

CLINICAL PRACTICE

## Diastolic Heart Failure

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

**A 78-year-old woman with a history of hypertension is admitted to the hospital with congestive heart failure. Physical examination reveals a blood pressure of 180/90 mm Hg, increased jugular venous pressure, peripheral edema, and pulmonary rales. A chest radiograph shows pulmonary edema and mild cardiomegaly. An echocardiogram (Fig. 1) shows increased thickness of the left ventricular wall, a left ventricular cavity of normal size, left atrial enlargement, and a left ventricular ejection fraction of 70 percent. The left ventricular Doppler filling pattern is abnormal and consistent with an elevated pulmonary-capillary wedge pressure. How should this patient be treated?**

### THE CLINICAL PROBLEM

Diastolic dysfunction refers to an abnormality of diastolic distensibility, filling, or relaxation of the left ventricle — regardless of whether the ejection fraction is normal or abnormal and whether the patient is symptomatic or asymptomatic.<sup>1</sup> Thus, an asymptomatic patient with hypertensive left ventricular hypertrophy and an echocardiogram showing a normal ejection fraction and abnormal left ventricular filling can be said to have diastolic dysfunction. If effort intolerance and dyspnea developed in such a patient, especially in combination with venous congestion and pulmonary edema, it would be appropriate to use the term “diastolic heart failure.”<sup>1-4</sup>

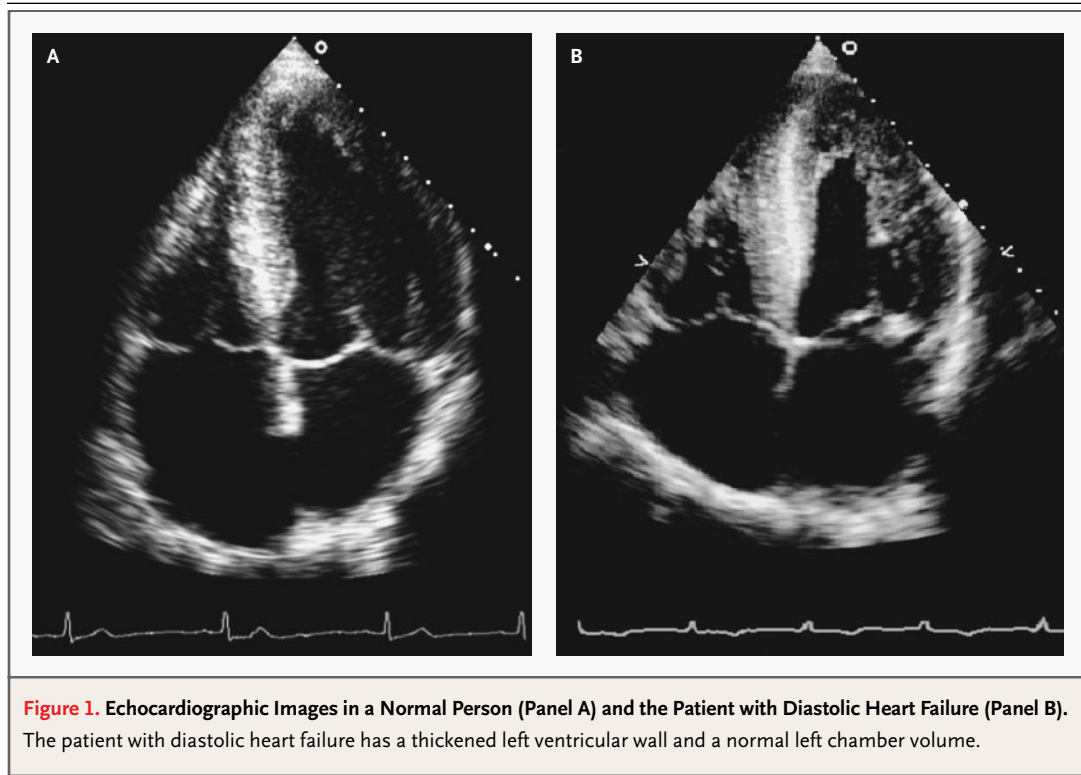
Cross-sectional and population-based studies indicate that at least one third of all patients with congestive heart failure have a normal or near-normal ejection fraction.<sup>1-12</sup> The prevalence of diastolic heart failure is highest in patients over the age of 75 years.<sup>1,5-7</sup> The mortality rate among patients with diastolic heart failure ranges from 5 to 8 percent annually, as compared with 10 to 15 percent among patients with systolic heart failure.<sup>12-17</sup> As is the case with systolic heart failure, the mortality rate is directly related to age and the presence or absence of coronary disease.<sup>3,11-17</sup> The morbidity associated with diastolic heart failure (including the rate of hospitalization) is similar to that associated with systolic heart failure.<sup>11-17</sup> There are fewer published data concerning the incidence of heart failure among patients with diastolic dysfunction, as demonstrated by Doppler echocardiography. In one population-based study, heart failure developed within five years in 11 to 15 percent of persons older than 65 years of age who had no clinical evidence of heart disease but had Doppler evidence of left ventricular diastolic dysfunction.<sup>10</sup>

The factors that promote fluid retention and precipitate overt heart failure are similar in patients with systolic heart failure and those with diastolic heart failure.<sup>18</sup> These factors include uncontrolled hypertension, atrial fibrillation, noncompliance with or inappropriate discontinuation of medications for heart failure, myocardial ischemia, anemia, renal insufficiency, use of nonsteroidal antiinflammatory drugs or thiazolidinediones,<sup>19</sup> and overindulgence in salty foods.

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#### **PATHOPHYSIOLOGICAL FEATURES**

Diastolic function is determined by the passive elastic properties of the left ventricle and by the process of active relaxation. Abnormal passive elastic properties generally are caused by a combination of increased myocardial mass and alterations in the extramyocardial collagen network.<sup>3</sup> The effects of impaired active myocardial relaxation can further stiffen the ventricle. As a result, the curve for left ventricular diastolic pressure in relation to volume is shifted upward and to the left (Fig. 2), chamber compliance is reduced, the time course of filling is altered, and the diastolic pressure is elevated.<sup>4</sup> Under these circumstances, a relatively small increase in central blood volume or an increase in venous tone, arterial stiffness, or both can cause a substantial increase in left atrial and pulmonary venous pressures and may result in acute pulmonary edema.<sup>3,4,20</sup>

The differences and similarities between diastolic and systolic heart failure are shown in Table 1. A substantial number of patients with diastolic heart failure have a low stroke volume and a reduced cardiac output despite a normal ejection fraction<sup>21</sup>; in many patients, the capacity to augment cardiac output during exercise is also limited.<sup>22</sup> Other subtle abnormalities in systolic function have been identi-

fied in patients with a normal ejection fraction,<sup>23</sup> but the predominant abnormality in this condition is in diastole. The left ventricular size and ejection fraction are normal, and the left ventricle has a limited capacity to fill at a normal left atrial pressure.<sup>4</sup>

Patients with diastolic dysfunction, with or without overt heart failure, have exercise intolerance for two principal reasons. First, elevated left ventricular diastolic and pulmonary venous pressures cause a reduction in lung compliance, which increases the work of breathing and evokes the symptom of dyspnea. Second, inadequate cardiac output during exercise can lead to fatigue of the legs and of the accessory muscles of respiration.<sup>24-26</sup> This latter mechanism helps to explain the relationship between poor exercise tolerance and changes in pulmonary-capillary wedge pressure.<sup>26</sup> Other non-cardiac mechanisms, especially physical deconditioning, also contribute to exercise intolerance.

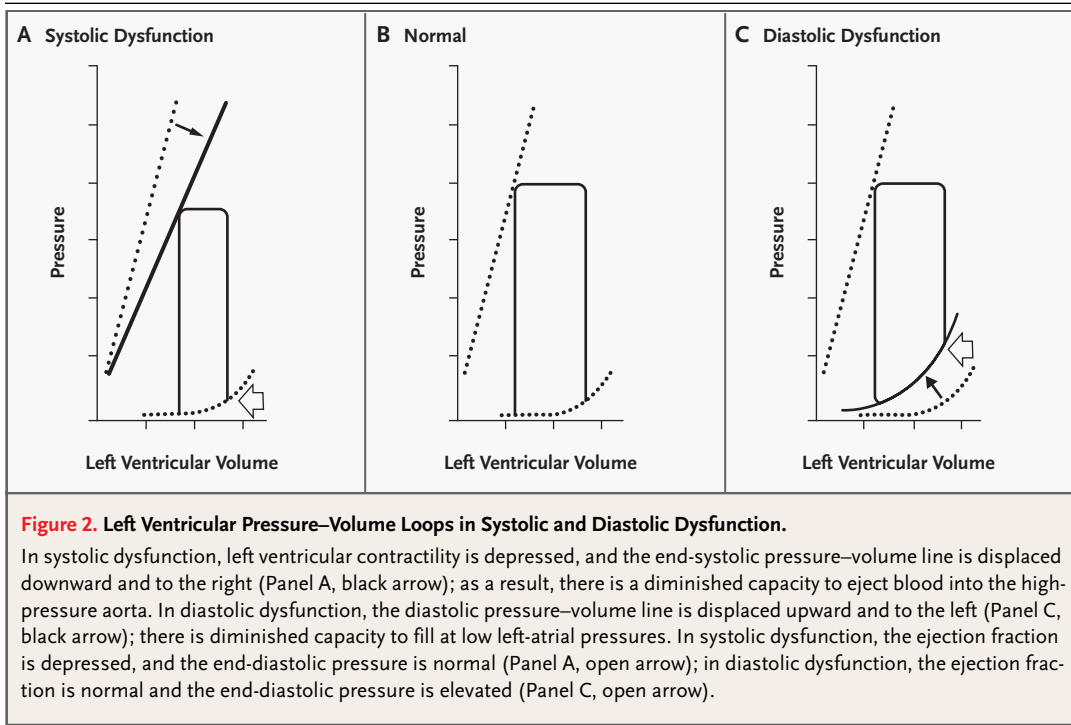
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#### STRATEGIES AND EVIDENCE

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#### **DIAGNOSTIC CRITERIA**

Guidelines from the American College of Cardiology and the American Heart Association suggest that “the diagnosis of diastolic heart failure is gen-



erally based on the finding of typical symptoms and signs of heart failure in a patient who is shown to have a normal left ventricular ejection fraction and no valvular abnormalities on echocardiography.<sup>27</sup> A European study group also requires “evidence of abnormal left ventricular relaxation, filling, diastolic distensibility or diastolic stiffness.”<sup>28</sup> Vasan and Levy suggest specific criteria for the diagnoses of definite, probable, and possible diastolic heart failure, all of which involve signs and symptoms of heart failure with a normal ejection fraction.<sup>29</sup> The criteria for definite diastolic heart failure are the presence of a normal ejection fraction (above 50 percent) within three days after an episode of heart failure and objective evidence of diastolic dysfunction (i.e., abnormal left ventricular relaxation, filling, or distensibility as measured during cardiac catheterization). Others, however, argue that the diagnosis of diastolic heart failure can be made clinically, if there is reliable evidence of congestive heart failure and a normal ejection fraction, and that objective evidence of diastolic dysfunction obtained in the catheterization laboratory merely confirms the diagnosis.<sup>30</sup> This conclusion is consonant with the American College of Cardiology and American Heart Association guidelines.<sup>27</sup> These guidelines use the term “diastolic heart failure,” as opposed to

the more general term “heart failure with normal ejection fraction,” which encompasses conditions such as acute severe mitral regurgitation and other circulatory congestive states.

#### DIAGNOSTIC TECHNIQUES

Echocardiography plays a critical diagnostic role in patients with heart failure, in part because the physical examination, electrocardiogram, and chest radiograph do not provide information that distinguishes diastolic from systolic heart failure.<sup>1,31</sup> The documentation of a normal or near-normal left ventricular ejection fraction (e.g., >40 percent to 50 percent) is necessary for the diagnosis. In addition, echocardiographic evaluation can rapidly rule out diagnoses such as acute mitral or aortic regurgitation or constrictive pericarditis, which are also associated with signs and symptoms of heart failure and a normal ejection fraction.

Doppler echocardiography, which measures the velocity of intracardiac blood flow, can be helpful in the assessment of diastolic function. In normal sinus rhythm, diastolic flow from the left atrium to the left ventricle across the mitral valve has two components — the E wave, which reflects early diastolic filling, and the A wave, in late diastole, which reflects atrial contraction. Because the velocity of

**Table 1. Characteristics of Diastolic Heart Failure as Compared with Those of Systolic Heart Failure.\***

Characteristic	Diastolic Heart Failure	Systolic Heart Failure
Clinical features		
Symptoms (e.g., dyspnea)	Yes	Yes
Congestive state (e.g., edema)	Yes	Yes
Neurohormonal activation (e.g., brain natriuretic peptide)	Yes	Yes
Left ventricular structure and function		
Ejection fraction	Normal	Decreased
Left ventricular mass	Increased	Increased
Relative wall thickness†	Increased	Decreased
End diastolic volume	Normal	Increased
End diastolic pressure	Increased	Increased
Left atrial size	Increased	Increased
Exercise		
Exercise capacity	Decreased	Decreased
Cardiac output augmentation	Decreased	Decreased
End diastolic pressure	Increased	Increased

\* The clinical features of diastolic heart failure are similar to those of systolic heart failure, but left ventricular structure and function are distinctly different.

† The descriptor of left ventricular geometry is the relative wall thickness, defined as the ratio of left ventricular wall thickness to the radius of the left ventricular cavity.

blood flow across the mitral valve depends on the transmitral pressure gradient, the E-wave velocity is influenced by both the rate of early diastolic relaxation and the left atrial pressure. Alterations in the pattern of these velocities give insight into left ventricular diastolic function and into prognosis,<sup>10,32</sup> although standard mitral inflow patterns (Fig. 3) are extremely sensitive to loading conditions, particularly to left atrial pressure. Other non-invasive approaches to assessing diastolic function include Doppler assessment of flow into the left atrium through the pulmonary veins, and tissue Doppler imaging, which allows for direct measurement of the velocity of change in myocardial length, an index of left ventricular relaxation. The latter technique, in particular, is less sensitive to preload than are standard Doppler approaches and permits more accurate estimation of the filling pressures. These techniques are discussed in detail elsewhere.<sup>2,33,34</sup> Cardiac catheterization can confirm elevated left ventricular filling pressures, but in practice, this procedure is usually performed only when myocardial ischemia is suspected — for example, when heart failure is preceded or accompanied by angina, when there is biochemical evidence of myocardial injury, or when there is a rapid onset of heart failure in the absence of hypertension or another obvious precipitant.

## MANAGEMENT

The management of diastolic heart failure has two major objectives: to reverse the consequences of diastolic dysfunction (e.g., venous congestion and exercise intolerance) and to eliminate or reduce the factors responsible for the diastolic dysfunction.

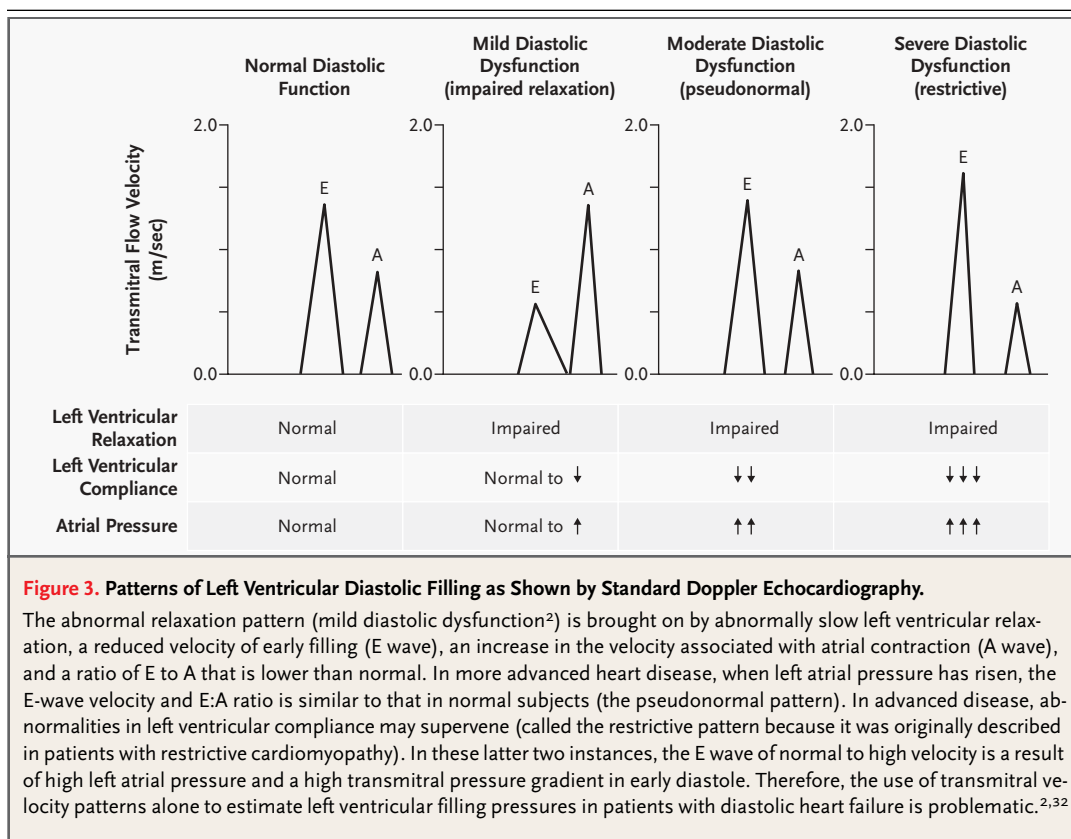
### INITIAL MANAGEMENT

The initial treatment of patients with diastolic heart failure, like that of patients with systolic heart failure, is aimed at reducing pulmonary venous pressure and congestion, and such treatment usually requires therapy with diuretics.<sup>35</sup> Pulmonary edema, with or without signs of systemic venous congestion, can be treated with supplemental oxygen, morphine, parenteral diuretics, and nitroglycerin. Aggressive diuresis may result in serious hypotension in patients with diastolic heart failure because of the steep curve for left ventricular diastolic pressure in relation to volume. If severe hypertension is present and does not respond to these initial measures, it may be necessary to administer a parenteral agent such as sodium nitroprusside. If myocardial ischemia is present, nitroglycerin and other medical therapies may be used. A detailed discussion of the management of acute ischemia and severe hypertension is beyond the scope of this article, but the topic has been reviewed elsewhere.<sup>36,37</sup>

Tachycardia causes an increase in demand for myocardial oxygen and a decrease in coronary perfusion time, which may lead to myocardial ischemia, even in the absence of obstructive coronary artery disease. In addition, there may be insufficient time for complete relaxation, with a resultant increase in diastolic pressure; ventricular filling may also be compromised. Thus, in patients with diastolic dysfunction, the development of atrial fibrillation, especially if the ventricular response is rapid, may result in pulmonary edema and hypotension, in some cases requiring urgent cardioversion. There are no data to support the use of a particular pharmacologic agent or strategy over another for rate control in patients with diastolic heart failure and atrial fibrillation, but beta-blockers<sup>27</sup> or nondihydropyridine calcium-channel blockers<sup>38</sup> can be used to prevent tachycardia or to slow the heart rate in patients who have diastolic heart failure.

### LONG-TERM MANAGEMENT

With the exception of the recently reported findings of the Candesartan in Heart Failure — Assessment



of Reduction in Mortality (CHARM)-Preserved study,<sup>39</sup> data from long-term investigations of any agent compared with placebo in patients with diastolic heart failure are lacking, as are data from studies comparing agents of different classes. However, the available data provide some guidance. Several small, short-term studies of patients with hypertensive disease, coronary heart disease, or both (and a normal or near-normal ejection fraction) indicate that calcium-channel blockers, angiotensin-converting-enzyme inhibitors, or angiotensin-receptor blockers may be useful in improving exercise capacity.<sup>40-43</sup> Another study, involving patients with prior myocardial infarction, heart failure, and an ejection fraction greater than 40 percent, showed that treatment with propranolol was associated with reduced mortality; exercise capacity was not assessed in this study.<sup>41</sup>

The CHARM-Preserved study compared candesartan with placebo in patients with a history of class II, III, or IV heart failure, a hospitalization for cardiac reasons, and an ejection fraction greater than 40 percent; at the study's inception, patients could also be taking beta-blockers, diuretics, cal-

cium-channel blockers, spironolactone, or some combination of these agents. Over a median follow-up period of 36 months, treatment with candesartan was associated with significantly fewer hospitalizations for heart failure. In addition, there was a non-significant trend toward a reduction in the composite primary end point of hospitalization for heart failure and death from cardiac causes, with no significant reduction in the risks of stroke, myocardial infarction, and coronary revascularization.<sup>39</sup>

#### REVASCULARIZATION

If myocardial ischemia is contributing to diastolic dysfunction, percutaneous techniques or coronary-artery bypass surgery may be indicated. However, the apparently high rate of recurrent heart failure in patients with hypertension, coronary disease, and a normal ejection fraction, even after successful coronary-artery bypass surgery, suggests that symptoms of congestive heart failure in these patients are not entirely due to ischemia.<sup>44</sup>

#### TREATMENT OF HYPERTENSION

The treatment of hypertension, including isolated

systolic hypertension in the elderly, results in a dramatic reduction in the incidence of heart failure.<sup>45</sup> Details of antihypertensive therapy are available in the guidelines from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure<sup>46</sup> and were reviewed previously in the *Journal*.<sup>37</sup> In the Systolic Hypertension in the Elderly Program, a thiazide diuretic-based regimen resulted in an average blood pressure of 143/68 mm Hg, as compared with 155/72 mm Hg in the placebo group, and was associated with a 50 percent reduction in the rate of heart failure.<sup>45</sup> Although the ejection fraction was not reported, the reduction in the rate of heart failure was observed among patients with and those without electrocardiographic evidence of prior myocardial infarction.<sup>45</sup> There appears to be an improvement in exercise capacity and quality of life when an exaggerated blood pressure response during exercise (e.g., a peak systolic pressure above 200 mm Hg) is attenuated by treatment with an angiotensin-receptor blocker.<sup>43</sup>

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#### AREAS OF UNCERTAINTY

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The clinician's ability to diagnose diastolic heart failure has been questioned.<sup>47</sup> Moreover, it has been argued that there are often alternative explanations for symptoms of heart failure in patients with preserved systolic function.<sup>48</sup> This notion assumes that the diagnosis of congestive heart failure is based only on symptoms. However, both symptoms and physical signs of heart failure should be present before the diagnosis of diastolic heart failure is considered.<sup>30</sup> A chest radiograph, although not specified in any of the guidelines, is useful to support the diagnosis of pulmonary edema. Levels of brain natriuretic peptide are elevated in patients with cardiac (as opposed to pulmonary) causes of dyspnea.<sup>49,50</sup> Available data indicate that brain natriuretic peptide levels are not as high in diastolic heart failure as they are in systolic heart failure,<sup>31,49,50</sup> but more data are needed to assess the role of brain natriuretic peptide in the diagnosis of diastolic heart failure.

As noted above, there are insufficient data from randomized trials to assess the effects of various pharmacologic agents on congestive heart failure and on other cardiovascular outcomes or to support a preference for one agent or class of agents over another. Certain pharmacologic agents have been proposed for use in patients with diastolic dysfunction

because of their biologic effects, such as the elimination of tachycardia, ischemia, or both (e.g., beta-blockers and rate-lowering calcium-channel blockers<sup>35</sup>) or the regression of left ventricular hypertrophy (e.g., diuretics and angiotensin-converting-enzyme inhibitors<sup>51,52</sup>) and fibrosis (e.g., spironolactone<sup>53</sup>) (Table 2). Agents that inhibit the renin-angiotensin-aldosterone system may have several of these effects.<sup>54-56</sup> However, more data are needed to demonstrate that such biologic effects reduce the risk of heart failure.<sup>52</sup>

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#### GUIDELINES

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Two professional societies have published guidelines that specifically address diastolic heart failure,<sup>27,56</sup> and neither set of guidelines can be considered evidence-based. A report by a task force of the European Society of Cardiology,<sup>56</sup> while acknowledging the lack of data from large, randomized placebo-controlled trials, recommends beta-blockers or rate-lowering calcium-channel blockers to slow the heart rate; long-term diuretic therapy, when appropriate, to control or prevent edema; and angiotensin-converting-enzyme inhibitors to treat hypertension and to promote the regression of left ventricular hypertrophy.<sup>56</sup> The guidelines from the American College of Cardiology and the American Heart Association<sup>27</sup> emphasize control of blood pressure (to a level below 130/80 mm Hg), the use of diuretics to relieve congestion, treatment of ischemia, and control of the heart rate and elimination of tachycardia, without recommending specific agents to achieve these goals.

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#### CONCLUSIONS AND RECOMMENDATIONS

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In the patient described in the vignette, the diagnosis of diastolic heart failure<sup>29,30</sup> can be made on the basis of left ventricular hypertrophy, clinical evidence of heart failure, and a normal ejection fraction, as well as Doppler findings that are consistent with diastolic dysfunction and elevated filling pressures. The initial treatment of diastolic heart failure should be directed at reducing the congestive state (with the use of diuretics). Long-term goals are to control congestion and to eliminate or reduce the factors, including hypertension, tachycardia, and ischemia, that confer a predisposition to diastolic dysfunction. Recognizing that there are limited pub-

**Table 2. Management Principles for Patients with Diastolic Heart Failure.**

Goal	Treatment*	Daily Dose of Medication†
Reduce the congestive state	Salt restriction	<2 g of sodium per day
	Diuretics	Furosemide, 10–120 mg Hydrochlorothiazide, 12.5–25 mg
	ACE inhibitors	Enalapril, 2.5–40 mg Lisinopril, 10–40 mg
Maintain atrial contraction and prevent tachycardia	Angiotensin II–receptor blockers	Candesartan, 4–32 mg Losartan, 25–100 mg
	Cardioversion of atrial fibrillation	
	Sequential atrioventricular pacing	
Treat and prevent myocardial ischemia	Beta-blockers	Atenolol, 12.5–100 mg Metoprolol, 25–100 mg Verapamil, 120–360 mg Diltiazem, 120–540 mg
	Calcium-channel blockers	
	Radiofrequency ablation modification of atrioventricular node and pacing	
Control hypertension	Nitrates	Isosorbide dinitrate, 30–180 mg Isosorbide mononitrate, 30–90 mg
	Beta-blockers	Atenolol, 12.5–100 mg Metoprolol, 25–200 mg
	Calcium-channel blockers	Diltiazem, 120–540 mg Verapamil, 120–360 mg
	Coronary-artery bypass surgery, percutaneous coronary intervention	
<b>Measures with Theoretical Benefit in Diastolic Heart Failure</b>		
Promote regression of hypertrophy and prevent myocardial fibrosis	Antihypertensive agents	Chlorthalidone, 12.5–25 mg Hydrochlorothiazide, 12.5–50 mg Atenolol, 12.5–100 mg Metoprolol, 12.5–200 mg Amlodipine, 2.5–10 mg Felodipine, 2.5–20 mg Enalapril, 2.5–40 mg Lisinopril, 10–40 mg Candesartan, 4–32 mg Losartan, 50–100 mg
	ACE inhibitors	Enalapril, 2.5–40 mg Lisinopril, 10–40 mg Ramipril, 5–20 mg Captopril, 25–150 mg
	Angiotensin-receptor blockers	Candesartan, 4–32 mg Losartan, 50–100 mg
	Spironolactone	25–75 mg

\* Treatments listed for the first four goals are those generally used in clinical practice. Angiotensin-converting–enzyme (ACE) inhibitors, angiotensin-receptor blockers, and spironolactone inhibit the renin–angiotensin–aldosterone system and thus have a theoretical benefit, but more data are required to show that they reduce the risk of heart failure.

† The list of medications is not comprehensive but, rather, includes examples that are in common clinical use or have been included in studies of pathophysiologic mechanisms in diastolic dysfunction or heart failure or were included in larger trials that generally were not designed to assess outcomes in diastolic heart failure. Candesartan is the only agent studied in a randomized, controlled trial involving patients with diastolic heart failure.<sup>39</sup> A more exhaustive list of antihypertensive agents can be found in the guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.<sup>46</sup>

lished data to guide therapy, we recommend salt restriction, the use of diuretics (with a subsequent dosage adjustment, depending on the clinical response), and an angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker for control

of blood pressure and blood volume (Table 2). If the blood pressure is not controlled with this regimen, or if resting tachycardia is present, additional antihypertensive agents, including a beta-blocker, should be administered.

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