CLINICAL PRACTICE

Diastolic Heart Failure

Gerard P. Aurigemma, M.D., and William H. Gaasch, M.D.

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.[1] 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."[1-4]

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.[1-12] The prevalence of diastolic heart failure is highest in patients over the age of 75 years.[1,5-7] 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.[12-17] As is the case with systolic heart failure, the mortality rate is directly related to age and the presence or absence of coronary disease.[3,11-17] The morbidity associated with diastolic heart failure (including the rate of hospitalization) is similar to that associated with systolic heart failure.[11-17] 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.[10]

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.[18] 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,[19] and overindulgence in salty foods.

From the Division of Cardiology, Department of Medicine, University of Massachusetts Medical School, Worcester (G.P.A.); and the Department of Cardiovascular Medicine, Lahey Clinic, Burlington, Mass. (W.H.G.). Address reprint requests to Dr. Aurigemma at the University of Massachusetts Medical School, 55 Lake Ave. N., Worcester, MA 01655, or at aurigemg@ummhc.org.

N Engl J Med 2004;351:1097-105.

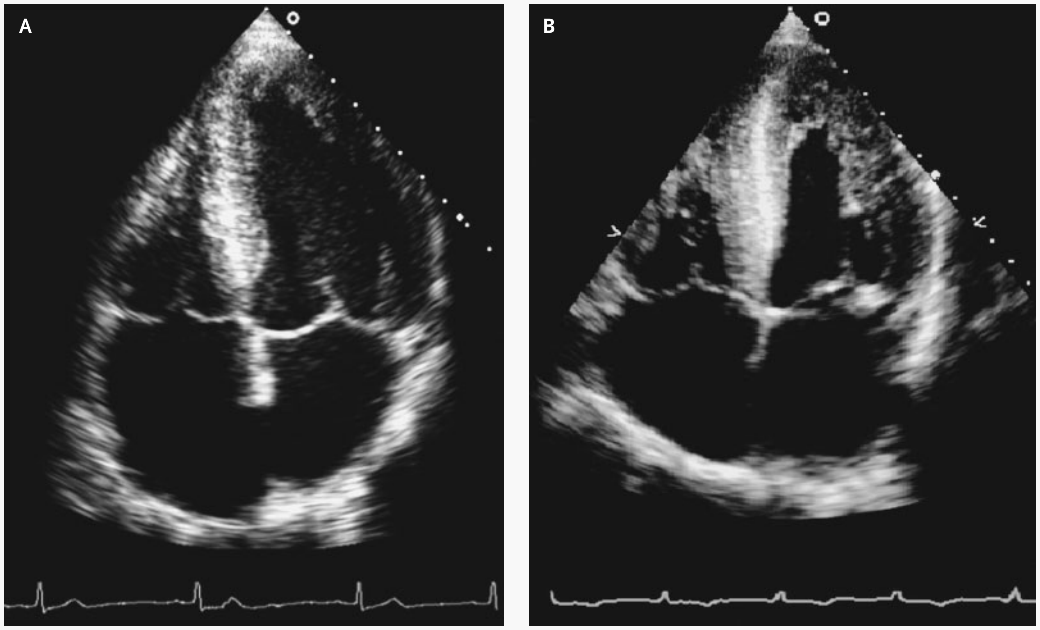


Figure 1. Echocardiographic Images in a Normal Person (Panel A) and the Patient with Diastolic Heart Failure (Panel B).
The patient with diastolic heart failure has a thickened left ventricular wall and a normal left chamber volume.

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.[3] 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.[4] 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.[3,4,20]

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[21]; in many patients, the capacity to augment cardiac output during exercise is also limited.[22] Other subtle abnormalities in systolic function have been identified in patients with a normal ejection fraction,[23] 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.[4]

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.[24-26] This latter mechanism helps to explain the relationship between poor exercise tolerance and changes in pulmonary-capillary wedge pressure.[26] Other noncardiac mechanisms, especially physical deconditioning, also contribute to exercise intolerance.

STRATEGIES AND EVIDENCE

DIAGNOSTIC CRITERIA

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

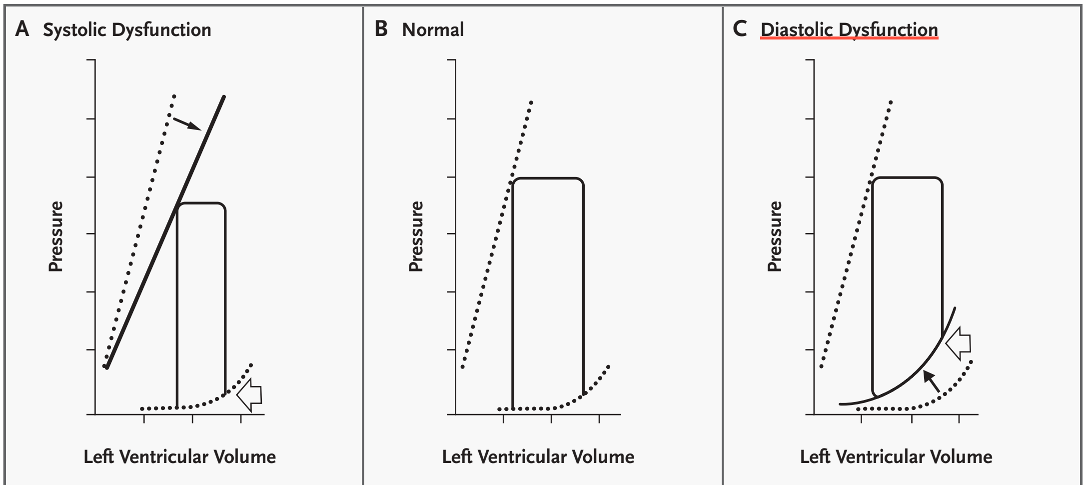


Figure 2. Left Ventricular Pressure–Volume Loops in Systolic and Diastolic Dysfunction.

In systolic dysfunction, left ventricular contractility is depressed, and the end-systolic pressure–volume line is displaced downward and to the right (Panel A, black arrow); as a result, there is a diminished capacity to eject blood into the high-pressure aorta. In diastolic dysfunction, the diastolic pressure–volume line is displaced upward and to the left (Panel C, black arrow); there is diminished capacity to fill at low left-atrial pressures. In systolic dysfunction, the ejection fraction is depressed, and the end-diastolic pressure is normal (Panel A, open arrow); in diastolic dysfunction, the ejection fraction is normal and the end-diastolic pressure is elevated (Panel C, open arrow).

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."[27] A European study group also requires "evidence of abnormal left ventricular relaxation, filling, diastolic distensibility or diastolic stiffness."[28] 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.[29] 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.[30] This conclusion is consonant with the American College of Cardiology and American Heart Association guidelines.[27] 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.[1,31] 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,[10,32] although standard mitral inflow patterns (Fig. 3) are extremely sensitive to loading conditions, particularly to left atrial pressure. Other noninvasive 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.[2,33,34] 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.

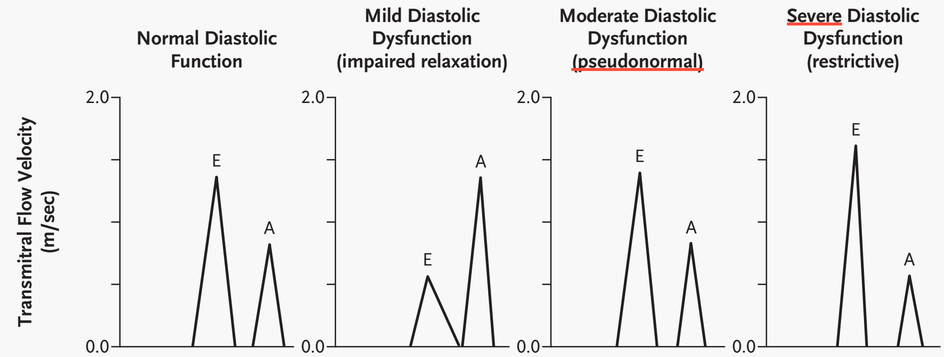
INITIAL MANAGEMENT

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.[35] 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.[36,37]

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[27] or nondihydropyridine calcium-channel blockers[38] 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



	Normal Diastolic Function	Mild Diastolic Dysfunction (impaired relaxation)	Moderate Diastolic Dysfunction (pseudonormal)	Severe Diastolic Dysfunction (restrictive)
Left Ventricular Relaxation	Normal	Impaired	Impaired	Impaired
Left Ventricular Compliance	Normal	Normal to ↓	↓↓	↓↓↓
Atrial Pressure	Normal	Normal to ↑	↑↑	↑↑↑

Figure 3. Patterns of Left Ventricular Diastolic Filling as Shown by Standard Doppler Echocardiography.

The abnormal relaxation pattern (mild diastolic dysfunction[2]) is brought on by abnormally slow left ventricular relaxation, a reduced velocity of early filling (E wave), an increase in the velocity associated with atrial contraction (A wave), and a ratio of E to A that is lower than normal. In more advanced heart disease, when left atrial pressure has risen, the E-wave velocity and E:A ratio is similar to that in normal subjects (the pseudonormal pattern). In advanced disease, abnormalities in left ventricular compliance may supervene (called the restrictive pattern because it was originally described in patients with restrictive cardiomyopathy). In these latter two instances, the E wave of normal to high velocity is a result of high left atrial pressure and a high transmitral pressure gradient in early diastole. Therefore, the use of transmitral velocity patterns alone to estimate left ventricular filling pressures in patients with diastolic heart failure is problematic.[2,32]

of Reduction in Mortality (CHARM)–Preserved study,[39] 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.[40-43] 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.[41]

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, calcium-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 nonsignificant 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.[39]

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.[44]

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.[45] 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[46] and were reviewed previously in the *Journal*.[37] 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.[45] 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.[45] 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.[43]

AREAS OF UNCERTAINTY

The clinician's ability to diagnose diastolic heart failure has been questioned.[47] Moreover, it has been argued that there are often alternative explanations for symptoms of heart failure in patients with preserved systolic function.[48] 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.[30] 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.[49,50] Available data indicate that brain natriuretic peptide levels are not as high in diastolic heart failure as they are in systolic heart failure,[31,49,50] 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[35]) or the regression of left ventricular hypertrophy (e.g., diuretics and angiotensin-converting–enzyme inhibitors[51,52]) and fibrosis (e.g., spironolactone[53]) (Table 2). Agents that inhibit the renin–angiotensin–aldosterone system may have several of these effects.[54-56] However, more data are needed to demonstrate that such biologic effects reduce the risk of heart failure.[52]

GUIDELINES

Two professional societies have published guidelines that specifically address diastolic heart failure,[27,56] and neither set of guidelines can be considered evidence-based. A report by a task force of the European Society of Cardiology,[56] 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.[56] The guidelines from the American College of Cardiology and the American Heart Association[27] 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.

CONCLUSIONS AND RECOMMENDATIONS

In the patient described in the vignette, the diagnosis of diastolic heart failure[29,30] 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
	Angiotensin II–receptor blockers	Candesartan, 4–32 mg Losartan, 25–100 mg
Maintain atrial contraction and prevent tachycardia	Cardioversion of atrial fibrillation	
	Sequential atrioventricular pacing	
	Beta-blockers	Atenolol, 12.5–100 mg Metoprolol, 25–100 mg Verapamil, 120–360 mg
	Calcium-channel blockers	Diltiazem, 120–540 mg
	Radiofrequency ablation modification of atrioventricular node and pacing	
Treat and prevent myocardial ischemia	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	
Control hypertension	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
Measures with Theoretical Benefit in Diastolic Heart Failure		
Promote regression of hypertrophy and prevent myocardial fibrosis	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.[39] 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.[46]

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.

REFERENCES

1. Gaasch WH, Zile MR. Left ventricular diastolic dysfunction and diastolic heart failure. Annu Rev Med 2004;55:373-94.

2. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194-202.

3. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation 2002;105:1387-93.

4. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure — abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004;350:1953-9.

5. Gaasch WH. Diagnosis and treatment of heart failure based on left ventricular systolic or diastolic dysfunction. JAMA 1994; 27:1276-80.

6. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol 1995;26: 1565-74.

7. Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation 1998;98:2282-9.

8. Gottdiener JS, Arnold AM, Aurigemma GP, et al. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. J Am Coll Cardiol 2000;35:1628-37.

9. Kitzman DW, Gardin JM, Gottdiener JS, et al. Importance of heart failure with preserved systolic function in patients ≥65 years of age. Am J Cardiol 2001;87:413-9.

10. Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: The Cardiovascular Health Study. J Am Coll Cardiol 2001;37:1042-8.

11. Gandhi SK, Powers JC, Nomeir AM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 2001;344:17-22.

12. Vasan R, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 1999;33:1948-55.

13. Dauterman KW, Massie BM, Gheorghiade M. Heart failure associated with preserved systolic function: a common and costly clinical entity. Am Heart J 1998;135: S310-S319.

14. O'Conner CM, Gattis WA, Shaw L, Cuffe MS, Califf RM. Clinical characteristics and long-term outcomes of patients with heart failure and preserved systolic function. Am J Cardiol 2000;86:863-7.

15. Setaro JF, Soufer R, Remetz MS, Perlmutter RA, Zaret BL. Long-term outcome in patients with congestive heart failure and intact systolic left ventricular performance. Am J Cardiol 1992;69:1212-6.

16. Judge KW, Pawitan Y, Caldwell J, Gersh BJ, Kennedy JW. Congestive heart failure symptoms in patients with preserved left ventricular systolic function: analysis of the CASS registry. J Am Coll Cardiol 1991;18: 377-82.

17. Brogan WC III, Hillis LD, Flores ED, Lange RA. The natural history of isolated left ventricular diastolic dysfunction. Am J Med 1992;92:627-30.

18. Tsuyuki RT, McKelvie RS, Arnold JM, et al. Acute precipitants of congestive heart failure exacerbations. Arch Intern Med 2001;161:2337-42.

19. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Diabetes Care 2004;27:256-63.

20. Gaasch WH, Blaustein AS, LeWinter MM. Heart failure and clinical disorders of left ventricular diastolic dysfunction. In: Gaasch WH, LeWinter MM, eds. Left ventricular diastolic dysfunction and heart failure. Philadelphia: Lea & Febiger, 1994:245-58.

21. Aurigemma GP, Gaasch WH, McLaughlin M, McGinn R, Sweeney A, Meyer TE. Reduced left ventricular systolic pump performance and depressed myocardial contractile function in patients >65 years of age with normal ejection fraction and high relative wall thickness. Am J Cardiol 1995; 76:702-5.

22. Kitzman DW, Higginbotham BM, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol 1991;17:1065-72.

23. Aurigemma GP, Silver KH, Priest MA, Gaasch WH. Geometric changes allow normal ejection fraction despite depressed myocardial shortening in hypertensive left ventricular hypertrophy. J Am Coll Cardiol 1995;26:195-202.

24. Massie B, Conway M, Yonge R, et al. Skeletal muscle metabolism in patients with congestive heart failure: relation to clinical severity and blood flow. Circulation 1987; 76:1009-19.

25. Mancini DM, Henson D, LaManca J, Levine S. Respiratory muscle function and dyspnea in patients with chronic congestive heart failure. Circulation 1992;86:909-18.

26. Frenneaux MP, Porter A, Caforio ALP, Odawara H, Counihan PJ, McKenna WJ. Determinants of exercise capacity in hypertrophic cardiomyopathy. J Am Coll Cardiol 1989;13:1521-6.

27. Hunt SA, Baker DW, Chin MH, et al. Guidelines for the evaluation and management of chronic heart failure in the adult: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2001;38:2101-13. (Accessed August 16, 2004, at http://www.acc.org/clinical/guidelines/failure/VI_diastolic.htm.)

28. European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. Eur Heart J 1998;19:990-1003.

29. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation 2000;101:2118-21.

30. Zile MR, Gaasch WH, Carroll JD, et al. Heart failure with a normal ejection fraction: is measurement of diastolic function necessary to make the diagnosis of diastolic heart failure? Circulation 2001;104:779-82.

31. Vinch CS, Aurigemma GP, Hill JC, et al. Usefulness of clinical variables, echocardiography, and levels of brain natriuretic peptide and norepinephrine to distinguish systolic and diastolic causes of acute heart failure. Am J Cardiol 2003;91:1140-3.

32. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. J Am Coll Cardiol 1997;30:8-18.

33. Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. J Am Coll Cardiol 1998;32:865-75.

34. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527-33.

35. Gaasch WH, Schick EC, Zile MR. Management of left ventricular diastolic dysfunction. In: Smith TW, ed. Cardiovascular therapeutics: a companion to Braunwald's *Heart Disease*. Philadelphia: W.B. Saunders, 1996:237-42.

36. ACC/AHA Guidelines for the management of patients with acute myocardial infarction: 1999 updated guideline (Web version). (Accessed August 16, 2004, at http://www.acc.org/clinical/guidelines/nov96/1999/index.htm.)

37. August P. Initial treatment of hypertension. N Engl J Med 2003;348:610-7.

38. Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients

With Atrial Fibrillation): developed in collaboration with the North American Society of Pacing and Electrophysiology. J Am Coll Cardiol 2001;38:1231-66.
39. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-81.
40. Aronow WS, Kronzon I. Effect of enalapril on congestive heart failure treated with diuretics in elderly patients with prior myocardial infarction and normal left ventricular ejection fraction. Am J Cardiol 1993;71:602-4.
41. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. Am J Cardiol 1997;80:207-9.
42. Setaro JF, Zaret BL, Schulman DS, Black HR, Soufer R. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. Am J Cardiol 1990;66:981-6.
43. Warner JG, Metzger DC, Kitzman DW, Wesley DJ, Little WC. Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. J Am Coll Cardiol 1999;33:1567-72.
44. Kramer K, Kirkman P, Kitzman D, Little WC. Flash pulmonary edema: association with hypertension and reoccurrence despite coronary revascularization. Am Heart J 2000;40:451-5.
45. Kostis JB, Davis BR, Cutler J, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension: SHEP Cooperative Research Group. JAMA 1997;278:212-6.
46. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. JAMA 2003;289:2560-72. [Erratum, JAMA 2003;290:197.]
47. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. BMJ 2000;321:215-8.
48. Banerjee P, Banerjee T, Khand A, Clark AL, Cleland JG. Diastolic heart failure: neglected or misdiagnosed? J Am Coll Cardiol 2002;39:138-41.
49. Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol 2001;37:379-85.
50. Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002;288:2144-50.
51. Gottdiener JS, Reda DJ, Massie BM, Materson BJ, Williams DW, Anderson RJ. Effect of single-drug therapy on reduction of left ventricular mass in mild to moderate hypertension: comparison of six antihypertensive agents: the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Circulation 1997;95:2007-14.
52. Mathew J, Sleight P, Lonn E, et al. Reduction of cardiovascular risk by regression of electrocardiographic markers of left ventricular hypertrophy by the angiotensin-converting enzyme inhibitor ramipril. Circulation 2001;104:1615-21.
53. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709-17.
54. Brilla CG, Funck RC, Rupp H. Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. Circulation 2000;102:1388-93.
55. Díez J, Querejeta R, López B, et al. Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. Circulation 2002;105:2512-7.
56. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527-60. [Erratum, Eur Heart J 2001;22:2217-8.]