Diastolic Dysfunction and Diastolic Heart Failure: Mechanisms and Epidemiology

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Studies have demonstrated that diastolic dysfunction is frequently present in asymptomatic community-based individuals, especially in the elderly with hypertension, coronary artery disease, and diabetes. The presence of diastolic dysfunction is a predictor for the development of heart failure (HF) and confers a higher risk of mortality. These findings have raised the question of whether treating preclinical diastolic dysfunction will be helpful in preventing or delaying the onset of clinical HF and mortality, as has been proven with treatment of asymptomatic left ventricular systolic dysfunction. In addition, in some individuals, diastolic dysfunction in the presence of a normal ejection fraction is associated with exercise intolerance as well as symptomatic clinical HF, referred to as diastolic HF. Patients with diastolic HF, who are more often elderly women, have a significant mortality and morbidity burden compared with age-matched controls. Studies that further our understanding of mechanisms underlying diastolic dysfunction and diastolic HF will provide potential new targets for development of effective therapies for these conditions.

Introduction

As the elderly population in the United States continues to grow, there will continue to be an increase in the prevalence of heart failure (HF). The majority of studies in patients with HF have focused on the natural history, pathophysiology, and treatment of HF associated with left ventricular (LV) systolic dysfunction or systolic HF. However, it has been increasingly recognized that 30% to 50% of patients with HF have a normal or only slightly reduced ejection fraction (EF). In these patients, diastolic dysfunction is thought to be the major cause of HF; therefore, these patients are labeled as having diastolic HF. This review focuses on the concepts of diastolic dysfunction as well as the current knowledge about the pathophysiologic basis for the entity of HF with preserved EF or diastolic HF.

Diastolic Dysfunction: Pathophysiology

Diastolic dysfunction refers to abnormal mechanical properties of the myocardium and includes abnormal LV diastolic distensibility, impaired filling, and slow or delayed relaxation, regardless of whether the EF is normal or depressed and whether the patient is asymptomatic or symptomatic. Diastolic dysfunction implies that the myofibrils do not rapidly or completely return to their resting length; the ventricle cannot accept blood at low pressures, and ventricular filling is slow or incomplete unless atrial pressure rises [1]. Thus, there in an increased dependence on filling through atrial contraction, as well as higher atrial pressures to maintain filling or cardiac output [2].

Diastole encompasses the isovolumic relaxation and filling phases of the cardiac cycle and has active and passive components. Diastolic filling of the left ventricle is generally biphasic, with rapid filling in early diastole and active filling due to atrial contraction in late diastole. Early diastolic filling of the LV occurs when left atrial pressure exceeds LV pressure. This crossover pressure is determined by both left atrial pressure and the rate of LV relaxation. Late diastolic filling of the left ventricle coincides with atrial contraction during sinus rhythm. The late filling is determined by atrial contraction, left atrial pressure, and LV operating chamber stiffness, that is, the slope of the diastolic pressure-volume relation. Abnormalities in diastolic function can result from abnormalities in the different processes involved in diastole; clinically, the common manifestation of abnormal diastolic function is an elevated LV end-diastolic pressure and altered filling patterns, though the underlying causes may be varied.

Impaired relaxation delays the onset of early LV filling, thus decreasing the rate of ventricular filling at a fixed heart rate, and may change the shape of the instantaneous diastolic pressure-volume relationship during early diastole. Thus, with impaired relaxation, higher left atrial pressures could be required to achieve normal filling volumes, especially at fast heart rates [3,4]. Myocardial relaxation requires that the strongly bound actin-myosin filaments

return to a low-force–generating state. Therefore, anything that interferes with cross-bridge detachment or with preceding calcium removal from the cytosol can potentially delay relaxation. Impaired relaxation can occur as a consequence of pathologic LV hypertrophy such as that which occurs secondary to hypertension or aortic stenosis, with ischemia, aging, and hypothyroidism [5–7]. Global LV relaxation may also be slowed in the presence of regional mechanical asynchrony as seen after segmental myocardial infarction [7]. Cardiac afterload, especially related to arterial stiffness, also affects relaxation. An increase in load early in systole (such as hypertension) may prolong relaxation [6,8].

Diastolic dysfunction during the late filling phase of diastole can be a result of increased LV operating stiffness (diastolic stiffness). LV chamber stiffness is determined by both myocardial mass as well as myocardial composition. Aging as well as increased LV wall thickness relative to cavity size, such as with systemic hypertension or valvular aortic stenosis, will increase LV chamber stiffness; that is, decrease LV compliance [7]. In the myocardium, changes in both intracellular and extracellular structures can lead to changes in stiffness. For example, intracellularly, any change in titin isoforms or distribution or an increase in mictrotubule density and/or distribution can increase myocardial stiffness [9–11]. Extracellularly, changes in the fibrillar collagen, in its amount, degree of cross-linking, distribution, and ratio of collagen type I to type III, as may occur in hypertrophy, after infarction, and with aging, can lead to changes in myocardial stiffness [6]. In addition, infiltrative cardiomyopathies such as amyloidosis increase myocardial stiffness. It has been hypothesized that in addition to structural proteins such as titin and collagen, diastolic stiffness may be under active control. Active myocardial tone contributed to by calcium-myofilament interaction may potentially explain some acute episodes of HF that occur during periods of abrupt hypertension or anginal/ischemic episodes [6]. In addition, neurohormonal and cardiac endothelial activity also modulate ventricular stiffness and relaxation [1].

Measurement of Diastolic Function

Measurements of diastolic function can be divided into those that reflect the process of active relaxation and those that reflect passive stiffness. This division is in some ways arbitrary, because structures and processes that alter relaxation can also result in measurable abnormalities in stiffness. The gold standard of diastole assessment is using specialized invasive measurements with cardiac catheterization. These include quantification of the isovolumic relaxation by calculation of the peak instantaneous rate of LV pressure decline, peak (-) dP/dt, and the time constant of isovolumic LV pressure decline, τ, using micromanometer catheters, as well as assessment of chamber stiffness and myocardial stiffness by examination of pressure-volume relationships and examination of myocardial stress, strain, and strain-rate relationships during diastole [12]. The finding of elevated LV end-diastolic pressure is usually the common final result of any combination of diastolic abnormalities. Echocardiographic Doppler techniques are a widely available noninvasive tool to evaluate various diastolic parameters. However, it is important to note that most diastolic measurements with echocardiography are influenced by loading conditions and do not always reflect only intrinsic myocardial diastolic parameters. Details about the invasive and noninvasive measurement of diastolic dysfunction have recently been reviewed and are not further described here [12,13].

Prevalence and Prognostic Importance of Diastolic Dysfunction

Cardiovascular diseases such as hypertension, coronary artery disease (CAD), and cardiomyopathies often result in systolic and diastolic dysfunction. Nearly all patients with systolic dysfunction have some coexisting diastolic dysfunction, specifically impaired relaxation and decrease in ventricular compliance [14]. In addition, it has been increasingly recognized that patients with normal EFs can also have marked impairment in diastolic function which may or may not be associated with clinical evidence of HF [15].

A few studies have examined the prevalence of diastolic dysfunction in community-based cohorts as well as the predictive value of abnormal diastolic parameters for the development of HF and for mortality. In the second Strong Heart Study of 3008 population-based, middle-aged and elderly (45–74 years) American Indians, Bella *et al.* [16] followed patients over an average of 3 years to assess risk of all-cause and cardiac death associated with abnormal E/A ratio (E/A < 0.6 or E/A > 1.5) on mitral Doppler echocardiography. At baseline, 81% of participants had normal E/A ratios, 16% had E/A less than 0.6 and 3% had E/A ratio greater than 1.5. During follow-up, all-cause mortality was higher with E/A ratios under 0.6 and E/A ratios over 1.5 (12% and 13%, respectively, compared with 6% in patients with a normal E/A ratio) as was cardiac mortality (4.5% and 6.5% vs 1.6% in normal patients; $P < 0.001$ for both). After adjusting for age, sex, body mass index, blood pressure, ejection fraction, and other comorbidities, the relative risk of all-cause death with E/A ratio over 1.5 was 1.73 (95% CI 0.99–3.03; $P = 0.05$) and relative risk of cardiac death was 2.8 (95% CI 1.19–6.75; $P < 0.05$); however, E/A ratios under 0.6 did not remain an independent predictor of all-cause or cardiac mortality. Of note, E/A ratios over 1.5 were associated with an increased risk of mortality even in the absence of HF and in patients with preserved EF.

In the Cardiovascular Health Study of the elderly (aged ≥ 65 years), Aurigemma *et al.* [17] assessed the ability of echocardiographic indices of diastolic and systolic dysfunc-

tion to predict incident HF. Echocardiographic data were obtained in 2671 men and women without known CAD, HF, or atrial fibrillation at baseline. After a mean follow-up of 5.2 years, 6.4% of the cohort developed HF. Although 96% of these participants had normal or borderline EF at baseline, only 57% had normal or borderline EF at the time of the incident HF. In multivariate modeling, peak mitral Doppler E wave velocity independently predicted incident HF (relative risk 1.15 for each 0.1 m/sec increment; 95% CI 1.02–1.21),in addition to fractional shortening at the endocardium and at mid wall. In addition, abnormal mitral Doppler E/A ratios indicative of diastolic dysfunction (low E/A ratio < 0.7 or high E/A ratio > 1.5), were independently predictive of the development of clinical HF with a risk ratio of 1.88 (95% CI 1.33–2.68) for E/A ratio below 0.7 and risk ratio of 3.50 (95% CI 1.80–6.80) for E/A above 1.5 compared with the normal or intermediate ratio of E/A. The findings from these studies indicate that echocardiographic abnormalities including Doppler abnormalities of diastolic dysfunction may help to identify older adults predisposed to adverse outcomes. It has been shown that control of hypertension and regression of LVH may improve LV diastolic filling [18]; however, the impact of these interventions on the prevention or delay in development of HF or on survival remains to be elucidated.

Most recently, Redfield *et al.* [19••] examined the prevalence of preclinical diastolic dysfunction in 2042 randomly selected residents of Olmstead County, MN aged 45 years or older and also evaluated whether the presence of diastolic dysfunction was a predictor of all-cause mortality. In this study, participants had more in-depth echocardiographic evaluations of diastolic function compared with the two studies described above. Impaired diastolic dysfunction was based on mitral inflow Doppler (including change with Valsalva), Doppler tissue imaging (DTI) and pulmonary venous flow Doppler. The investigators found that diastolic dysfunction was common; overall 20.8% had mild, 6.6% had moderate, and 0.7% had severe diastolic dysfunction. In addition, 5.6% had moderate or severe diastolic dysfunction with a normal EF. The prevalence of diastolic dysfunction was found to increase with age, was more common in participants with cardiovascular disease, diabetes, or systolic dysfunction, and was equally prevalent in men and women. Figure 1 demonstrates the increasing prevalence of diastolic dysfunction with advancing age. The frequency of clinical HF increased dramatically with increasing severity of diastolic dysfunction, but in patients with moderate diastolic dysfunction, only 6% had clinically documented HF and even in patients with severe diastolic dysfunction, only about 50% had a diagnosis of HF. Patients with diastolic dysfunction without clinical HF could therefore be considered to have preclinical diastolic dysfunction. Furthermore, the presence of diastolic dysfunction was associated with a significant increase in mortality, with more severe diastolic dysfunction being associated with higher mortality (Fig. 2). Diastolic dysfunction remained an independent predictor of mortality even after adjusting for age, sex, and LVEF (hazard ration 8.31, 95% CI 3.0–23.1, for mild diastolic dysfunction vs normal diastolic function and hazard ratio 10.2, 95% CI 3.3–31.0, for moderate to severe diastolic dysfunction vs normal function) [19••]. Again, this study raises the issue of whether treating preclinical diastolic dysfunction will be helpful in preventing or delaying the onset of clinical HF or of mortality, as has been proven with the treatment of asymptomatic LV systolic dysfunction.

Symptomatic Diastolic Dysfunction and Diastolic Heart Failure

Nearly all patients with symptomatic systolic dysfunction have some coexisting diastolic dysfunction, specifically, impaired relaxation and decrease in ventricular compliance [14]. In addition, it has been increasingly recognized that patients with normal EFs can also have marked impairment in diastolic function which may be associated with no symptoms (isolated diastolic dysfunction), with only symptoms of exercise intolerance and dyspnea without clinical signs of HF on examination or with symptoms and signs of HF, referred to as diastolic HF [15].

Exercise Intolerance with Diastolic Dysfunction

Patients with diastolic dysfunction may exhibit exercise intolerance for several reasons. The ability to increase cardiac output during exercise without an abnormal elevation in left atrial pressure depends on the capacity of the left ventricle to enhance its diastolic filling. Patients with diastolic dysfunction have an abnormal increase in LV diastolic/left atrial pressure with exercise and may therefore have significant exercise intolerance even without clinical evidence of congestion at rest. The elevated LV diastolic and pulmonary venous pressure causes a reduction in lung compliance, which increases the work of breathing and evokes the symptom of dyspnea. In addition, the majority of patients with diastolic dysfunction have LV hypertrophy, high relative wall thickness, and a small end-diastolic volume, and therefore have a low stroke volume and depressed cardiac output during exercise [20]; a ventricle with a normal EF cannot produce a normal stroke volume if the chamber size is small. During exercise, patients with diastolic dysfunction have a very limited ability to increase end-diastolic volume and stroke volume via the Frank-Starling mechanism despite elevated LV filling pressure during exercise [1,21,22]. This limited preload reserve, especially if coupled with chronotropic incompetence that is seen with advancing age, limits the cardiac output during exercise, which may be associated with early skeletal muscle lactate formation and severe fatigue. Furthermore, elevated systolic arterial blood pressure increases LV afterload, thus slowing LV relaxation and reducing the extent of ejection. The ventricle operates at higher volumes (utilization of preload) and there is an increase in left atrial pressure in

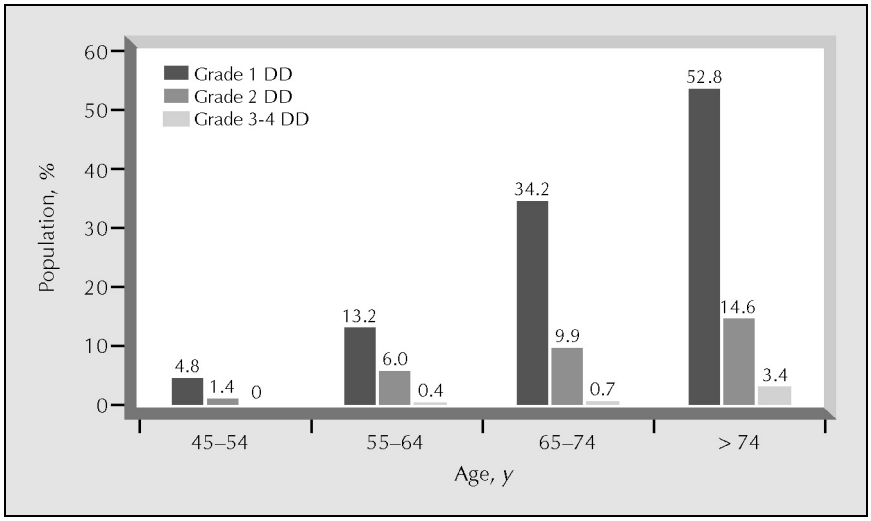

Figure 1. Prevalence of diastolic dysfunction (DD) according to age. Data obtained from 2042 randomly selected residents of Olmstead County, MN. Grade I DD = mild diastolic dysfunction, grade II = moderate diastolic dysfunction, grade III and IV = severe diastolic dysfunction. (*Data from* Redfield *et al.* [19••].)

response to increased systolic load. In the elderly and hypertensive patients (the group of patients that have diastolic dysfunction), the increase in systolic pressure with exercise is frequently exaggerated, with resultant worsening of diastolic dysfunction and a further elevation in LV filling pressure and thus wedge pressure during exercise. There are data to suggest that this exercise-induced increase in blood pressure is mediated by exercise-induced elevations of angiotensin II, which itself may also contribute to further impairment of LV relaxation. A reduction in angiotensin II levels during exercise using angiotensin receptor blockers may therefore be useful in decreasing exercise-induced hypertension and thereby improving exercise tolerance in patients with diastolic dysfunction [23,24].

Diastolic Heart Failure

A number of studies have shown that 30% to 50% of patients presenting with clinical signs and symptoms of HF have a normal or near normal LVEF [25,26•,27]. In the absence of significant valvular or pericardial abnormalities, the elevated LV diastolic and pulmonary venous pressures are predominantly a result of diastolic dysfunction. Zile *et al.* [15] evaluated diastolic function in 63 patients with a history of HF, normal EF, and at least borderline mild hypertrophy on echocardiogram. None of the patients in this study had evidence of CAD. Sixteen patients had measurement of LV diastolic pressure with fluid-filled catheters and 47 underwent combined echocardiographic-hemodynamic (micromanometer) studies. All patients were found to have an abnormality in at least one index of diastolic dysfunction. The investigators concluded that objective measurement of LV diastolic function just confirms the diagnosis, but is not required to make the diagnosis of diastolic HF. In the group of 47 patients with complete echocardiographic and hemodynamic-manometric studies, further analyses demonstrated significant abnormality of active relaxation (including longer time constant of isovolumic-pressure decline or τ) and an increase in LV chamber stiffness (resulting in a shift of the diastolic LV pressure-volume curve up and to the left) compared with normal controls [28].

These studies confirmed that patients with HF and normal EF have abnormalities in the diastolic properties of the heart (abnormal relaxation and increased passive stiffness) that can explain the hemodynamic abnormalities evidenced clinically as HF.

In patients with diastolic dysfunction, other factors may also contribute to the development of clinical HF. For example, increased arterial stiffness (which increases with increasing age and with hypertension), may exacerbate the underlying LV diastolic abnormalities [15,29]. Kawaguchi *et al.* [30] demonstrated an increase in both arterial and LV systolic stiffness in patients with HF with a normal EF. They hypothesized that the combined ventricular-vascular stiffening could contribute to the development of HF in several ways. First, increased basal LV systolic stiffness can blunt contractile reserve in response to positive inotropy. Second, the increased ventricular-arterial stiffening can increase systolic blood pressure sensitivity to circulating blood volume and may trigger rapid-onset pulmonary edema. The increased combined stiffness predicts pressure-load dependence, perhaps favoring blood redistribution into more compliant pulmonary veins. Third, the combined stiffening may increase cardiac energy costs to provide blood flow that may limit reserve in those with concomitant coronary artery or other heart disease. Lastly, the increased ventricular-arterial stiffening along with the resulting rise in systolic pressure during stress can lead to further worsening in diastolic function with delayed relaxation, impaired filling, and elevation of diastolic pressures [30]. Neurohormonally mediated increases in venous tone and systemic arterial pressure may also lead to a shifting of blood to the central circulation. The increase in ventricular volume could be associated with a large increase in LV diastolic pressure and HF. Furthermore, even though LVEF is normal, studies have shown that LV systolic function may not be completely normal in patients with diastolic

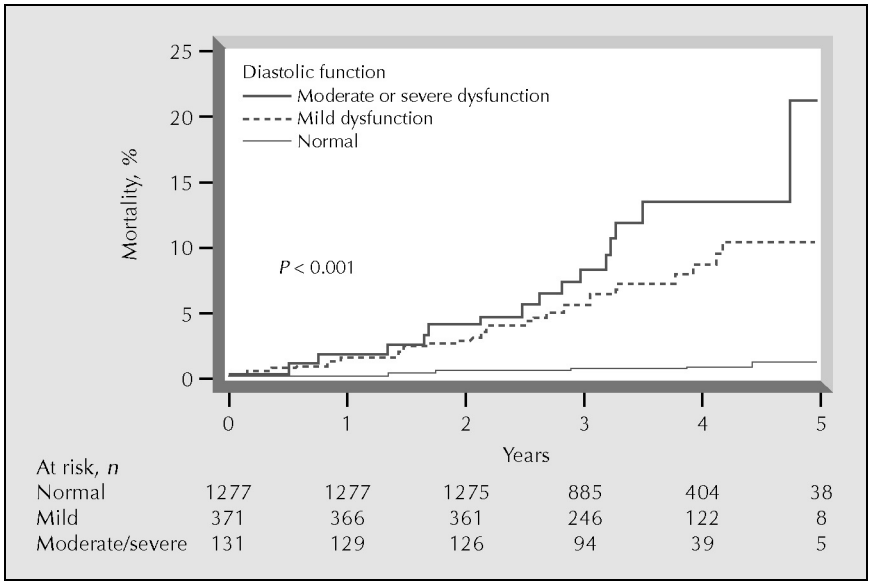

Figure 2. Prognostic implications of severity of diastolic dysfunction. Kaplan-Meier mortality curves for residents of Olmstead County, MN with normal diastolic function, mild diastolic dysfunction, or moderate to severe diastolic dysfunction. (*From* Redfield *et al.* [19••]; with permission.)

HF, and early contractile dysfunction may be another contributor to the development of HF [31,32]. In patients with underlying diastolic dysfunction, common clinical precipitants of HF can include uncontrolled hypertension, atrial fibrillation, nonadherence with medical regimen or with a low-salt diet, myocardial ischemia, anemia, renal insufficiency, or the use of nonsteroidal anti-inflammatory drugs.

Epidemiology of Diastolic Heart Failure

Though various definitions of diastolic HF have been proposed [33,34], epidemiologically, diastolic HF has been defined by clinical signs and symptoms of HF along with a preserved EF. The cutoff for EF has, however, varied between studies with an EF greater than or equal to 40% to 55% being considered as preserved EF [25,26•,27]. It may be better to restrict the term diastolic HF to patients with an EF greater than or equal to 50%, because patients with an EF between 40% and 50% may have significant systolic dysfunction too. Of note, isolated diastolic HF is considered present only in the absence of significant valvular and pericardial abnormalities, restrictive or infiltrative heart disease as well as the absence of other comorbidities such as severe anemia, pulmonary disease, obesity and hyperthyroidism or hypothyroidism that may contribute to the presentation of HF.

The epidemiology of diastolic HF has been reviewed in a number of recent publications [26•,27]. In recent community-based studies, diastolic HF has constituted 40% to 50% of all cases of HF [19••,35–37]. Diastolic HF is more prevalent in the elderly and in women. Patients with diastolic HF are more likely to have hypertension and associated LV hypertrophy and less likely to have CAD compared with patients with systolic HF. Although the risk of mortality associated with diastolic HF is lower than that for systolic HF, mortality still significantly exceeds that for age-matched controls [12]. In contrast, morbidity as measured by hospitalization and readmission for diastolic HF is substantial and comparable to that of patients with systolic HF. To date, only one large randomized clinical trial demonstrating no beneficial effect on mortality, but a modest 11% reduction in HF hospitalizations, with the angiotensin receptor blocker, candesartan, has been completed in this patient population [38]. Because of the significant morbidity and mortality burden associated with the condition, the results of ongoing trials evaluating potential therapy for diastolic HF are eagerly awaited.

Conclusions

The presence of diastolic dysfunction is a predictor for the development of HF and confers a higher risk of mortality, raising the question of whether treating preclinical diastolic dysfunction will be helpful in preventing or delaying the onset of clinical HF and mortality, as has been proven with treatment of asymptomatic LV systolic dysfunction. In addition, diastolic HF is also associated with a significant mortality and morbidity burden. Studies that further our understanding of mechanisms underlying diastolic dysfunction and diastolic HF will provide potential new targets for development of effective therapies for these conditions.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Gaasch WH, Zile MR: **Left ventricular diastolic dysfunction and diastolic heart failure.** *Annu Rev Med* 2004, **55:**373–394.
2. Redfield MM: **Understanding "diastolic" heart failure.** *N Engl J Med* 2004, **350:**1930–1931.
3. Hay I, Rich J, Ferber P, *et al.*: **The role of impaired myocardial relaxation in the production of elevated left ventricular filling pressure.** *Am J Physiol Heart Circ Physiol* 2005, **288:**H1203–H1208.
4. Maurer MS, Spevack D, Burkhoff D, Kronzon I: **Diastolic dysfunction: can it be diagnosed by Doppler echocardiography?** *J Am Coll Cardiol* 2004, **44:**1543–1549.
5. Angeja BG, Grossman W: **Evaluation and management of diastolic heart failure.** *Circulation* 2003, **107:**659–663.
6. Kass DA, Bronzwaer JG, Paulus WJ: **What mechanisms underlie diastolic dysfunction in heart failure?** *Circ Res* 2004, **94:**1533–1542.
7. Litwin SE, Grossman W: **Diastolic dysfunction as a cause of heart failure.** *J Am Coll Cardiol* 1993, **22:**49A–55A.
8. Zile MR, Gaasch WH: **Mechanical loads and the isovolumic and filling indices of left ventricular relaxation.** *Prog Cardiovasc Dis* 1990, **32:**333–346.
9. Bell SP, Nyland L, Tischler MD, *et al.*: **Alterations in the determinants of diastolic suction during pacing tachycardia.** *Circ Res* 2000, **87:**235–240.
10. Cazorla O, Freiburg A, Helmes M, *et al.*: **Differential expression of cardiac titin isoforms and modulation of cellular stiffness.** *Circ Res* 2000, **86:**59–67.
11. Zile MR, Richardson K, Cowles MK, *et al.*: **Constitutive properties of adult mammalian cardiac muscle cells.** *Circulation* 1998, **98:**567–579.
12. 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:**1387–1393.
13. • Ommen SR, Nishimura RA: **A clinical approach to the assessment of left ventricular diastolic function by Doppler echocardiography: update 2003.** *Heart* 2003, **89:**18iii–23iii.

A review of echocardiographic modalities utilized for the measurement of diastolic dysfunction.

14. Young BA, Pugh JA, Maynard C, Reiber G: **Diabetes and renal disease in veterans.** *Diabetes Care* 2004, **27:**B45–B49.
15. 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:**779–782.
16. Bella JN, Palmieri V, Roman MJ, *et al.*: **Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the Strong Heart Study.** *Circulation* 2002, **105:**1928–1933.
17. Aurigemma GP, Gottdiener JS, Shemanski L, *et al.*: **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:**1042–1048.
18. Wachtell K, Bella JN, Rokkedal J, *et al.*: **Change in diastolic left ventricular filling after one year of antihypertensive treatment: The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study.** *Circulation* 2002, **105:**1071–1076.
19. •• Redfield MM, Jacobsen SJ, Burnett JC, Jr., *et al.*: **Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic.** *JAMA* 2003, **289:**194–202.

Cross-sectional study of the prevalence and prognostic implication of diastolic and systolic dysfunction in the community.

20. Aurigemma GP, Gaasch WH, McLaughlin M, *et al.*: **Reduced left ventricular systolic pump performance and depressed myocardial contractile function in patients > 65 years of age with normal ejection fraction and a high relative wall thickness.** *Am J Cardiol* 1995, **76:**702–705.
21. Kitzman DW, Higginbotham MB, Cobb FR, *et al.*: **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:**1065–1072.
22. Kitzman DW: **Diastolic heart failure in the elderly.** *Heart Fail Rev* 2002, **7:**17–27.
23. Little WC, Kitzman DW, Cheng CP: **Diastolic dysfunction as a cause of exercise intolerance.** *Heart Fail Rev* 2000, **5:**301–306.
24. Warner JG, Jr., Metzger DC, Kitzman DW, *et al.*: **Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise.** *J Am Coll Cardiol* 1999, **33:**1567–1572.
25. Senni M, Redfield MM: **Heart failure with preserved systolic function.** *A different natural history? J Am Coll Cardiol* 2001, **38:**1277–1282.
26. • Hogg K, Swedberg K, McMurray J: **Heart failure with preserved left ventricular systolic function, epidemiology, clinical characteristics, and prognosis.** *J Am Coll Cardiol* 2004, **43:**317–327.

Recent review of the epidemiology of HF with preserved EF.

27. Thomas MD, Fox KF, Coats AJ, Sutton GC: **The epidemiological enigma of heart failure with preserved systolic function.** *Eur J Heart Fail* 2004, **6:**125–136.
28. 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:**1953–1959.
29. Avolio AP, Deng FQ, Li WQ, *et al.*: **Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China.** *Circulation* 1985, **71:**202–210.
30. 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:**714–720.
31. Yu CM, Lin H, Yang H, *et al.*: **Progression of systolic abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction.** *Circulation* 2002, **105:**1195–1201.
32. Bruch C, Gradaus R, Gunia S, *et al.*: **Doppler tissue analysis of mitral annular velocities: evidence for systolic abnormalities in patients with diastolic heart failure.** *J Am Soc Echocardiogr* 2003, **16:**1031–1036.
33. Vasan RS, Levy D: **Defining diastolic heart failure: a call for standardized diagnostic criteria.** *Circulation* 2000, **101:**2118–2121.
34. European Study Group on Diastolic Heart Failure: **How to diagnose diastolic heart failure.** *Eur Heart J* 1998, **19:**990–1003.
35. Kitzman DW, Gardin JM, Gottdiener JS, *et al.*: **Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study.** *Am J Cardiol* 2001, **87:**413–419.
36. Devereux RB, Roman MJ, Liu JE, *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:**1090–1096.
37. Vasan RS, Larson MG, Benjamin EJ, *et al.*: **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:**1948–1955.
38. 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:**777–781.