic dysfunction is not evident by measurement of ejection fraction but is sufficient to induce a neurohormonal response that can lead to salt and water retention.<sup>22,47</sup>

### Diagnosis

The gold standard for evaluating LV function is the direct measurement of LV pressure by cardiac catheterization. However, such an invasive procedure is not feasible in all patients in whom diastolic dysfunction is suspected. As a result of poor consensus concerning the specific criteria and lack of a single noninvasive test to confirm this diagnosis, identification of LV diastolic dysfunction and DHF remains a challenge.

In 1998, the European Society of Cardiology proposed the presence of all of the following criteria<sup>48</sup> to make the diagnosis of DHF:

- signs and symptoms of CHF
- normal or mildly abnormal LV systolic function (LVEF  $\geq 45\%$ )
- evidence of abnormal LV relaxation, filling, diastolic distensibility, or diastolic stiffness

Vasan and Levy<sup>49</sup> modified these criteria by categorizing patients in three diagnostic groups: definite, probable, and possible.<sup>49</sup> Patients with definite DHF have the signs and symptoms of CHF and documented abnormal LV relaxation during catheterization. In patients without documented abnormal LV relaxation during catheterization with the signs and symptoms of CHF, DHF was considered probable.<sup>23</sup> Patients without documented abnormal LV relaxation during cardiac catheterization were classified as possible DHF. The study<sup>23</sup> further suggested that the diagnosis of possible CHF might be upgraded to probable if there is evidence of severe hypertension during the acute event. Although an LVEF greater than 50% within 72 hours of the heart failure event was required to meet any of these grouping criteria, this measurement has been challenged as an indicator of DHF. In some studies,<sup>15,50</sup> echocardiographic findings in this timeframe are unchanged when compared with posttreatment findings in patients who present with severe hypertension and acute pulmonary edema.

Echocardiography continues to be used as an important tool for the diagnosis of LV diastolic dysfunction.<sup>51</sup> With the onset of LV filling, the early atrioventricular pressure gradient causes the blood to flow across the mitral valve, resulting in an early filling wave (E wave). As the blood enters the left ventricle, the LV pressure increases and the left atrial (LA) pressure decreases until the pressure gradient across the mitral valve disappears, causing a deceleration of the early doppler filling wave. After a period of diastolic left atrium contractions, the flow across the mitral valve (A wave) accelerates. In healthy young adults, the E/A wave ratio of the mitral inflow pattern is usu-

ally greater than 1. As patients age, this ratio reverses and the relaxation time increases. If the LV end diastolic pressure continues to rise, the LA to LV pressures equalize, therefore shortening the deceleration time. Further progression of diastolic dysfunction results in a restrictive filling pattern with a very short deceleration time. In addition, shorter deceleration of the E wave is associated with increased LV stiffness.<sup>52</sup>

While standard pulsed-wave Doppler echocardiography provides the temporal distribution of blood flow velocities in a specific location, color M-mode Doppler echocardiography reveals the spatiotemporal distribution of these velocities across a vertical line. Thus, the information displayed in a color M-mode recording of the LV inflow is comparable with multiple simultaneous pulse Doppler tracings obtained at different levels from the mitral orifice to the LV apex. A first wave propagates from the LA to the LV apex, corresponding to early filling, and a second wave follows atrial contraction. The magnitude of these velocities is highest above the mitral leaflet tips and decreases as flow approaches the apex. In health ventricles, the spatial position of the maximal velocity is closer to the ventricular apex for the E wave than it is for the A wave, suggesting that intraventricular pressure gradients during early filling produce a suction force that accelerates flow beyond the mitral orifice. The velocity at which flow propagates within the ventricle is given by the slope of the wavefront, which is used to assess LV diastolic function.

Tissue Doppler echocardiography provides additional information that helps to accurately quantify LV diastolic function. Tissue Doppler echocardiography may be used to quantify myocardial velocities in multiple segments of the myocardium from different echocardiographic acoustic windows. If we examine a typical spectral display, we can observe a velocity signal directed toward the LV centroid during systole and two distinct signals directed away from the centroid during early and late diastole. Both of these parameters are important in establishing the diagnosis of LV dysfunction.

The general clinical and echocardiographic evaluation of diastolic function recognizes four distinct stages from normal to advanced disease, incorporating color M-mode and tissue Doppler parameters to the criteria accepted by the Canadian Consensus on Diastolic Dysfunction (*Figure 1*).<sup>53</sup> These patterns are not unique to a specific disease but represent a spectrum, which may be influenced by aging and changing hemodynamic variables.<sup>54</sup>

A normal filling pattern (ie, no diastolic dysfunction) is seen in patients with normal LV relaxation rate, compliance, and filling pressures, with a minimal atrial contribution to LV filling. A delayed relaxation pattern, stage I of diastolic dysfunction, is seen in patients with a reduced LV relaxation rate but relatively normal compliance and filling pressures. In these patients, atrial contribution to LV filling is increased, frequently greater than 30% of the stroke volume.

The pseudonormal pattern, stage II of diastolic dysfunction,

is often the most difficult to identify. In affected patients, filling indices resemble those found in healthy subjects. Left ventricular relaxation rate and compliance are reduced, but filling pressure increases as a compensatory mechanism to maintain cardiac output. Stage III of diastolic dysfunction is the restrictive filling pattern. This stage is seen in the presence of profound abnormalities of LV compliance and a markedly increased filling pressure. Left ventricular relaxation is reduced, perhaps with the only exception being in patients with isolated constrictive pericarditis. Echocardiographic features of advanced structural heart disease are typically evident.

### Treatment

In contrast to the treatment of patients with heart failure caused by systolic dysfunction, few trials are available to guide the management of heart failure that is the result of diastolic dysfunction. Verapamil hydrochloride (a calcium channel blocker) and candesartan cilexetil (an angiotensin receptor blocker) are among the few drugs that have been shown by objective criteria to improve diastolic dysfunction, ameliorate symptoms, and improve exercise tolerance.<sup>55,56</sup>

Calcium channel blockers are believed to help control heart rate, lower blood pressure, and treat ischemia.<sup>57,58</sup> By causing regression of LV hypertrophy, calcium channel blockers may also improve the diastolic properties of the left ventricle.<sup>57,58</sup> In patients with DHF, verapamil improved clinical status, exercise tolerance, and diastolic filling.<sup>55</sup> In a small prospective study,<sup>57</sup> an improvement was evident after 2 weeks of verapamil treatment (mean, 256 mg/d) in patients with CHF and an ejection fraction greater than 45%. In a hypertensive rat model,<sup>59</sup> amlodipine besylate prevented an elevation of LV end-diastolic pressure and transition to overt DHF by controlling blood pressure and reducing myocardial stiffness. However, as a result of the small number of patients studied in these trials, the usefulness of calcium channel blockers in diastolic dysfunction and DHF remains debatable.

The *Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM-Preserved)* study<sup>56</sup> is perhaps the only completed large-scale prospective randomized trial to specifically address the impact of pharmacotherapy on outcomes in a subgroup of patients with CHF and a preserved ejection fraction. In this study, 3023 patients who had DHF were randomized to 32 mg of candesartan daily or to placebo. At 37-month median follow-up, candesartan reduced hospitalization for CHF by 11%. The annual event rates (ie, hospital admission for heart failure) were 8% in the candesartan group and 9% in the placebo group.<sup>56</sup>

The effects of aldosterone antagonism on myocardial function in hypertensive patients with suspected diastolic heart failure has been studied in randomized, double-blinded, placebo-controlled trials by using sensitive quantitative echocardiographic techniques.<sup>60-62</sup> One study<sup>60</sup> demonstrated that in an ambulatory hypertensive population with isolated LV dias-

Stage of Diastolic Dysfunction	Doppler Echocardiography Type				
	Standard			M-Mode V <sub>p</sub> , cm/s	Tissue E <sub>m</sub> , cm/s
	E/A Ratio, cm/s	IVRT, ms	DT, ms		
Normal*	>1	<100	<220	>45	>8
I. Delayed Relaxation	<1	>100	>220	<45	<8
II. Pseudonormal	1-2	60-100	150-200	<45	<8
III. Restrictive Filling	>2	<60	<150	<45	<8

**Figure 1.** Criteria as measured by three types of Doppler echocardiography in determining the stage of diastolic dysfunction in a patient. \*Values indicated for flow propagation velocity (V<sub>p</sub>) and peak early diastolic myocardial velocity (E<sub>m</sub>) are for older adults. Values for younger adults are greater than 55 cm/s and greater than 10 cm/s, respectively. **Abbreviations:** DT, early left ventricular filling deceleration time; E/A, early-to-atrial left ventricular filling ratio; IVRT, isovolumic relaxation time. **Source:** J Am Coll Cardiol. 1998;32:865-875.<sup>53</sup>

tolic dysfunction and reduced functional capacity because of exertional dyspnea, myocardial function improved after 6 months with aldosterone antagonism by using a hemodynamically insignificant dose of spironolactone.

Digoxin, an antiarrhythmic drug, is not specifically indicated for the treatment of patients with DHF. However, it has been reported to reduce the hospitalization rate in patients who had CHF and an LVEF greater than 45%.<sup>63</sup> Any benefits of digoxin in treating patients with DHF may be related to controlling heart rate, especially in the presence of atrial arrhythmia.<sup>63</sup>

In the absence of large controlled clinical trials, DHF is determined by a set of logical principles.<sup>64</sup> For example, physicians' and patients' goals should be to control systemic arterial blood pressure and tachycardia, reduce central venous blood volume, and alleviate myocardial ischemia.<sup>64</sup> The American College of Cardiology and American Heart Association Task Force guidelines for the management of heart failure and the preservation of left ventricular systolic function are provided in Figure 2.<sup>64</sup> Improving alveolar hypoxemia and pulmonary arterial hypertension, when present, are also important treatment goals.<sup>65</sup> Together, these interventions minimize right ventricular overload influences on the left ventricle.

### Prognosis

The prognosis of LV diastolic dysfunction and DHF is slightly less ominous than that of systolic heart failure. The annual mortality rate in patients who have diastolic dysfunction or DHF is 5% to 8% while the rate is 10% to 15% in those who have systolic dysfunction or systolic heart failure.<sup>9,50,66-68</sup> By comparison, the annual mortality rate in the general popula-

tion without heart failure and of a similar age is 1%.<sup>9</sup> Presence of coronary disease, age, and the LVEF cut-off value are important factors in the prognosis.<sup>69</sup> For example, when patients who have ischemic heart disease are excluded, annual mortality for DHF falls to 2% to 3%.<sup>63</sup> However, in patients older than 70 years who have CHF, mortality is similar in systolic and diastolic heart failure.<sup>14,70</sup>

### Conclusion

Left ventricular diastolic dysfunction and heart failure are common and may account for as much as 50% of the heart failure cases in elderly patients.<sup>6-10</sup> As with systolic heart failure, DHF is associated with substantial morbidity and mortality.<sup>9,50,66-68</sup> There are differences in the pathogenesis, prognosis, and treatment of diastolic dysfunction leading to DHF and systolic heart failure. Current clinical management is based on symptom relief and modification of underlying cardiac conditions. Maintenance of euvolemia, rate control of atrial fibrillation, and management of systemic arterial hypertension are key elements of the treatment process. Evidence

#### ■ Class I

- Control of systolic and diastolic hypertension in accordance with published guidelines\*
- Control of ventricular rate in patients who also have atrial fibrillation
- Diuretics to control pulmonary congestion and peripheral edema

#### ■ Class IIa

- Coronary revascularization in patients who also have coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to have an adverse effect on diastolic function

#### ■ Class IIb

- Restoration of sinus rhythm in patients who also have atrial fibrillation
- Use of β-adrenergic blocking agents, angiotensin converting inhibitors, angiotensin receptor blockers, or calcium channel blockers in patients who also have controlled hypertension
- Use of digitalis to minimize symptoms of heart failure

**Figure 2.** The American College of Cardiology and the American Heart Association guidelines for the treatment of patients who have heart failure and normal left ventricular ejection fraction. \*Recommendation derived from multiple randomized controlled trials or meta-analyses. All other recommendations were derived from expert consensus statements, case studies, or standard-of-care. **Source:** ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult.<sup>64</sup>

from large-scale randomized controlled trials (RCTs) has been scarce, but a search on <http://www.clinicaltrials.gov> reveals that several clinical trials are under way. As more RCTs of patients with diastolic dysfunction and DHF are completed, treatment recommendations will further evolve. It is therefore important for primary care physicians to recognize the difference between DHF and systolic heart failure and modify their approach to treating patients with DHF as outlined to improve the prognosis of this condition.

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