Diastolic heart failure

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Diastolic heart failure is characterized by the presence of heart failure with preserved left ventricular ejection fraction (LVEF): documentation of diastolic dysfunction, usually by Doppler echocardiography, is strongly recommended. Heart failure with preserved LVEF is a heterogeneous and common condition, especially in the elderly, among whom represents up to 50% of all heart failure patients. Mortality is generally lower than in patients with heart failure and low LVEF, and depends on etiology, patient conditions, and comorbidities. Anyway, morbidity is very high. So far, treatment of diastolic heart failure is empirical, and is aimed to maintain cardiac output, reduce filling pressure, control heart rate and rhythm, and antagonize disease progression with diuretics, inhibitors of the renin-angiotensin-aldosterone system, nitrates, and digoxin.

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Only in the last 20-30 years attention has been given to diastolic dysfunction and to the consequent diastolic heart failure (DHF) syndrome as a specific entity.

Heart failure is a clinical syndrome characterized by typical symptoms and signs related to volume overload and/or reduced cardiac output[1,2]. DHF is defined as heart failure occurring in patients with normal or preserved left ventricular ejection fraction (LVEF), and with documentation of abnormalities in diastolic function[3].

The cut-off value for definition of "normal" or "preserved" LVEF (from 40 to 50%)[4-6] varies among authors and groups, resulting in differences in patient characterization, that generate confusion in interpreting the data regarding epidemiology, treatment, and outcome. Moreover, the demonstration of diastolic dysfunction may be difficult in the clinical setting. Abnormalities in cardiac relaxation and/or myocardial stiffness can be studied non-invasively with echocardiography[3,7,8] and invasively with left heart catheterization[9]. Both methods are time-consuming and require skilled personnel that is not always widely available. Anyway, some degree of diastolic dysfunction is almost invariably present in patients with clinical heart failure and preserved LVEF, making its direct demonstration probably pleonastic[10]. In any case, the diagnosis of DHF cannot be made on the basis of history, physical examination, ECG or chest radiography alone; it requires at least the documentation of a preserved LVEF. Since normal LVEF is ≥ 50%, in the authors' opinion an appropriate and more precise clinical definition of DHF could be "heart failure syndrome occurring in patients with LVEF ≥ 50%".

Similarly to heart failure with systolic dysfunction, DHF is a heterogeneous condition that may result from a variety of etiologies and mechanisms, whose individual role may be not always easy to identify. The same causes (e.g. ischemic or hypertensive heart disease) can determine diastolic dysfunction alone, or diastolic plus systolic dysfunction. Some of the causes of diastolic dysfunction and DHF are listed in table I. In some cases, diastolic dysfunction may precede systolic dysfunction, and preclinical diastolic dysfunction may precede the occurrence of heart failure syndrome[4,11].

The prevalence of classic symptoms and signs of heart failure is similar in patients with reduced or normal LVEF[1,12] (Fig. 1).

Table I. Main causes of diastolic heart failure.

Ageing
Hypertension
Diabetes
Obesity
Ischemic heart disease
Myocardial hypertrophy (hypertrophic cardiomyopathy, aortic stenosis, etc.)
Infiltrative disorders (amyloidosis, etc.)
Restrictive cardiomyopathy (eosinophilic cardiomyopathy, etc.)

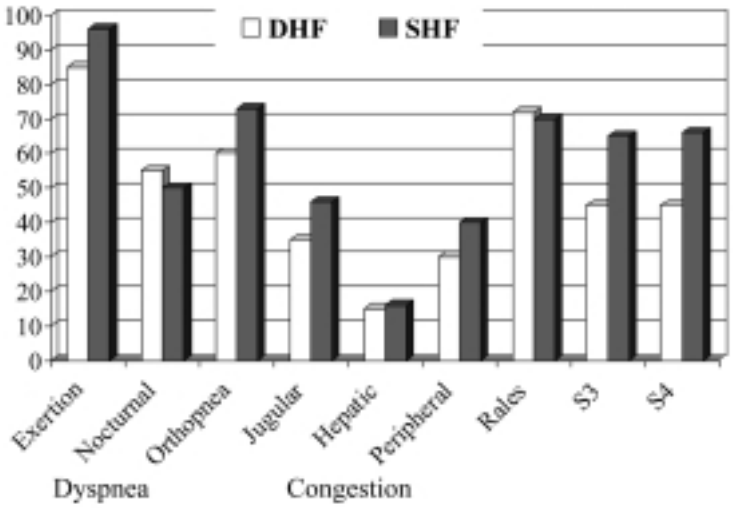

Figure 1. *Symptoms and signs in diastolic (DHF) and systolic (SHF) heart failure. The figure indicates the prevalence of symptoms and signs of heart failure. S3 = third heart sound; S4 = fourth heart sound.*

Epidemiology of diastolic dysfunction and diastolic heart failure

DHF causes significant morbidity and mortality; it accounts for up to 34-50% of the incident and hospitalized cases of heart failure, and its prevalence is higher in the elderly population[4,5,13-18].

As observed regarding asymptomatic systolic left ventricular dysfunction, diastolic dysfunction may be present in the community as a preclinical condition. A recent publication from the MONICA study[11] reports the data regarding 1274 patients aged 25-75 years, without clinical heart failure or systolic dysfunction. According to echocardiographic criteria, patients were classified as having normal diastolic function, diastolic abnormalities, or diastolic dysfunction. The following conditions were recognized as risk factors for diastolic abnormalities and dysfunction: age > 65 years, hypertension, diabetes, obesity, history of myocardial infarction, and left ventricular hypertrophy. The probability of having diastolic abnormalities and dysfunction increased according to the number of risk factors. Another study evaluated the incidence of clinical heart failure in the long-term follow-up of 2671 elderly subjects (≥ 65 years), with respect to their clinical and echocardiographic characteristics at baseline[4]. Patients with a history of myocardial infarction and patients with heart failure or atrial fibrillation were excluded. During follow-up, 170 patients (6.4%) developed heart failure, at an average time interval of 5.4 years. Clinical variables associated with incident heart failure were age, male gender, hypertension, diabetes, and obesity. Among a myriad of echocardiographic variables associated with incident heart failure during follow-up, there were left ventricular and left atrial diameter (high), wall thickness (high), and fractional shortening (low). Some variables related to diastolic function behaved in a non-linear fashion: the incidence of heart failure was the lowest (4.8%) in subjects with intermediate values of the E/A ratio, intermediate (11%) in those with the highest E/A ratio values (> 1.5), and the highest (14.5%) in those with the lowest E/A ratio values (< 0.7). In other words, both a preclinical restrictive pattern (high E/A ratio) and an accentuated abnormal relaxation pattern (low E/A ratio) were associated with an increased risk for developing heart failure. At multivariable analysis, fractional shortening (low), peak E velocity (high) and an E/A ratio < 0.7 or > 1.5 were independent predictors for incident heart failure. At the time of the appearance of heart failure syndrome, LVEF was still preserved (≥ 45%) in only 37% of the patients with normal LVEF at baseline, reflecting the progression from diastolic dysfunction to heart failure with or without systolic dysfunction during follow-up. A third study surveyed 2042 subjects aged ≥ 45 years, with or without clinically diagnosed heart failure, in whom clinical and echocardiographic data were collected[6]. The average follow-up was 3.5 years. Both systolic and diastolic dysfunction were higher with increasing age. Diastolic dysfunction was classified as mild, moderate or severe according to a constellation of echo-Doppler parameters[19,20], which are summarized in table II. At least mild diastolic dysfunction was demonstrated in 80% of the patients with LVEF ≤ 50%, who were 6.4% of the entire population. Isolated diastolic dysfunction was observed in 5.6% of the subjects with normal LVEF (> 50%). A clinical diagnosis of congestive heart failure had been made in 20% of the patients with LVEF ≤ 50% vs 2.4 and 5.1% of those with mild and moderate diastolic dysfunction respectively. When only significant systolic dysfunction (LVEF ≤ 40%) or diastolic dysfunction were considered, the proportion of patients with clinical heart failure was similar (45 and 46.2%). Moderate-to-severe diastolic dysfunction was an independent predictor of all-cause mortality during follow-up after correction for age, gender, and LVEF.

Table II. Echocardiographic parameters for the evaluation of diastolic dysfunction.

	Normal	Mild	Moderate	Severe	
				Reversible restrictive	Fixed restrictive
Mitral					
E/A ratio	> 0.75, < 1.5	≤ 0.75	> 0.75, < 1.5	> 1.5	> 1.5
DT (ms)	> 140	> 140	> 140	< 140	< 140
ΔE/A-Valsalva maneuver	< 0.5	≥ 0.5	≥ 0.5	≥ 0.5	< 0.5
TDI mitral annulus	E/e' < 10	E/e' < 10	E/e' ≥ 10	E/e' ≥ 10	E/e' ≥ 10
PV flow					
S/D ratio	S ≥ D	S > D	S < D or	S < D or	S < D or
AR duration	< Adur	< Adur	> Adur+30 ms	> Adur+30 ms	> Adur+30 ms
Interpretation					
LV relaxation	Normal	Impaired	Impaired	Impaired	Impaired
LV compliance	Normal	Normal/↓	↓↓	↓↓↓	↓↓↓↓
LA pressure	Normal	Normal	↑↑	↑↑↑	↑↑↑↑

A = mitral flow, atrial contraction velocity; AR = pulmonary vein reversal flow (to the left atrium); D = diastolic forward flow; DT = deceleration time; TDI = tissue Doppler imaging; dur = duration; E = mitral flow, peak early filling velocity; e' = velocity of the mitral annulus at early diastole; LA = left atrial; LV = left ventricular; PV = pulmonary venous; S = systolic forward flow. From Redfield et al.[6], modified.

Pathophysiology and mechanisms of diastolic dysfunction and diastolic heart failure

The mechanisms that may lead to clinical heart failure despite normal or nearly normal systolic function, or at least normal or only mildly depressed LVEF, are not always easy to interpret. In fact, some authors warn against the risk of overdiagnosis or misdiagnosis of DHF in all the patients with symptoms possibly related to heart failure and normal LVEF, suggesting that the mere presence of echocardiographic markers of diastolic dysfunction do not exclude the relevance of other etiologies for dyspnea symptoms, such as obesity or pulmonary disease[21].

It has also been inferred that transient systolic dysfunction *during* an acute congestive heart failure episode may occur in patients with normal or nearly normal LVEF *after* its resolution. This does not seem to be the case, at least in a small experience reported by Gandhi et al.[22], who studied with echocardiography 38 patients; 18 had a normal LVEF both during and after pulmonary edema (average 58 and 61% respectively). Patients with pulmonary edema and normal LVEF had lower left ventricular volumes (both end-diastolic and end-systolic) than patients with reduced LVEF, both during and after the acute episode; on average, they had a lower stroke volume only during – and not after – pulmonary edema. This small study reminds that the major feature of DHF may be a reduced left ventricular volume resulting in increased filling pressure, and a reduced stroke volume resulting in reduced cardiac output. A normal LVEF *per se* does not preclude the occurrence of the two main hemodynamic abnormalities of heart failure, that are increased filling pressure and reduced cardiac output. This issue is thoroughly discussed in a recent and intriguing paper[23].

Moreover, a normal LVEF does not automatically implies normal systolic function. Evaluating regional myocardial velocity during systole, abnormalities in systolic function can be found in more than 50% of the patients classified as having "DHF" on the basis of normal LVEF[24].

In any case, alterations in loading conditions and/or in myocardial relaxation and stiffness may justify the occurrence of heart failure with preserved LVEF. Diastolic dysfunction is characterized by delayed and/or slowed and/or altered diastole, resulting in an abnormal increase of left ventricular filling pressure, that may be corrected at the expense of a reduced left ventricular end-diastolic volume and stroke volume[1]. Factors leading to diastolic dysfunction can be classified as extramyocardial or myocardial. Among extramyocardial factors, besides acute changes in pre- and afterload (e.g. volume overload, hypertensive crisis), it must be remembered the role of arterial stiffness, that may contribute to increase cardiac energy expenditure at a given blood pressure[25].

Both cellular and extracellular mechanisms are involved in determining myocardial alterations that result in diastolic dysfunction[2]. Regarding cellular mechanisms, the main process is calcium-dependent dissociation of contractile proteins. Adenosine triphosphate (ATP) hydrolysis is required for myosin detachment from actin, calcium dissociation from troponin C, and calcium reuptake by the sarcoplasmic reticulum. Calcium handling depends on sarcolemmal integrity, on functioning of the sodium-calcium exchange pump, and on availability of sarcoplasmic reticulum Ca^{2+} ATPase, which in turn depends on the phosphorylation state of regulatory proteins such as phospholamban, calmodulin, and calsequestrin. Thus, relaxation is not a passive process, but requires energy expenditure. An

increase of cytosolic diastolic calcium concentration results in altered relaxation and increased myocardial stiffness. The cardiomyocyte cytoskeleton is also involved in conditioning viscoelastic stiffness[26,27].

Extracellular mechanisms seem to involve mostly the turnover of fibrillar proteins. In conditions associated with diastolic dysfunction, such as hypertension and hypertrophy induced by aortic valve disease, alterations in collagen (amount, distribution, and ratio between type I and III) have been demonstrated, which could be corrected with treatment[28-31]. Collagen synthesis is regulated by load, neurohormonal activation, and growth factors; its degradation is regulated by proteolytic enzymes, of which the best known are the matrix metalloproteinases.

Activation of the renin-angiotensin-aldosterone system and of the sympathetic system is known to be involved in hypertrophy, and is obviously also involved in diastolic dysfunction. Chronic activation of the renin-angiotensin-aldosterone system also facilitates fibrosis mediated by an increase of extracellular collagen, that can be at least partly corrected by pharmacological antagonists. Endothelium-dependent nitric oxide release at the cardiac level peaks during relaxation and filling, and plays an important role in myocardial distensibility[32]; therapeutic agents that increase myocardial nitric oxide delivery, such as ACE-inhibitors, may be useful in treating DHF[33].

All these different mechanisms are more or less relevant in individual cases according to etiology and severity. For example, hypertensive heart disease with significant hypertrophy may be associated with cardiac alterations involving both cardiomyocytes and the extracellular matrix, and also with increased afterload due to arterial stiffness. On the other side, cardiac amyloidosis is primarily characterized by alterations in the extracellular matrix due to amyloid fibril deposition.

Diagnosis and prognosis of diastolic dysfunction and diastolic heart failure

Ideally, three main criteria should be fulfilled for diagnosing DHF:

• clinical heart failure syndrome, as evaluated with the Framingham criteria[14];

• preserved LVEF, commonly evaluated by echocardiography. As pointed out above, different cut-off values have been used for defining a normal/preserved LVEF, ranging from 40 to 50%. Thus, patient populations included in studies are non-homogeneous, making more difficult their comparison and the interpretation of the results;

• demonstration of left ventricular diastolic dysfunction by means of echocardiography or cardiac catheterization; the latter is much less used due to costs and invasivity.

Many recommendations regarding the echocardiographic assessment of diastolic function and the diagnosis of diastolic dysfunction have been published[3,7,8,19,34]. The Doppler indices derived from mitral flow and pulmonary venous flow, and tissue Doppler imaging can be used for diagnostic purposes, for estimation of prognosis, and for evaluation of the effects of therapies. The criteria for evaluation and interpretation of these indices are listed in table II.

Echocardiographic evaluation of diastolic function requires time and specific skills, and has not been integrated into routine clinical practice in most of the echocardiography laboratories. Anyway, complex measurement could not be needed in patients with a definite clinical diagnosis of heart failure and normal LVEF, since diastolic dysfunction is invariably present[10]. Variables related to diastolic function depend not only on chronic conditions, but also on transient changes in pre- and/or afterload; moreover, they do not necessarily behave in a linear fashion[6], making their interpretation more difficult. Tissue Doppler imaging has been suggested to be less influenced by preload; it is possible that this technique could provide a more objective evaluation of left ventricular relaxation[8]. So far, accurate evaluation of diastolic function has been used mostly for clinical research, prognostic evaluation, and preclinical identification of dysfunction in epidemiologic studies.

The prognostic implications of preclinical isolated diastolic dysfunction have been discussed previously. DHF is probably associated with a lower mortality than systolic heart failure, at least in ambulatory patients; in the hospitalized population, this issue is more controversial[13-16,18]. The different criteria for diagnosis (cut-off point for defining "preserved LVEF") and the age of the study patients may contribute to the differences observed in prognostic estimates. The observed annual mortality rate in DHF is about 5-8 vs 10-15% in heart failure with low LVEF. In any case, morbidity and recurrent hospitalizations are quite high in DHF, up to 50% at 1 year in patients aged > 50 years. Many factors besides the severity of diastolic dysfunction may influence prognosis. In a prospective study of 2498 patients with heart failure and LVEF > 40%, whose mean age was 63 years, O'Connor et al.[5] observed a 28% 5-year mortality; risk factors for death were age (high), NYHA functional class IV symptoms, LVEF (low), an index of severity of coronary artery disease (high), diabetes, peripheral vascular disease, and non-white ethnic group. Age, etiology and comorbidities are obviously important in conditioning patient outcome. Another important issue is whether prognosis is evaluated in ambulatory patients or during hospitalization. A recent paper analyzed prognostic factors in 400 patients hospitalized for congestive heart failure according to age (< 75 vs ≥ 75 years) and LVEF (< 40 vs ≥ 40%)[35]. After a mean follow-up of 25 months, mortality was 29 vs 38% in patients aged < 75

years with preserved vs reduced LVEF (p = NS), and 36 vs 54% in patients aged ≥ 75 years with preserved vs reduced LVEF (p = 0.03). The latter finding is somehow in contrast with previous reports of similar mortality in systolic heart failure and DHF in patients > 70 years[14]. Predictors of prognosis were different between the four groups. In particular, in patients with preserved LVEF, the independent predictors of mortality were male gender, use of calcium channel blockers, and furosemide dose > 40 mg in younger patients, and only blood urea nitrogen in older patients. Although the patient number in each group was relatively small, and the interpretation of the role of therapies in observational studies is always difficult, this paper suggests that prognostic indices derived from large patient cohorts that include all the heart failure patients, irrespective of age and pathophysiology, may be inaccurate for predicting the individual patient outcome.

Treatment of diastolic heart failure

In comparison with heart failure with reduced LVEF, much less evidence-based guidelines are available for the treatment of DHF. The main objectives of therapy are basically the same for all the patients with heart failure: to reduce symptoms and to reverse or slow the progression of underlying disease. In the acute phase of congestive heart failure, hemodynamic targets are to maintain or increase cardiac output and to reduce filling pressure.

Since hypertension may be associated with preclinical diastolic dysfunction, aggressive treatment of hypertension according to current guidelines[36] is an important measure for preventing or delaying the occurrence of heart failure. In patients with diastolic dysfunction and a marked increase in systolic blood pressure during exercise, angiotensin II receptor blockers have been shown to blunt the hypertensive response to exercise, to increase exercise tolerance, and to improve quality of life[37].

When treating patients with decompensated DHF, it is important to keep in mind the specific pathophysiology of the disease. Pulmonary congestion should be treated with diuretics to reduce volume overload and filling pressure. It must be remembered that in patients with DHF, whose left ventricular volume is relatively small, excessive diuresis determines a downshift in pressure-volume loop that may result in reduced end-diastolic volume and low cardiac output. Nitrates can be useful to lower filling pressure, and to increase the availability of nitric oxide at the endothelial level. Tachycardia may worsen DHF because it is associated with an increased oxygen demand and decreased coronary flow, due to a reduced diastolic time. In these cases, beta-receptor antagonists and calcium channel blockers may be useful to reduce heart rate. Anyway, when myocardial stiffness prevails and both end-diastolic volume and stroke volume are fixed, heart rate may be the only mechanism that maintains cardiac output. Atrial fibrillation can precipitate heart failure in patients with significant diastolic dysfunction, and acute decompensation in those with chronic DHF.

Concerning long-term treatment, again it is mostly based on pathophysiology rather than on demonstration of efficacy in randomized trials. Interestingly, in the Digitalis Investigation Group trial, the small proportion of patients with preserved LVEF had an equal or even more marked benefit from active treatment in terms of the combined endpoint of death and heart failure hospitalizations[38]. This datum is somehow unexpected, since digoxin is known to increase myocyte calcium availability[39], and could be related to its contribution to heart rate and rhythm control.

Myocardial stiffness attenuates the increase of left ventricular end-diastolic volume during exercise, justifying the functional limitation often complained by patients with DHF. Beta-adrenergic receptor antagonists and angiotensin II receptor antagonists have been shown to improve symptoms and exercise tolerance[37,40].

Generally speaking, the treatment of chronic DHF with antagonists of the renin-angiotensin-aldosterone system appears to be logical, since they contribute to antagonize fibrosis and improve intracellular calcium handling. Anyway, the definite demonstration of their efficacy in this setting is still lacking, and the results of non-randomized, observational studies are controversial[41,42]. The most important trial in patients with heart failure and preserved LVEF conducted so far is the CHARM-Preserved study[43]. Within this trial, 3023 patients with heart failure and LVEF > 40% were randomized to receive candesartan or placebo; after a median follow-up of 37 months, candesartan was associated with a strong trend toward a reduction in the composite endpoint of cardiovascular deaths or hospital admissions for heart failure, consistent with the other component trials of the CHARM program, but failing to reach statistical significance. Cardiovascular mortality was 11% in both treated and placebo groups. Fewer candesartan-treated patients were hospitalized for heart failure compared with the placebo group (241 vs 276, relative risk 0.85, p = 0.047). Consistently with the observations with ramipril in the HOPE (Heart Outcomes Prevention Evaluation) trial[44] and with losartan in LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) study[45], a significant 40% reduction was seen in the development of new diabetes mellitus in the candesartan group compared with placebo (4 vs 7%, p = 0.005). This study corroborates the rationale for treating patients with DHF with an angiotensin receptor blocker, at least for reducing symptoms.

In conclusion, DHF is a common and heterogeneous condition, associated with relevant morbidity and mortality. Further trials targeted to well-characterized patient populations are still warranted.

Riassunto

Lo scompenso diastolico si caratterizza per l'associazione di insufficienza cardiaca e frazione di eiezione ventricolare sinistra (FEVS) normale o solo lievemente ridotta; per la precisazione diagnostica, si raccomanda la documentazione di disfunzione diastolica con l'ecocardiografia. L'insufficienza cardiaca con FEVS conservata è una condizione eterogenea e frequente, in particolare negli anziani, tra i quali rappresenta fino al 50% di tutti i pazienti con insufficienza cardiaca. La mortalità è generalmente più bassa rispetto a quella dei pazienti con insufficienza cardiaca e FEVS ridotta, e dipende dall'eziologia, dalle condizioni del paziente, dalle comorbilità. In ogni caso, la morbilità è molto alta. Allo stato attuale, la terapia dello scompenso diastolico è empirica, ed è diretta a mantenere la portata cardiaca, ridurre la pressione di riempimento, controllare la frequenza cardiaca e il ritmo, e antagonizzare la progressione della malattia, mediante l'impiego di diuretici, inibitori del sistema renina-angiotensina-aldosterone, nitrati e digossina.

References

1. 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.
2. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure. Part II: causal mechanisms and treatment. Circulation 2002; 105: 1503-8.
3. European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. Eur Heart J 1998; 19: 990-1003.
4. 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.
5. O'Connor 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.
6. 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.
7. Rakowski H, Appleton C, Chan KL, et al. Canadian consensus recommendations for the measurement and reporting of diastolic dysfunction by echocardiography: from the Investigators of Consensus on Diastolic Dysfunction by Echocardiography. J Am Soc Echocardiogr 1996; 9: 736-60.
8. Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. J Am Coll Cardiol 1998; 32: 865-75.
9. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized criteria. Circulation 2000; 101: 2118-21.
10. 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.
11. Fischer M, Baessler A, Hense HW, et al. Prevalence of left ventricular diastolic dysfunction in the community. Results from a Doppler echocardiographic-based survey of a population sample. Eur Heart J 2003; 24: 320-8.
12. McDermott MM, Feinglass S, Sy J, et al. Hospitalized congestive heart failure patients with preserved versus abnormal left ventricular systolic function: clinical characteristics and drug therapy. Am J Med 1995; 99: 629-35.
13. Philbin EF, Rocco TA Jr. Use of angiotensin-converting enzyme inhibitors in heart failure with preserved left ventricular systolic function. Am Heart J 1997; 134: 188-95.
14. 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.
15. 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.
16. Kitzman DW, Gardin JM, Gottdiener JS, et al. Importance of heart failure with preserved systolic function in patients ≥ 65 years of age. CHS Research Group. Cardiovascular Health Study. Am J Cardiol 2001; 87: 413-9.
17. 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.
18. Dauterman KW, Massie BM, Gheorghiade M. Heart failure associated with preserved systolic function: a common and costly clinical entity. Am Heart J 1998; 135 (Part 2 Suppl): S310-S319.
19. 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.
20. Ommen SR, Nishimura RA, Appleton CP, et al. The clinical utility of Doppler echocardiography and tissue Doppler imaging in estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation 2000; 102: 1788-94.
21. 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: 215-9.
22. 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.
23. Andrew P. Diastolic heart failure demystified. Chest 2003; 124: 744-53.
24. Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction. Circulation 2002; 105: 1195-201.
25. 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.
26. Bell SP, Nyland L, Tischler MD, McNabb M, Granzier H, LeWinter MM. Alterations in the determinants of diastolic suction during pacing tachycardia. Circ Res 2000; 87: 235-40.
27. Harris TS, Baicu CF, Conrad CH, et al. Constitutive properties of hypertrophied myocardium: cellular contribution to changes in myocardial stiffness. Am J Physiol 2002; 282: H2173-H2182.

28. Villari B, Campbell SE, Hess OM, et al. Influence of collagen network on left ventricular systolic and diastolic function in aortic valve disease. J Am Coll Cardiol 1993; 22: 1477-84.
29. Villari B, Vassalli G, Monrad ES, Chiariello M, Turina M, Hess OM. Normalization of diastolic dysfunction in aortic stenosis late after valve replacement. Circulation 1995; 91: 2353-8.
30. Kato S, Spinale FG, Tanaka R, Johnson W, Cooper G 4th, Zile MR. Inhibition of collagen cross-linking: effects on fibrillar collagen and ventricular diastolic function. Am J Physiol 1995; 269: H863-H868.
31. Brilla CG, Funck RC, Rupp H. Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. Circulation 2000; 102: 1388-93.
32. Paulus WJ. Beneficial effects of nitric oxide on cardiac diastolic function: "the flip side of the coin". Heart Fail Rev 2000; 5: 337-44.
33. Brutsaert DL, Fransen P, Andries LJ, De Keulenaer GW, Sys SU. Cardiac endothelium and myocardial function. Cardiovasc Res 1998; 38: 281-90.
34. Cohen GI, Pietrolungo JF, Thomas JD, Klein AL. A practical guide to assessment of ventricular diastolic function using Doppler echocardiography. J Am Coll Cardiol 1996; 27: 1753-60.
35. Kerzner R, Gage BF, Freedland KE, Rich MW. Predictors of mortality in younger and older patients with heart failure and preserved or reduced left ventricular ejection fraction. Am Heart J 2003; 146: 286-90.
36. Chobanian AV, Bakris GL, Black HR, et al, for the National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. 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.
37. Warner JG Jr, 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.
38. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997; 336: 525-33.
39. Gheorghiade M, Pitt B. Digitalis Investigation Group (DIG): a trial stimulus for further research. Am Heart J 1997; 134: 3-12.
40. 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.
41. Ahmed A, Roseman JM, Duxbury AS, Allman RM, DeLong JF. Correlates and outcomes of preserved left ventricular systolic function among older adults hospitalized with heart failure. Am Heart J 2002; 144: 365-72.
42. Sueta CA, Russo A, Schenck A, Brown DW, Simpson RJ. Effect of angiotensin-converting inhibitor or angiotensin receptor blocker on one-year survival in patients ≥ 65 years hospitalized with a left ventricular ejection fraction ≥ 50%. Am J Cardiol 2003; 91: 363-5.
43. Yusuf S, Pfeffer MA, Swedberg K, et al, for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003; 362: 777-81.
44. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000; 342: 145-53.
45. Dahlof B, Devereux RB, Kjeldsen SE, et al, for the LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359: 995-1003.