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Review

Diastolic heart failure and left ventricular diastolic dysfunction: What we know, and what we don't know!

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Abstract

Diastolic heart failure is a common form of congestive heart failure that is responsible for significant morbidity and mortality. In contrast to heart failure caused by systolic left ventricular dysfunction, diastolic heart failure is harder to diagnose and less likely to be accepted as a diagnosis. In addition, treatment strategies are much less defined than those for heart failure caused by systolic dysfunction.

Keywords: Diastolic heart failure; Left ventricular diastolic dysfunction; Congestive heart failure

1. Introduction

Over 5 million people in the United States have heart failure and over 500,000 cases are diagnosed each year [1]. Heart failure is the most common discharge diagnosis in elderly patients and one of the most common causes for readmission [2]. The cost to the society is enormous and ranges from 28 to 50 billion dollars per year [1,3]. About 40%–50% of patients with congestive heart failure (CHF) have preserved ejection fraction (EF) [4–6]. Some prefer to use the term heart failure with preserved left ventricular systolic function instead of diastolic heart failure (DHF). This confusion is due in part to difficulty in measuring diastolic function and absence of clear diagnostic criteria for DHF. When the left ventricular EF is low, the diagnosis of CHF is seldom questioned and physicians are more likely to label these patients as CHF. However, the same physicians are less likely to commit to a diagnosis of CHF when the EF is normal.

2. Definition

Heart failure is the pathophysiological state in which the heart is unable to pump blood at a rate commensurate with the requirement of the metabolizing tissue or can do so only from an elevated filling pressure [7]. In patients with systolic heart failure (SHF), the primary abnormality is reduced contractile reserve of the left ventricle causing reduction in the stroke volume and cardiac output. DHF, however, occurs when the ventricle is unable to accept an adequate volume of blood in diastole at normal diastolic pressures and at volumes sufficient to maintain stroke volume and cardiac output. The low stroke volume and cardiac output are manifested as fatigue whereas the increased left ventricular end-diastolic pressure (LVEDP) is transmitted back to the pulmonary circulation causing dyspnea. Whereas diastolic dysfunction describes an abnormal mechanical property, diastolic heart failure describes a clinical syndrome. Some have questioned the term diastolic heart failure and proposed the use of heart failure with normal systolic function instead [8]. This is due to several factors, such as; difficulty to measure diastolic function, absence of clear diagnostic criteria for DHF and coexistence of systolic and diastolic heart failure in many patients.

3. Pathophysiology

Patients with DHF have increased left ventricular (LV) diastolic pressures and pulmonary venous pressures with secondary limitation in exercise tolerance. These patients

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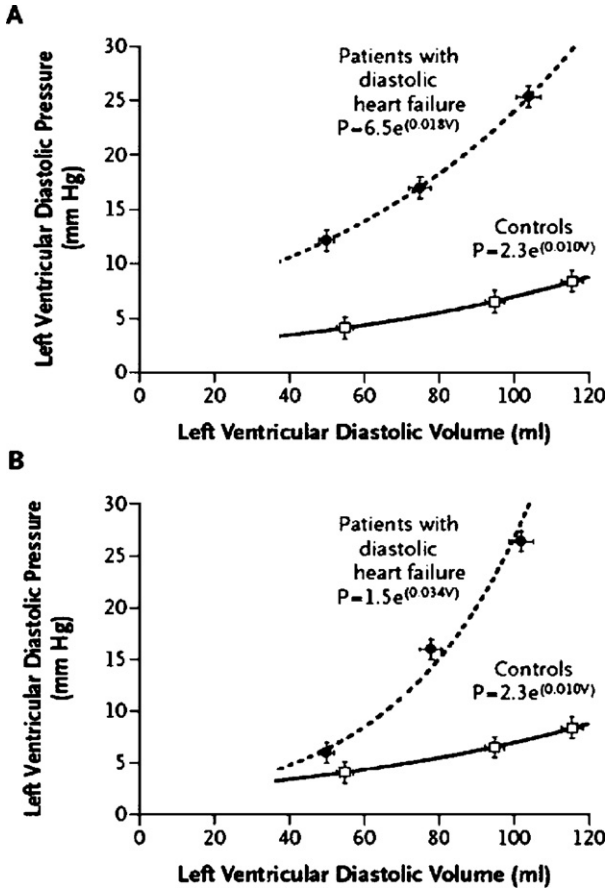

Fig. 1. Diastolic pressure–volume relation in patients with diastolic heart failure and in controls (reproduced with permission [9]. Copyright 2004 Massachusetts Medical Society. All rights reserved). Panel A shows measured values for the minimal left ventricular pressure, and panel B shows values for the minimal left ventricular pressure, corrected for slow relaxation. The exponential value in the equation for pressure (P) is the stiffness constant. The data in both panels indicates that there was a significant increase in the passive stiffness of the left ventricle in the patients with diastolic heart failure. V denotes volume and the I bars represent the standard error.

appear to have both an abnormal active relaxation and increased passive stiffness of the LV [9], which explains the large changes in LV diastolic pressure with small or barely detectable changes in ventricular volume making it impossible for the ventricle to accept additional venous return without high diastolic pressure and subsequent pulmonary edema [10–12]. That increased passive stiffness, and not just abnormal relaxation, is an independent factor in these patients was nicely documented by Ziles et al. when they showed that even after correction for slow relaxation, increased passive stiffness was found to be an important factor in LV diastolic dysfunction and DHF (Fig. 1) [9].

4. Prevalence

The prevalence of both systolic and diastolic heart failure increases with age with an estimated 10% over 70 years [13]. The proportion of heart failure patients with DHF has ranged from 13% to 80% [5,6,14–16]. Most common prevalence sited in the literature is 40–50%. The variation is due in part to absence of unified definition of DHF, difficulty in diagnosis, different EF cutoff used to define preserved EF, age of population studied and the setting they are studied in (i.e. whether inpatient or outpatient). The prevalence is substantially less in younger patients and can rise to over 70% in elderly patients [15–20]. Age is probably the single most important factor influencing the prevalence. Coronary artery disease, hypertension, atrial fibrillation and diabetes are all conditions that are known to be associated with or to exacerbate DHF and are also more common in the elderly. Women are more likely to have DHF than men [5,15,21,22]. Over 40% of patients with diabetes may have abnormal diastolic function on echocardiogram [23]. DHF is more common in the community than in hospitalized patients. Community-based studies of patients with CHF estimate that about 45%–55% have DHF [6,13,15,16] compared to 35%–40% in hospitalized patients [5,6,24,25].

5. Diagnosis

Diagnosing DHF has been challenging mainly due to lack of consensus on specific criteria and absence of a ‘single’ non-invasive test to confirm diagnosis. Clinical findings are non-specific and cannot differentiate DHF from systolic heart failure (Table 1) [10]. Diastolic heart failure describes a clinical syndrome whereas diastolic dysfunction describes a mechanical abnormality of the left ventricle. Indexes of diastolic dysfunction may be present without the “clinical syndrome” of diastolic heart failure and diastolic left ventricular dysfunction may coexist with systolic dysfunction in many patients [26].

Table 1
Prevalence of specific symptoms and signs in systolic vs. diastolic heart failure (reproduced with permission [10])

	Diastolic heart failure (EF>50%)	Systolic heart failure (EF<50%)
Symptoms		
Dyspnea on exertion	85	96
Paroxysmal nocturnal dyspnea	55	50
Orthopnea	60	73
Physical examination		
Jugular venous distension	35	46
Rales	72	70
Displaced apical impulse	50	60
S_3	45	65
S_4	45	66
Hepatomegaly	15	16
Edema	30	40
Chest radiograph		
Cardiomegaly	90	96
Pulmonary venous hypertension	75	80

As percentage of patients in each group with the listed symptom or sign of heart failure. There were no statistically significant differences between patients with an EF>50% vs. <50%.

Table 2
Proposed criteria for the diagnosis of diastolic heart failure [31]

	Heart failure	EF	EF measured within 72 h of event	Abnormal LV relaxation during catheterization
Definite	+	>50%	+	+
Probable	+	>50%	+	−
Possible	+	>50%	−	−

EF: ejection fraction, LV: left ventricle.

Finally, what is presumed to be preserved ejection fraction may not reflect normal systolic function when studied with advanced Doppler techniques such as strain rate imaging [27–29].

In an effort to improve the diagnosis of this disorder, the European Society of Cardiology proposed the presence of all of the following to make the diagnosis:

1. Signs and symptoms of CHF.
2. Normal or mildly abnormal left ventricular systolic function defined as EF ≥ 45%.
3. Evidence of abnormal left ventricular relaxation, filling, diastolic distensibility, or diastolic stiffness [30].

These criteria were later refined by Vasan and Levy [31] who proposed dividing these patients into three diagnostic classes: definite, probable and possible (Table 2). They suggested that the diagnosis of possible CHF might be upgraded to probable if there is evidence of severe hypertension during the acute event. Some have questioned the need to document a preserved EF on an echocardiogram done in close proximity to the decompensated event [5]. They argue that, in most patients, there is no significant difference in the EF measured during the acute event and that done at a later time when symptoms have resolved. Ghandi et al. also documented that the echo was unchanged when done acutely and after treatment in patients presenting with severe hypertension and acute pulmonary edema. They concluded that the presentation was secondary to diastolic dysfunction rather than transient LV dysfunction or acute mitral regurgitation [11].

The gold standard for evaluating LV diastolic function remains direct measurement of LV pressures via a catheter. However, such an invasive approach is not practical to apply to the many patients with suspected DHF. Echocardiography plays a central role in evaluating these patients. There are several echocardiographic parameters that are used to help in the diagnosis of diastolic dysfunction. Although no one measurement is diagnostic, the presence of multiple abnormalities is quite suggestive of diastolic dysfunction especially in the presence of abnormal left ventricular systolic function. Mitral inflow Doppler pattern, pulmonary venous inflow Doppler and tissue Doppler have all been used to assess the diastolic properties of the left ventricle (Figs. 2 and 3) [32]. In healthy young adults the E/A ratio of the mitral inflow pattern is usually >1. As we grow older, this ratio reverses and the relaxation time increases (Figs. 2 and 3A). If the LVEDP continues to rise, the left atrial (LA) to LV pressures tend to equalize leading to a shortening of the deceleration time and a pseudo-normal wave form (Figs. 2 and 3B) which can be unmasked with the valsalva maneuver. Further progression of the diastolic dysfunction results in a restrictive filling pattern with a very short deceleration time

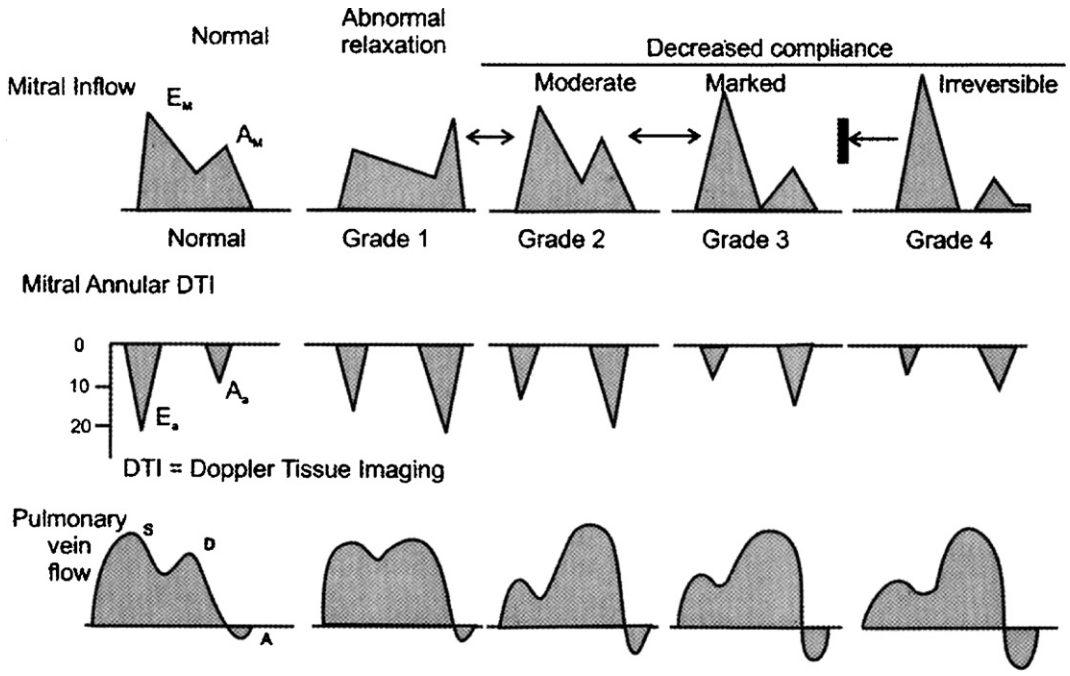

Fig. 2. Schematic representation of mitral inflow (top), mitral annular Doppler tissue imaging (middle), and pulmonary vein flow (bottom), in a normal individual and in various grades of diastolic dysfunction (reproduced with permission [32]).

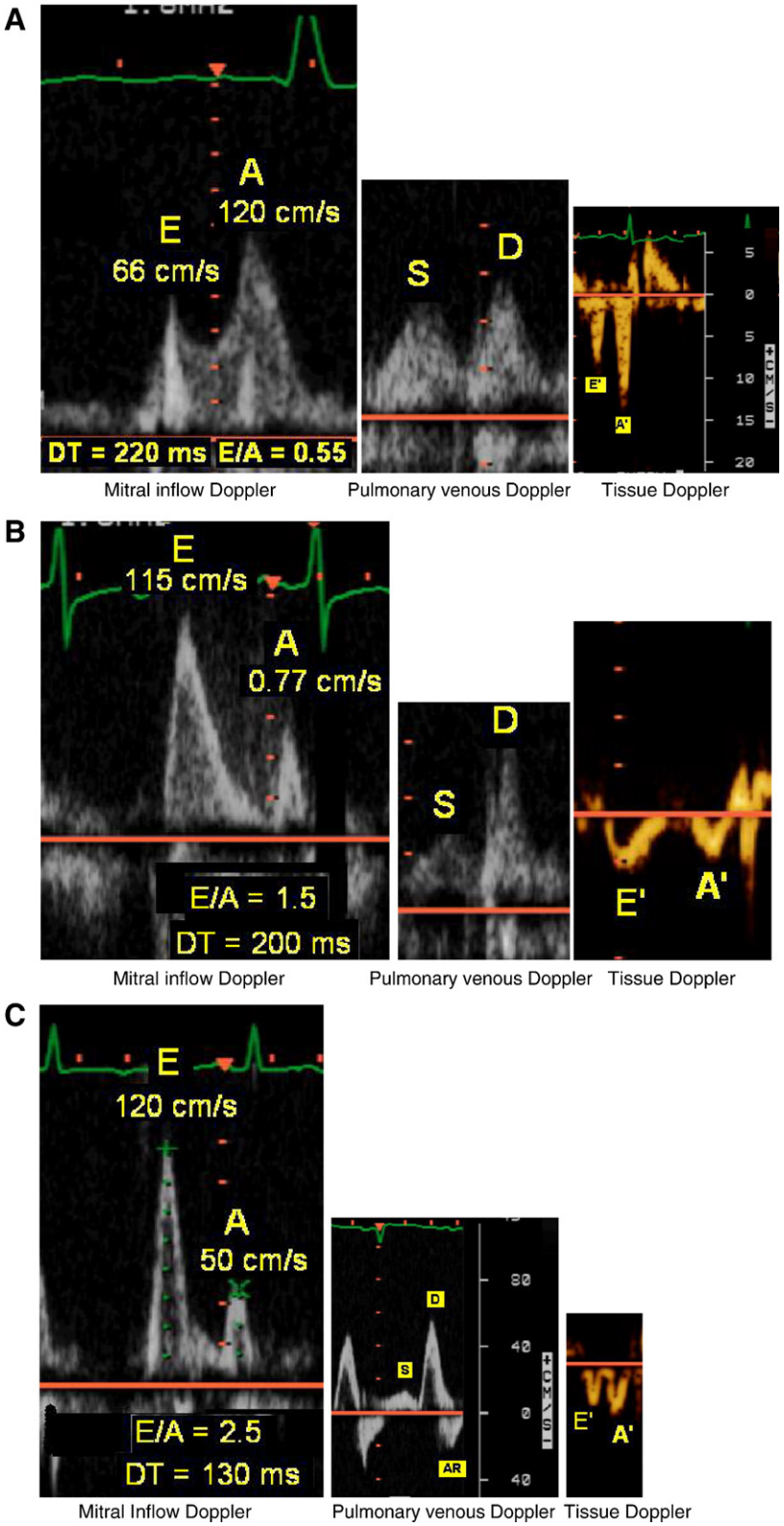

Fig. 3. (A) Grade 1 diastolic dysfunction. The mitral inflow Doppler reveals reversal of the E/A ratio. The pulmonary venous Doppler shows slight predominance of the diastolic flow component. The tissue Doppler demonstrates E′ < A′. (B) Grade 2 diastolic dysfunction. Mitral inflow Doppler shows a "pseudo-normal" pattern. The pulmonary vein Doppler shows dominance of the diastolic component and the tissue Doppler velocities are low. The abnormal tissue and pulmonary vein Doppler distinguish this pseudo-normal mitral inflow pattern from a truly normal pattern. (C) Grade 3 diastolic dysfunction. The mitral Doppler shows a tall E wave with increased E/A ratio of 2.5. In addition the deceleration time (DT) is shortened. The pulmonary vein Doppler imaging shows marked predominance of the diastolic component and increase in the duration of pulmonary vein atrial flow reversal wave (AR). The corresponding tissue Doppler shows very low velocities.

and marked increase in the E/A ratio (Figs. 2 and 3C). Mitral inflow patterns are however dependent on volume status.

Pulmonary venous Doppler usually consists of a biphasic flow pattern with both systolic and diastolic components in addition to the pulmonary vein atrial flow reversal wave (PVa) due to LA contraction (Fig. 2). The systolic component is typically dominant. As LV stiffness increases causing the LA pressure to be elevated at the onset of ventricular systole, less flow will occur during ventricular systole and the systolic component will be blunted (Fig. 3A). Additional increase in stiffness and worsening of relaxation will cause most of the flow to occur in diastole yielding a fairly dominant diastolic waveform. In addition, the PVa will prolong and increase in velocity (Fig. 3C). Several studies have indicated that if the duration of the PVa wave exceeded that of the mitral inflow A-wave, then the LVEDP is likely to be above 15 mm Hg [33].

Tissue Doppler imaging has improved our ability to assess the LV diastolic properties. As seen in Figs. 2 and 3, Doppler tissue imaging (DTI) also has two components; E′ and A′. Similar to mitral inflow waveform, the E′ is usually >A′. As diastolic dysfunction develops, the ratio reverses and the individual velocities decrease (Figs. 2 and 3A−C). Studies have shown that E/E′ >15 reflects a high left ventricular filling pressure or wedge pressure [34]. Combining the above Doppler modalities can make it easier to assess the diastolic properties.

Measurement of diastolic filling parameters, however, may not be needed to establish the diagnosis of DHF [35]. Zile et al. studied a group of patients with history of CHF and normal left ventricular systolic function who were scheduled for catheterization. They found that over 90% of the patients with normal EF, left ventricular hypertrophy and symptoms of CHF had abnormally elevated LVEDP.

Increased left atrial volume in the presence of normal EF has also been suggested as a marker for diastolic dysfunction by itself [36].

CHF in the presence of LVH with preserved EF and the precipitation of heart failure by tachycardia, hypertensive episode, or transient ischemia [35,37] are all suggestive of underlying diastolic dysfunction of the LV. Similarly, the improvement of symptoms with treatment of precipitating factors is also supportive of the diagnosis.

In addition to the clinical, echocardiographic and invasive diagnostic criteria, the measurement of BNP has been proposed as an adjunct for the diagnosis. There is a close relation between the BNP and myocyte hypertrophy [38,39]. Despite this, patients with acute CHF and normal EF on admission will have increased BNP levels that cannot be explained by the presence of LVH alone [40]. Elderly patients with isolated diastolic dysfunction are likely to have higher BNP levels with advanced filling abnormalities on echo Doppler than those with milder forms of relaxation abnormalities [41].

In patients with suspected DHF, there is a significant increase in the level of BNP at peak exercise especially in those who demonstrate echo Doppler evidence of elevated wedge pressure (increased E/E′) at peak exercise [42]. This study suggested that in hypertensive patients with exercise limitations but normal EF, a peak exercise BNP<38 pg/ml argues against significant elevation of LV filling pressures with exercise. However, the measurement of BNP may be of marginal benefit in ambulatory patients with mild symptoms of CHF [43]. In these patients the diagnostic threshold level seems to be quite low and is accompanied by loss of specificity.

Elevated BNP levels have also been attributed to ischemia in the absence of clinically evident CHF [44,45]. It has been suggested that BNP elevation in these patients may be through the mechanism of hypoxia induced up-regulation of the ventricular BNP gene expression [46]. Another mechanism is by ischemia increasing the wall stress transiently and releasing the BNP [45].

6. Prognosis

Reports about morbidity and mortality have varied widely depending on many factors including age, EF cutoff, underlying disease process causing DHF and presence of coexistent pathology (Table 3). Some community-based studies have reported very high, up to 60%, 3 year mortality rates for DHF especially in advanced age and in patients with NYHA class 3 and 4 heart failure [47]. Few others implied similar prognosis between DHF and heart failure with reduced EF [16]. However, most agree that CHF with preserved EF has a lower mortality than CHF with diminished EF [5,6,14,15,48] but a significantly higher mortality than the general population [6]. Advanced age adversely affects outcome in both groups [48]. In general, the annual mortality rate is quoted as 5%–8% compared to 10%–20% for those with systolic heart failure [17,49,50]. Morbidity for DHF is not much better than systolic heart failure. Rates of hospital readmission and functional decline are not different and patients with DHF may have a higher likelihood of functional limitations on follow-up [5].

Race has also been found to impact prognosis in DHF with African-Americans having a 34% higher mortality risk at 5 years than white patients [51].

7. Treatment

Although up to half of patients with CHF may have preserved EF, few treatments have specifically been evaluated in such patients. The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM-Preserved) [52] is perhaps the only completed large scale prospective randomized trial to specifically address the impact of certain pharmacotherapy on outcome in a subgroup of patients with CHF and preserved EF. Until now most of the treatments used in DHF focus on treating symptoms, underlying causes and exacerbating factors.

Table 3
Outcome of patients with diastolic heart failure as reported in different studies

Study	Number of patients	EF	Follow-up	Mortality	
				DHF	SHF
Smith et al. [5]	413	≥40%	6 months	13%	21%
Vasan et al. [6]	73	≥50%	6.2 years	8.7%	18.9%
Cohn et al. [14]	623	≥45%	1 year	8f%	19%
Judge et al. [17]	284	≥45%	6 years	18%	N/A
East et al. [51]	3303	≥40%	5 years	30%	N/A
Yusuf et al. [52]	3023	≥40%	3 years	11%	N/A

EF: ejection fraction, DHF: diastolic heart failure, SHF: systolic heart failure.

Treatment of underlying hypertension, especially when associated with left ventricular mass regression can improve the diastolic properties of the left ventricle [53]. There are few ongoing trials that specifically address the role of different therapies on clinical outcome in this interesting group of patients (Table 4). The results will hopefully add to our limited current knowledge.

8. Diuretics

Diuretics are usually the initial treatment in DHF with volume overload. Such treatment can also lower blood pressure which is an exacerbating factor for the development and propagation of DHF. Due to the stiffness of the left ventricle in these cases and the increased dependency on preload to maintain adequate cardiac output, aggressive diuresis may result in hypotension.

9. Digoxin

Digoxin is not specifically indicated for the treatment of diastolic heart failure. In the ancillary arm of the DIG study, digoxin reduced hospitalization rate in patients with CHF and EF over 45% [54]. Any benefits for digoxin in DHF may be related to controlling heart rate especially in the presence of atrial arrhythmias.

10. Beta-blockers

Beta-blockers may be helpful in several ways. Treatment with beta-blockers has been associated with regression of LV hypertrophy [53]. In addition beta-blockers may help by decreasing the incidence of tachycardia which can exacerbate DHF by shortening the filling time of the left ventricle. Furthermore, beta-blockers may improve LV diastolic properties in patients where ischemia is present and also by controlling blood pressure. Carvedilol has been associated with improvement of the echo Doppler-derived E/A ratio in patients with heart failure and preserved EF [55]. The SENIORS trial tested the effect of the beta-blocker, Nebivolol, in elderly patients with CHF. There was a significant reduction in the primary end point of combined all-cause mortality or cardiovascular hospitalization. The benefit was similar for patients with EF >35% and those lower than 35% suggesting that Nebivolol is an effective treatment in patients with mildly depressed and preserved EF [56].

In another retrospective community-based study, the use of beta-blockers was associated with decreased mortality in patients with CHF and EF >45% [47].

11. Calcium channel blockers

Like beta-blockers, calcium channel blockers may be beneficial by controlling heart rate, lowering blood pressure and treating ischemia. Also, by causing regression of left ventricular hypertrophy [57,58] calcium channel blockers may improve the diastolic properties of the left ventricle. In patients with DHF, clinical status, exercise tolerance and diastolic filling were all improved by verapamil [59]. In this small, prospective study the improvement was evident at 2 weeks using a mean daily dose of 256 mg when given to patients with CHF and EF >45%. In a hypertensive rat model, amlodipine prevented elevation of left ventricular end diastolic pressure and transition to overt diastolic heart failure through controlling blood pressure and improving myocardial stiffness [60].

12. Angiotensin converting enzyme inhibitors (ACE-I)

In contrast to the large body of evidence linking ACE-I to lower morbidity and mortality in patients with decreased EF, very little information is available about the effect of ACE-I in diastolic heart failure. The PEP-CHF is a large prospective trial evaluating the benefits of Perindopril in elderly patients with DHF [61]. The final results of this study are still pending. ACE-I, like many other antihypertensive agents,

Table 4
Ongoing prospective trials addressing the impact of specific therapies in patients with diastolic heart failure

Study	Drug	No. of patients	End point	EF
i-Preserve	Irbesartan	3600	Vascular and HF mortality	≥45%
PEP-CHF	Perindopril	1000	Death and HF mortality	≥40%
The Hong Kong Diastolic HF Study	Diuretic, Irbesartan, Ramipril	450	Death or HF admissions, quality of life and exercise capacity	≥45%
Aldosterone antagonism in DHF	Spironolactone	48	6 min walk test	≥50%
Use of Nesiritide in the management of acute DHF	Nesiritide (IV)	20	Left ventricular filling pressures	≥40%

EF: ejection fraction, HF: heart failure, DHF: diastolic heart failure, CV: cardiovascular.

have been shown to cause regression of left ventricular hypertrophy [62,63] and may improve diastolic filling through this mechanism.

In a retrospective community-based study in patients with CHF and EF >45%, treatment with ACE-I at discharge was associated with improved survival [47]. Decreased mortality and readmission rates were also reported in a similar registry-type, community-based study of patients with CHF and EF >40% [64]. In this study, the 6 months mortality was reduced from 16.8% to 11.3%.

13. Angiotensin receptor blockers

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM-Preserved) is perhaps the only completed randomized prospective trial that evaluated pharmacotherapy in a subgroup of patients with DHF [52]. Over 3000 patients with CHF and EF >40% were enrolled in this study and followed for 3 years. Treatment with Candesartan was associated with decreased heart failure hospitalization and a trend in favor of candesartan in combined mortality and heart failure admission. Interestingly, there was a 40% reduction in onset of new diabetes mellitus.

Losartan may improve exercise tolerance and quality of life in patients with Doppler evidence of mild diastolic dysfunction and hypertensive response to exercise [65]. The addition of an angiotensin receptor blocker such as Temocarpil to ACE-I provided further benefit in a hypertensive rat model [66]. This was felt to be secondary to inhibiting myocardial fibrosis and hypertrophy.

14. Aldosterone blockers

The RALES (Randomized Aldactone Evaluation study for CHF) showed benefit of aldactone in patients with systolic heart failure [67]. There is evidence to suggest that aldosterone may play a role in fibrosis and hypertrophy. In the RALES study, patients with the highest serum levels of marker for collagen turnover had the worst prognosis and these patients had the greatest response to spironolactone [68]. Elprelenone has been shown to cause regression of left ventricular hypertrophy with additional regression when added to enalapril [69]. This effect may help improve left ventricular relaxation. In addition, an animal study showed that the selective aldosterone blocker eplerenone improved diastolic function and normalized LV relaxation in post myocardial infarction rats, possibly due to a reduction or inhibition of interstitial fibrosis [70].

15. Conclusion

DHF is a common condition that is responsible for significant morbidity and mortality. It is more common in elderly hypertensive women and should be suspected in patients with normal EF who present with CHF without any other explanation especially if there is LVH and left atrial enlargement on the echocardiogram. In contrast to CHF with decreased EF, very little data is available about the long term benefits of specific interventions. Candesartan appears to have a modest long term benefit. Nebivolol also appeared to benefit patients with EF >35% in the SENIORS trial, although an EF >35% cannot be considered as "preserved" systolic function. Treatment of any exacerbating factors such as severe hypertension, atrial fibrillation and ischemia is also helpful. Our knowledge about this condition and proven therapies will undoubtedly grow as research in this area progresses in the near future.

References

[1] AHA. Heart Disease and Stroke Statistics—2005 Update.
[2] Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. Am Heart J 1999;137:352–60.
[3] O'Connell JB, Bristow MR. Economic impact of heart failure in the United States: time for a different approach. J Heart Lung Transplant 1994;13:S107–12.
[4] Vasan SR, Benjamin JE, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol 1995;26(7):1564–74.
[5] Smith GL, Masoudi FA, Vaccarino V, Radford M, Krumholz H. Outcomes in heart failure patients with preserved ejection fraction: mortality, readmission, and functional decline. J Am Coll Cardiol 2003;41:1510–8.
[6] 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.
[7] Colucci WS, Braunwald E. Pathophysiology of heart failure. In: Braunwald E, editor. Heart disease. W.B. Saunders Co.; 1996
[8] Maurer MS, Spevack D, Burkhoff D, Kronzon I. Diastolic dysfunction: can it be diagnosed by Doppler echocardiography? J Am Coll Cardiol 2004;44:1543.
[9] Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. NEJM 2004;350:1953–9.
[10] Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I. Circulation 2002;105:1387–93.
[11] Ghandi SK, Powers JC, Nomeir A, et al. The pathogenesis of acute pulmonary edema associated with hypertension. NEJM 2001;344 (1):17–22.
[12] Kitzman DW, Higginbothom MB, Cobb FR, Sheikh KS, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. JACC 1991;17:1065–72.
[13] Redfield MM, Jacobsen SJ, Burnett Jr JC, Mahoney DW, Baily 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.
[14] Cohn JN, Johnson G, Veterans Administration Cooperative Study Group. Heart failure with normal ejection fraction: the V-HeFT study. Circulation 1990;81(Suppl III):48–53.
[15] Mathew ST, Gottdiener JS, Kitzman D, Aurigemma G, Gardin MJ. Congestive heart failure in the elderly: the Cardiovascular Health Study. Am J Geriatr Cardiol 2004;13(2):61–8.
[16] Senni M, Tribouilloy CM, Rocleheffer J. Congestive heart failure in the community. A Study of all incident cases in Olmstead County, Minnesota, in 1991. Circulation 1998;98:2282–9.
[17] Judge KW, Pawitan Y, Caldwell J, Gersh BJ, Kennedy W. CASS participants. J Am Coll Cardiol 1991;18:377–82.

[18] Arbab-Zadeh A, Dijk E, Prasad A, et al. Effect of aging and physical activity on left ventricular compliance. Circulation 2004;110: 1799–805.
[19] Wong WF, Gold S, Fukuyama O, Blanchette PL. Diastolic dysfunction in elderly patients with congestive heart failure. Am J Cardiol 1989;63: 1526–8.
[20] Forman DE, Coletta D, Kenny D, et al. Clinical issues related to discontinuing digoxin therapy in elderly nursing home patients. Arch Intern Med 1991;151:2194–8.
[21] Kitzman DW, Gardin JM, Gottdiener JS, et al. For the Cardiovascular Health Study Research Group. Importance of heart failure with preserved systolic function in patients > or =65 years of age. Am J Cardiol 2001;87:413–9.
[22] Lindenfeld J, Krause-Steinrauf H, Salerno J. Where are all the women with heart failure? J Am Coll Cardiol 1997;30:1417–9.
[23] Zabalgoitia M, Ismaeil MF, Anderson L, Maklady F. Prevalence of diastolic dysfunction in normotensive asymptomatic patients with well-controlled type-2 diabetes mellitus. Am J Cardiol 2001;87:320–3.
[24] Miller LW, Missov ED. Epidemiology of heart failure. Cardiol Clin 2001;19:547–55.
[25] Pernenkil R, Vinson JM, Shah AS, Beckham V, Wittenberg C, Rich MW. Course and prognosis in patients > or =70 years of age with CHF and normal versus abnormal left ventricular ejection fraction. Am J Cardiol 1997;79:216–9.
[26] Yu CM, Lin H, Yang H, Kong S, Zhang Q, Lee S. Progression of Systolic abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction. Circulation 2002;105:1195–201.
[27] Niedeggen A, Breithardt OA, Franke A. Detection of early systolic dysfunction with strain rate imaging in a patient with light chain cardiomyopathy. Z Kardiol 2004;94(2):133–6.
[28] Mottram PM, Haluska B, Yuda S, Leano R, Marwick TH. Patients with a hypertensive response to exercise have impaired systolic function without diastolic dysfunction or left ventricular hypertrophy. J Am Coll Cardiol 2004;19:430–6.
[29] Fang ZY, Leano R, Marwich TH. Relationship between longitudinal and radial contractility in subclinical diabetic heart disease. Clin Sci 2004;106:53–60.
[30] European study group on diastolic Heart Failure. How to diagnose diastolic heart failure. Eur Heart J 1998;19:990–1003.
[31] Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation 2000;101:2118–21.
[32] Feigenbaum H. Evaluation of systolic and diastolic function of the left ventricle. In: Feigenbaum H, Armstrong WF, Ryan T, editors. Feigenbaum's echocardiography. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 138–80.
[33] Rosvoll O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. J Am Coll Cardiol 1993;21:1687–96.
[34] Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echo and tissue Doppler imaging in the estimation of left ventricular filling pressures. A comparative simultaneous Doppler. Circulation 2000;102:1788–94.
[35] 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.
[36] Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol 2002;90:1284–96.
[37] Arques S, Ambrosi P, Gelisse R, Roux E, Lambert M, Habib G. Prevalence of angiographic coronary artery disease in patients hospitalized for acute diastolic heart failure without clinical and electrocardiographic evidence of myocardial ischemia on admission. Am J Cardiol 2004;94:133–5.
[38] Nakagawa O, Ogawa Y, Itoh H, Suga S, Komatsu Y, Kishimoto I. Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy. J Clin Invest 1995;96: 1280–7.
[39] Liang F, Gardner DG. Mechanical strain activates BNP gene transcription through a p38/NF-kB-dependent mechanism. J Clin Invest 1999;104:1603–12.
[40] Yamaguchi H, Yoshida J, Yamamoto K, et al. Elevation of plasma brain natriuretic peptide is a hallmark of diastolic heart failure independent of ventricular hypertrophy. J Am Coll Cardiol 2004;43:55–60.
[41] Alehagen U, Eriksson H, Nylander E, Dahlstrom U. Heart failure in the elderly; characteristics of a Swedish primary health care population. Heart Drug 2002;2:211–20.
[42] Mottram PM, Haluska BA, Marwick TH. Response of B-type natriuretic peptide to exercise in hypertensive patients with suspected diastolic heart failure: correlation with cardiac function, hemodynamics and workload. Am Heart J 2004;148:365–70.
[43] Dahlstrom U. Can natriuretic peptides be used for the diagnosis of diastolic heart failure? Eur J Heart Fail 2004;6:281–7.
[44] Bibbins-Domingo K, Ansari M, Schiller NB, Massie B, Whooley MA. B-type natriuretic peptide and ischemia in patients with stable coronary disease: data from the heart and soul study. Circulation 2003;108:2987–92.
[45] Sabatine MS, Morrow DA, de Lemos JA, et al. Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia. J Am Coll Cardiol 2004;44:1988–95.
[46] Goetz JP, Christofferson C, Perko M, et al. Increased cardiac BNP expression associated with myocardial ischemia. FASEB J 2003;17: 1105–7.
[47] Chen HH, Lalnchbury JG, Redfield MM. Factors influencing survival of patients with diastolic heart failure in Olmstead County MN in 1996–1997. Circulation 2000;102(Suppl II):412.
[48] Rich MW, McSherry F, Williford WO, Yusuf S. Effect of age on mortality, hospitalizations, and response to digoxin in patients with heart failure: the DIG study. J Am Coll Cardiol 2001;38:806–13.
[49] Setaro JF, Soufer R, Remetz MS, Perlmutter RA, Zaret BL. Long-term outcome in patients with congestive heart failure and intact systolic left ventricular performance. Am J Cardiol 1992;69:1212–6.
[50] Brogan III WC, Hillis LD, Flores ED, Lange RA. The natural history of isolated left ventricular diastolic dysfunction. Am J Med 1992;92: 627–30.
[51] East MA, Peterson ED, Shaw LK, Gattis WA, O'Connor CM. Racial differences in the outcomes of patients with diastolic heart failure. Am Heart J 2004;148:151–6.
[52] Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of Candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. Lancet 2003;362:777–81.
[53] 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;105:1071–6.
[54] 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.
[55] Bergstrom A, Andersson B, Edner M, Nylander E, Persson H, Dahlstrom U. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). Eur J Heart Fail 2004 (Jun);6(4):453–61.
[56] Flather MD, Shibata MC, Coats AJS, et al. Randomized trial to determine the effect of Nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26:215–25.
[57] Schmieder RE, Messerli FH, Garavaglia GE, Nunez BD. Cardiovascular effects of verapamil in patients with essential hypertension. Circulation 1987;75:1030–6.
[58] Amodeo C, Kobrin I, Ventura HO, Messerli FH, Frohlich ED. Immediate and short-term hemodynamic effects of diltiazem in patients with hypertension. Circulation 1986;73:108–13.

[59] Setaro JF, Zaret BL, Schulman DS, Black HR, Soufer R. Usefulness of Verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. Am J Cardiol 1990;66:981–6.
[60] Nishikawa N, Masuyama T, Yamamoto K. Long-term administration of amlodipine prevents decompensation to diastolic heart failure in hypertensive rats. J Am Coll Cardiol 2001;38:1539–45.
[61] Cleland JG, Tendera M, Adamus J, et al. Perindopril for elderly people with chronic heart failure: the PEP-CHF study. Eur J Heart Fail 1999;1:211–7.
[62] Sheiban I, Arcaro G, Covi G, Accardi R, Zenorini C, Lechi A. Regression of cardiac hypertrophy after antihypertensive therapy with nifedipine and captopril. J Cardiovasc Pharmacol 1987;10(Suppl 10): 187–91.
[63] Grandi AM, Venco A, Barzizza F, Casadei B, Marchesi E, Finardi G. Effect of enalapril on left ventricular mass and performance in essential hypertension. Am J Cardiol 1989;63:1093–7.
[64] Philbin EF, Rocco TA, Lindenmuth NW, Jenkins PL. Angiotensin converting enzyme inhibitor use in diastolic heart failure is associated with a reduced risk of death. JACC 2000:232A.
[65] Warner JG, Metzger C, Kitzman DW, Wesley DJ, Little WC. Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. Am J Cardiol 1999;33:1567–72.
[66] Yoshida J, Yamamoto K, Mano T, et al. AT1 receptor blocker added to ACE inhibitor provides benefits at advanced stage of hypertensive diastolic heart failure. Hypertension 2004;43:686–91.
[67] Pitt B, Zannad F, Remme W, et al. For the Randomized Aldactone Evaluation Study (RALES) investigators. N Engl J Med 1999;341: 709–17.
[68] Zannad F, Alla F, Dousset B, Perez A, Pitt B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the Randomized Aldactone Evaluation Study (RALES). Circulation 2000;102:2700–6.
[69] Pitt B, Reichek N, Willenbrock R, et al. Effects of Eplerenone, Enalapril and Eplerenone/Enalapril in patients with essential hypertension and left ventricular hypertrophy. The 4E-left ventricular hypertrophy study. Circulation 2003;108:1831–8.
[70] Masson S, Staszewsky L, Annoni G, et al. Eplerenone, a selective aldosterone blocker, improves diastolic function in aged rats with small to moderate myocardial infarction. J Card Fail 2004;10:433–41.