Section 11: Evaluation and Management of Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction

Overview

A substantial number of patients with heart failure (HF) have preserved left ventricular ejection fraction (LVEF), variably defined as an LVEF > 40%, >45%, or >50%.[1,2] HF with preserved LVEF is not a distinct condition, but rather a syndrome with numerous possible causative or comorbid conditions, including hypertension, diabetes mellitus, vascular stiffness, renal impairment, and atrial fibrillation. There is no strong consensus about nomenclature and appropriate treatment strategies.[3–6]

Pathophysiology and Prognosis. The ventricle in HF with preserved LVEF is characterized by hypertrophy,[7] increased extracellular matrix,[8] and abnormal calcium handling with delayed relaxation.[6,9] Activation of the neurohormonal milieu, including the renin-angiotensin system (RAS) and the sympathetic nervous system, is common in HF with and without preserved EF.[6] An analysis from the Framingham Heart Study showed that patients with HF and preserved LVEF had improved survival compared with those with reduced LVEF.[10] However, in a study from Olmsted County, survival was similar for patients with HF and either reduced or preserved LVEF.[11] This variability in relative clinical outcomes reflects differences in criteria for the diagnosis of HF and the etiologic composition of the populations studied.

With systolic pressure overload, as in hypertension or aortic stenosis, the left ventricle responds with concentric hypertrophy. With volume overloading lesions, such as mitral or aortic regurgitation, the left ventricle responds with dilation and eccentric hypertrophy.[12] The mechanism for concentric hypertrophy, as opposed to eccentric hypertrophy, is uncertain at present.

A further analysis of pathophysiology has been based on adverse ventricular-vascular interaction.[13,14] Patients with HF and preserved LVEF showed a marked increase in arterial stiffness (elastance) compared with hypertensive patients without HF and other control subjects. Ventricular systolic stiffening was also greater than normal. The increased arterial stiffness was related to delayed ventricular relaxation and to elevated diastolic pressure during exercise. These findings were not seen in patients with HF and reduced LVEF, even though their end-diastolic pressure was elevated. Thus the excess arterial stiffening in HF with preserved EF, coupled to the LV sensitivity to this stiffening, has been postulated to be the cause of sudden pulmonary edema in this setting. Others have observed reduced aortic distensibility[15] or a marked elevation in pulmonary capillary wedge pressure with no demonstrable increase in LV end-diastolic volume during ergometer exercise.[16]

Diagnosis. The diagnosis of HF with preserved LVEF can be made by the combination of (1) clinical signs and symptoms of HF and (2) findings of preserved or relatively preserved LVEF using an imaging method. Echocardiographic or hemodynamic findings supporting the diagnosis of diastolic dysfunction may further aid in the diagnosis,[17] although most of these indicators lack sensitivity or specificity. Catheterization-derived hemodynamic abnormalities do not aid substantially in the diagnosis.[18]

Prevalence. In prospective studies, approximately 40% of the population of patients with HF has normal or near normal resting LVEF.[2,3,10,11,19] HF with preserved LVEF is particularly prevalent among the elderly, females, and patients with hypertension.[2,11,20,21] Among 4 prospective studies of HF with normal LVEF, the average age range of patients was 73 to 79 years, and the percentage of females ranged from 61% to 76%.[2,19,22]

Mortality and Morbidity. The mortality of patients with HF and preserved LVEF is considerable, although less than in patients with LV dilation and reduced LVEF.[2,10,19]

As has been indicated, results from the Rochester Epidemiology Project suggested that survival was equally poor in patients with LVEF above or below 50%.[11] The authors postulated that this may have been due to the advanced age in their population (77 ± 12 years). In their recent review, mortality in HF with preserved EF was similar to that in patients with HF and reduced EF when patients were older than 65; among patients younger than 65, mortality was lower in those with preserved LVEF.[20]

Women make up a large majority of patients with HF and preserved EF.[10,19,23] Most studies have shown no difference in survival by gender, but in the Digitalis Investigation Group (DIG) study [24] and 1 other study,[10] female gender was associated with improved survival.

An analysis of the Coronary Artery Surgery Study registry showed that the presence of coronary artery disease was an adverse factor for survival in patients with HF and LVEF >45%.[25] A review of the available literature in 2002 showed that the prevalence of CAD in patients with HF and preserved EF ranged widely from 0% to 67%.[26]

A recent study comparing patients with normal or depressed EF found similar rates of hospital readmissions, HF readmissions, and functional decline.[2] Others have found a trend to fewer readmissions in patients with preserved EF.[22]

1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2005.11.016

Recommendation

11.1 Careful attention to differential diagnosis is recommended in patients with HF and preserved LVEF to distinguish among a variety of cardiac disorders, because treatments may differ. These various entities may be distinguished based on echocardiography, electrocardiography, and stress imaging (via exercise or pharmacologic means, using myocardial perfusion or echocardiographic imaging). See algorithm in Figure 11.1 for a detailed approach to differential diagnosis. (Strength of Evidence = C)

Background

Diagnosis. The clinical diagnosis of HF depends on the presence of commonly accepted signs and symptoms. Preserved LVEF may be shown by quantifying LVEF and LV volumes or dimensions through imaging techniques such as echocardiography, radionuclide ventriculography, contrast ventriculography, or cardiac magnetic resonance imaging. Among these, echocardiography is the most commonly used and has several advantages, including availability and the ability to provide information about LV wall thickness, filling patterns, cardiac anatomy, and valvular function.

Confirmation of increased LV wall stress by documenting elevation of B-type natriuretic peptide (BNP or NT-proBNP) may be useful when dyspnea may be due to noncardiac causes.[27] Increased BNP or NT-proBNP identifies patients with elevation of the LV end-diastolic pressure, but does not differentiate patients with preserved versus reduced LVEF.[28] HF with reduced LVEF tends to be associated with greater elevation of BNP than does HF with preserved EF, but BNP is above normal in both categories of HF.[29] There is some overlap with the normal range.[27,28,30]

Differential Diagnosis. LV hypertrophy (LVH), diagnosed by echocardiography or electrocardiography, is present in the most prevalent forms of HF with preserved LVEF. Doppler echocardiography frequently demonstrates abnormalities in LV diastolic filling.

Classification by the presence or absence of LVH has been based on the most common presentation of the disorders listed in Table 11.1. Restrictive myopathies may also be divided on the basis of myocardial disorders (noninfiltrative, infiltrative, or storage disorders) and endomyocardial disorders. In the presence of hypertrophy, the most prevalent form of HF with preserved LVEF is hypertensive-hypertrophic cardiomyopathy. The echocardiogram is more sensitive than the electrocardiogram for the diagnosis of LVH.[31] In addition to chronic systemic hypertension, LVH may be due to other causes of LV pressure overload, such as aortic stenosis or aortic coarctation.

Detecting LVH in the absence of an obvious cause for LV pressure overload supports the diagnosis of hypertrophic cardiomyopathy. This condition is usually regional (eg, septal, apical), but may be global. It is usually familial and genetically mediated.[32,33] Increased wall thickness by

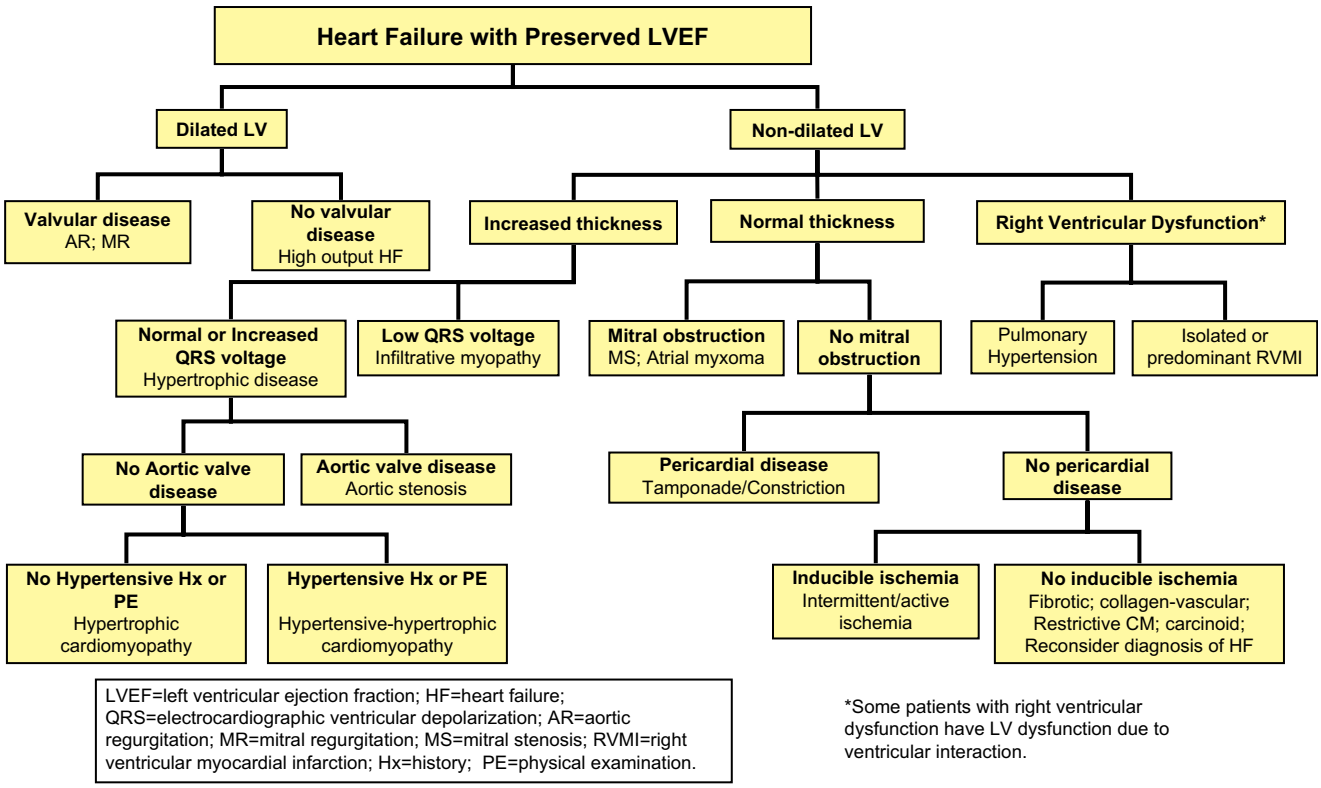

Fig. 11.1. Diagnostic Categories of HF with Preserved LVEF. (Figure courtesy of Marvin A. Konstam, MD, and Marvin W. Kronenberg, MD.)

Table 11.1. Common Diagnostic Groupings of Patients With HF and Preserved LVEF

Hypertensive hypertrophic heart disease
Familial hypertrophic cardiomyopathy
Ischemic HF
Valvular heart disease
Infiltrative (restrictive) cardiomyopathy
Pericardial constriction
High cardiac output state
RV dysfunction

echocardiography, coupled with low voltage on the electrocardiogram, strongly supports the diagnosis of an infiltrative cardiomyopathy. Among the most common infiltrative disorders is amyloidosis,[34] a disorder with a very poor prognosis.[35] In addition to low voltage, pseudo-infarction Q waves may be present. In the absence of hypertrophy, other infiltrative processes include sarcoidosis and Gaucher's disease. Sarcoid nodules in the myocardium rarely cause LV restrictive physiology, but pulmonary sarcoidosis may commonly cause pulmonary hypertension and right HF.[36]

Less common storage disorders include hemochromatosis. Rare disorders include Fabry disease and glycogen storage diseases. Hemochromatosis has several etiologies (familial, idiopathic, and acquired) and is manifested primarily as a dilated cardiomyopathy with reduced systolic performance, but occasionally as a non-dilated, restrictive cardiomyopathy.[37] Fabry disease may be associated initially with normal LV mass, but later with hypertrophy. Restrictive disorders are rare, and may be associated with either LVH or normal LV mass.[38] Endomyocardial disorders include endomyocardial fibrosis (usually in tropical climates); the hypereosinophilic syndrome, which may or may not be related to endomyocardial fibrosis; and carcinoid.

In the absence of aortic or mitral regurgitation, LV volume overload denotes a high cardiac output because of ventricular septal defect, patent ductus arteriosus or other arteriovenous shunt, chronic anemia, thyrotoxicosis, or chronic liver disease.

It is essential to clarify the diagnosis of pericardial constriction versus restrictive disorders. In the absence of substantial pericardial fluid, the diagnosis of pericardial disease may require invasive hemodynamics, computerized tomography, or magnetic resonance imaging to identify pericardial thickening.[39]

In contrast to the rarer forms of restrictive and infiltrative cardiomyopathies and to pericardial disease, ischemic heart disease with transient LV dysfunction is much more common. It is considered here and in other sections, particularly Section 13.

Right ventricular (RV) dysfunction is most commonly caused by LV dysfunction. In such conditions, there is pulmonary hypertension. Other causes of pulmonary hypertension, such as pulmonary thromboembolic disorders and intrinsic lung disease, may also precipitate RV dysfunction. Occasionally severe RV dysfunction may follow RV infarction. This is usually transient, but occasionally chronic RV dysfunction can cause LV dysfunction resulting from ventricular interaction, a situation in which RV pressure-volume overload may deform and displace the interventricular septum toward the LV, increasing LV diastolic pressure even as LV volume remains constant or decreases. Such conditions reduce LV compliance.

In summary, there is a broad differential diagnosis of HF with relatively preserved LVEF, and this must be kept in mind during the initial evaluation of such patients. After other disorders have been eliminated, hypertensive LVH is the most common cause of HF with relatively preserved LVEF. In analyzing HF in such patients, most emphasis has centered on LV diastolic dysfunction. Nevertheless, at the present state of knowledge, one must consider that hypertension with abnormal vascular-ventricular interaction may play a significant, causative role in the pathophysiology of the HF by severely increasing the LV diastolic pressure.

Recommendation

11.2 Evaluation for the possibility of ischemic heart disease and inducible myocardial ischemia is recommended in patients with HF and preserved LVEF (see Section 13). (Strength of Evidence = C)

Background

Section 13 provides a detailed approach to the diagnosis of ischemic heart disease in patients with HF by noninvasive stress imaging and by cardiac catheterization. Ischemic mitral regurgitation, acute or chronic, may aggravate HF with normal systolic performance.

Recommendations

11.3 Aggressive blood pressure monitoring is recommended in patients with HF and preserved LVEF (Section 14, Recommendation 14.1). (Strength of Recommendation = C)

11.4 Counseling on the use of a low-sodium diet (Section 6) is recommended for all patients with HF, including those with preserved LVEF. (Strength of Evidence = C)

11.5 Diuretic treatment is recommended in all patients with HF and clinical evidence of volume overload, including those with preserved LVEF. Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. (Strength of Evidence = C)

Background

In conditions with LVH, restrictive or constrictive physiology, a small decrease in intravascular volume may be

associated with significant reduction in LV preload, resulting in decreased cardiac output. Orthostatic changes and prerenal azotemia provide evidence for excessive preload reduction.[6] Acutely, in addition to diuretics, nitrates may have a role in diminishing pulmonary venous pressure and clinical congestion. Chronically, the effects may be similar, but one must be alert to the possibility of excess reduction in LV preload.

Recommendations

11.6 Angiotensin receptor blockers (ARBs) or ACE inhibitors should be considered in patients with HF and preserved LVEF.
- **ARBs (Strength of Evidence = B)**
- **ACE inhibitors (Strength of Evidence = C)**

11.7 ACE inhibitors should be considered in all patients with HF and preserved LVEF who have symptomatic atherosclerotic cardiovascular disease or diabetes and one additional risk factor. (Strength of Evidence = C)

In patients who meet these criteria but are intolerant to ACE inhibitors, ARBs should be considered. (Strength of Evidence = C)

Background

A trial of the ARB, candesartan, in patients with HF and preserved LVEF showed a trend toward reduction in the primary endpoint of cardiovascular death or hospitalization (unadjusted hazard ratio 0.89, CI 0.77–1.03, $P = .118$; adjusted hazard ratio 0.86, CI 0.74–1.00, $P = .051$).[40] At enrollment, approximately 20% of patients were receiving ACE inhibitors and 55% were receiving β-adrenergic blocking drugs. There was no subset analysis of the combination of these drugs in these specific patients, but the candesartan group showed a reduction in both hospitalizations and blood pressure.

Studies supporting the use of ACE inhibitors in patients with HF and preserved LVEF did not enroll patients with known HF. A secondary endpoint of the Heart Outcomes Prevention Evaluation (HOPE) trial was progression to HF in the following high risk patients: those older than age 55 years with either documented vascular disease or multiple cardiac risk factors, one of which was diabetes.[41] In this randomized study, 9297 patients received double-blind placebo or ramipril 10 mg daily and were followed for 4.5 years. The annual risk for development of HF was approximately 2.5%, which was reduced by 23% with the ACE inhibitor. The risk reduction was independent of multiple covariates. The presence of a subsequent MI during the study increased the risk of developing HF more than eightfold. Treatment with ramipril was associated with a 33% reduction in the development of HF in those with a baseline systolic pressure above the median of 139 mm Hg versus only 9% in those whose systolic blood pressure was below the median ($P = .024$).

The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) trial studied high dose ACE inhibitor therapy versus placebo in patients older than age 18 with documented coronary artery disease.[42] A mean follow-up of 4.2 years showed that perindopril reduced total mortality by 14% (from 6.9% to 6.1%), recurrent MI by 22% (6.2% to 4.8%), and hospital admission for HF by 39%. All findings were statistically significant, were consistent in all predefined subgroups, were independent of coexistent β-blocker therapy, and were seen in the setting of aggressive treatment of vascular disease, as determined by the high rate of antiplatelet (92%), antilipid (58%), and β-blocker (62%) usage.

Recommendation

11.8 β-blocker treatment is recommended in patients with HF and preserved LVEF who have:
- **Prior myocardial infarction (Strength of Evidence = A)**
- **Hypertension (see Section 14) (Strength of Evidence = B)**
- **Atrial fibrillation requiring control of ventricular rate (Strength of Evidence = B)**

Background

No large-scale studies to date have demonstrated improvement in clinical outcomes from β-blockers specifically in patients with HF and preserved LVEF. However, as with ACE inhibitors, large subsets of this population fall into one or another category for which β-blockers have either proven beneficial or are highly likely to achieve clinical benefit.

In failing hearts, rapid rates are associated with progressively reduced contractile force and increased resting tension. The increased resting tension is related to incomplete relaxation due to incomplete reuptake of calcium to storage sites in the sarcoplasmic reticulum.[9] In a noninvasive study of hypertrophic cardiomyopathy, β-adrenergic blocking drugs prolonged diastolic filling time, suggesting better LV filling.[43] In the presence of coronary artery disease, tachycardia is associated with a prompt increase in LV diastolic pressure.[44] Thus reducing the heart rate with β-adrenergic blocking drugs should be beneficial for LV filling and a reduction in the LV end-diastolic pressure. Furthermore, retrospective studies have suggested substantial benefit of adequate rate control on systolic function in patients with atrial fibrillation with a rapid ventricular response.[45,46] Patients with sinus tachycardia may benefit from a reduction in heart rate; however, because the tachycardia may reflect an inability to increase stroke volume, care must be taken in using β-blockade.

Recommendation

11.9 Calcium channel blockers should be considered in patients with:

- **Atrial fibrillation requiring control of ventricular rate in whom β-blockers have proven inadequate for this purpose because of intolerance. In these patients, diltiazem or verapamil should be considered. (Strength of Evidence = C)**
- **Symptom-limiting angina. (Strength of Evidence = A)**
- **Hypertension. Amlodipine should be considered. (Strength of Evidence = C)**

Background

Although controlled clinical trial data are lacking, several properties of the calcium channel blocking drugs (eg, verapamil, diltiazem), suggest they may benefit patients with HF and preserved LVEF. Beyond these circumstances, calcium channel blockers are not routinely recommended, despite small studies showing hemodynamic benefit in select patients.

An important effect of these drugs is slowing heart rate. This effect should enhance calcium removal from the myocyte and calcium reuptake in the sarcoplasmic reticulum.[6,9,12] This should lower end-diastolic pressure[12] and improve passive ventricular filling.[47] Improved passive ventricular filling is associated with long-term improvement in exercise capacity in patients with hypertrophic obstructive cardiomyopathy, a clinical condition which, like HF with preserved LVEF, may be associated with significant abnormalities in myocardial relaxation.[47] Numerous studies have shown benefit from verapamil or diltiazem in chronic stable angina pectoris, although the patients likely did not have HF with preserved EF.[48] Verapamil has been shown to acutely reduce arterial stiffness in elderly normal subjects. The improvement is due to improved arterioventricular interaction, and this reduction in arterial stiffness has been related to improved exercise performance.[49]

Recommendation

11.10 Measures to restore and maintain sinus rhythm should be considered in patients who have symptomatic atrial flutter-fibrillation, but this decision should be individualized. (Strength of Evidence = C)

Background

In patients with atrial fibrillation or flutter who remain symptomatic after adequate rate control, it is reasonable to consider restoration of sinus rhythm. Because studies comparing rhythm control to rate control in patients with atrial fibrillation have generally excluded symptomatic patients, there are no randomized clinical trials for guidance. Nevertheless, retrospective evaluation of studies of patients with HF suggest that in the subset of patients with atrial fibrillation both amiodarone and dofetilide increased conversion to sinus rhythm and maintenance of sinus rhythm.[50–52] These trials also demonstrated the safety of these drugs in patients with HF. Early experience suggests that catheter ablation of atrial fibrillation may also be considered in patients with HF to improve symptoms.[53]

References

1. Gaasch WH. Diagnosis and treatment of heart failure based on left ventricular systolic or diastolic dysfunction. JAMA 1994;271:1276–80.
2. Smith GL, Masoudi FA, Vaccarino V, Radford MJ, Krumholz HM. Outcomes in heart failure patients with preserved ejection fraction: mortality, readmission, and functional decline. J Am Coll Cardiol 2003;41:1510–8.
3. 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.
4. Konstam MA. "Systolic and diastolic dysfunction" in heart failure? Time for a new paradigm. J Card Fail 2003;9:1–3.
5. Zile MR. Heart failure with preserved ejection fraction: is this diastolic heart failure? J Am Coll Cardiol 2003;41:1519–22.
6. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part II: causal mechanisms and treatment. Circulation 2002;105:1503–8.
7. Pearlman ES, Weber KT, Janicki JS, Pietra GG, Fishman AP. Muscle fiber orientation and connective tissue content in the hypertrophied human heart. Lab Invest 1982;46:158–64.
8. Huysman JA, Vliegen HW, Van der Laarse A, Eulderink F. Changes in nonmyocyte tissue composition associated with pressure overload of hypertrophic human hearts. Pathol Res Pract 1989;184:577–81.
9. Gwathmey JK, Copelas L, MacKinnon R, Schoen FJ, Feldman MD, Grossman W, et al. Abnormal intracellular calcium handling in myocardium from patients with end-stage heart failure. Circ Res 1987;61:70–6.
10. Vasan RS, 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.
11. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, 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.
12. Grossman W. Diastolic dysfunction in congestive heart failure. N Engl J Med 1991;325:1557–64.
13. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation 2003;107:714–20.
14. Burkhoff D, Maurer MS, Packer M. Heart failure with a normal ejection fraction: is it really a disorder of diastolic function? Circulation 2003;107:656–8.
15. Hundley WG, Kitzman DW, Morgan TM, Hamilton CA, Darty SN, Stewart KP, et al. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. J Am Coll Cardiol 2001;38:796–802.
16. Kitzman DW, Higginbotham MB, 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.
17. How to diagnose diastolic heart failure. European Study Group on Diastolic Heart Failure. Eur Heart J 1998;19:990–1003.
18. Zile MR, Gaasch WH, Carroll JD, Feldman MD, Aurigemma GP, Schaer GL, 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.
19. Philbin EF, Rocco TA Jr, Lindenmuth NW, Ulrich K, Jenkins PL. Systolic versus diastolic heart failure in community practice: clinical

features, outcomes, and the use of angiotensin-converting enzyme inhibitors. Am J Med 2000;109:605–13.
20. Senni M, Redfield MM. Heart failure with preserved systolic function. A different natural history? J Am Coll Cardiol 2001;38:1277–82.
21. Chen HH, Lainchbury JG, Senni M, Bailey KR, Redfield MM. Diastolic heart failure in the community: clinical profile, natural history, therapy, and impact of proposed diagnostic criteria. J Card Fail 2002;8:279–87.
22. McDermott MM, Feinglass J, Lee PI, Mehta S, Schmitt B, Lefevre F, et al. Systolic function, readmission rates, and survival among consecutively hospitalized patients with congestive heart failure. Am Heart J 1997;134:728–36.
23. Devereux RB, Roman MJ, Liu JE, Welty TK, Lee ET, Rodeheffer R, et al. Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study. Am J Cardiol 2000;86:1090–6.
24. Jones RC, Francis GS, Lauer MS. Predictors of mortality in patients with heart failure and preserved systolic function in the Digitalis Investigation Group trial. J Am Coll Cardiol 2004;44:1025–9.
25. 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.
26. Choudhury L, Gheorghiade M, Bonow RO. Coronary artery disease in patients with heart failure and preserved systolic function. Am J Cardiol 2002;89:719–22.
27. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161–7.
28. Yamamoto K, Burnett JC Jr, Jougasaki M, Nishimura RA, Bailey KR, Saito Y, et al. Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. Hypertension 1996;28:988–94.
29. Maisel AS, McCord J, Nowak RM, Hollander JE, Wu AH, Duc P, et al. Bedside B-Type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. J Am Coll Cardiol 2003;41:2010–7.
30. Massie BM. Natriuretic peptide measurements for the diagnosis of ''nonsystolic'' heart failure: good news and bad. J Am Coll Cardiol 2003;41:2018–21.
31. Reichek N, Devereux RB. Left ventricular hypertrophy: relationship of anatomic, echocardiographic and electrocardiographic findings. Circulation 1981;63:1391–8.
32. Maron BJ. Hypertrophic cardiomyopathy. Lancet 1997;350:127–33.
33. Marian AJ, Roberts R. Recent advances in the molecular genetics of hypertrophic cardiomyopathy. Circulation 1995;92:1336–47.
34. Kyle RA, Greipp PR. Amyloidosis (AL). Clinical and laboratory features in 229 cases. Mayo Clin Proc 1983;58:665–83.
35. Kyle RA, Gertz MA, Greipp PR, Witzig TE, Lust JA, Lacy MQ, et al. Long-term survival (10 years or more) in 30 patients with primary amyloidosis. Blood 1999;93:1062–6.
36. Sharma OP, Maheshwari A, Thaker K. Myocardial sarcoidosis. Chest 1993;103(1):253–8.
37. Arnett EN, Nienhuis AW, Henry WL, Ferrans VJ, Redwood DR, Roberts WC. Massive myocardial hemosiderosis: a structure-function conference at the National Heart and Lung Institute. Am Heart J 1975; 90:777–87.
38. Angelini A, Calzolari V, Thiene G, Boffa GM, Valente M, Daliento L, et al. Morphologic spectrum of primary restrictive cardiomyopathy. Am J Cardiol 1997;80:1046–50.
39. Karia DH, Xing YQ, Kuvin JT, Nesser HJ, Pandian NG. Recent role of imaging in the diagnosis of pericardial disease. Curr Cardiol Rep 2002;4:33–40.
40. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, 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.
41. Arnold JM, Yusuf S, Young J, Mathew J, Johnstone D, Avezum A, et al. Prevention of Heart Failure in Patients in the Heart Outcomes Prevention Evaluation (HOPE) Study. Circulation 2003;107:1284–90.
42. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003;362:782–8.
43. Alvares RF, Goodwin JF. Non-invasive assessment of diastolic function in hypertrophic cardiomyopathy on and off beta adrenergic blocking drugs. Br Heart J 1982;48:204–12.
44. Aroesty JM, McKay RG, Heller GV, Royal HD, Als AV, Grossman W. Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischemia. Circulation 1985;71: 889–900.
45. Grogan M, Smith HC, Gersh BJ, Wood DL. Left ventricular dysfunction due to atrial fibrillation in patients initially believed to have idiopathic dilated cardiomyopathy. Am J Cardiol 1992;69:1570–3.
46. Redfield MM, Kay GN, Jenkins LS, Mianulli M, Jensen DN, Ellenbogen KA. Tachycardia-related cardiomyopathy: a common cause of ventricular dysfunction in patients with atrial fibrillation referred for atrioventricular ablation. Mayo Clin Proc 2000;75:790–5.
47. Bonow RO, Dilsizian V, Rosing DR, Maron BJ, Bacharach SL, Green MV. Verapamil-induced improvement in left ventricular diastolic filling and increased exercise tolerance in patients with hypertrophic cardiomyopathy: short- and long-term effects. Circulation 1985;72: 853–64.
48. Brodsky SJ, Cutler SS, Weiner DA, McCabe CH, Ryan TJ, Klein MD. Treatment of stable angina of effort with verapamil: a double-blind, placebo-controlled randomized crossover study. Circulation 1982;66: 569–74.
49. Chen CH, Nakayama M, Talbot M, Nevo E, Fetics B, Gerstenblith G, et al. Verapamil acutely reduces ventricular-vascular stiffening and improves aerobic exercise performance in elderly individuals. J Am Coll Cardiol 1999;33:1602–9.
50. Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the veterans affairs congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT). The Department of Veterans Affairs CHF-STAT Investigators. Circulation 1998;98: 2574–9.
51. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, Kober L, Sandoe E, Egstrup K, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. N Engl J Med 1999;341: 857–65.
52. Pedersen OD, Bagger H, Keller N, Marchant B, Kober L, Torp-Pedersen C. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a Danish investigations of arrhythmia and mortality on dofetilide (diamond) substudy. Circulation 2001;104:292–6.
53. Hsu LF, Jais P, Sanders P, Garrigue S, Hocini M, Sacher F, et al. Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med 2004;351:2373–83.