



## Heart Failure with Preserved EF: A bird eye view

Fahad Aziz,<sup>1</sup> Luqman-Arfath Thazhatauveetil-Kunhahamed,<sup>1</sup> Chijioke Enweluzo,<sup>1</sup> Misbah Zaeem<sup>1</sup>

<sup>1</sup>Wake Forest School of Medicine, 295 Chelsea Village Cir, Winston Salem, NC 27103, USA.

### ABSTRACT

The concept of “diastolic” heart failure grew out of the observation that many patients who have the symptoms and signs of heart failure had an apparently normal left ventricular (LV) ejection fraction. Thus it was assumed that since systolic function was “pre-served” the problem must lie in diastole, although it is not clear by whom or when this assumption was made. Nevertheless, many guidelines followed on how to diagnose “diastolic” heart failure backed up by indicators of diastolic dysfunction derived from Doppler echoardiography. Diastolic heart failure is associated with a lower annual mortality rate of approximately 8% as compared to annual mortality of 19% in heart failure with systolic dysfunction, however, morbidity rate can be substantial. Thus, diastolic heart failure is an important clinical disorder mainly seen in the elderly patients with hypertensive heart disease. Early recognition and appropriate therapy of diastolic dysfunction is advisable to prevent further progression to diastolic heart failure and death. There is no specific therapy to improve LV diastolic function directly. Medical therapy of diastolic dysfunction is often empirical and lacks clear-cut pathophysiologic concepts. Nevertheless, there is growing evidence that calcium channel blockers, beta-blockers, ACE-inhibitors and ARB as well as nitric oxide donors can be beneficial. Treatment of the underlying disease is currently the most important therapeutic approach.

**Keywords:** *diastolic heart failure; doppler echocardiography; treatment.*

### INTRODUCTION

Heart failure is most commonly associated with impaired Left Ventricular (LV) systolic function. However, as many as 30–40% of all patients with typical symptoms of Congestive Heart Failure (CHF), have a normal or slightly reduced ejection fraction. In these patients, diastolic dysfunction is implicated as a major contributor, if not the primary cause of CHF.<sup>1,2</sup> The syndrome of clinical Heart Failure with normal Left Ventricular Systolic Function in the absence of cardiac valvular lesions is often referred to as Diastolic Heart Failure (DHF). However, the diagnosis of isolated

diastolic dysfunction as a cause of heart failure remains controversial.

Primary diastolic dysfunction is typically seen in patients with hypertension and hypertrophic or restrictive cardiomyopathy but can also occur in a variety of other clinical disorders and has a particularly high prevalence in the elderly population.<sup>3,4</sup> In the Helsinki Ageing Study, 51% of patients aged 75–86 years with clinical heart failure were thought to have DHF.<sup>5</sup>

Although diastolic heart failure is common in clinical practice worldwide, its existence has been questioned

**Correspondence:** Dr. Fahad Aziz, Wake Forest School of Medicine, 295 Chelsea Village Cir, Winston Salem, NC 27103, USA. Email: fahadaziz.md@gmail.com, Phone: 347-461-6570.

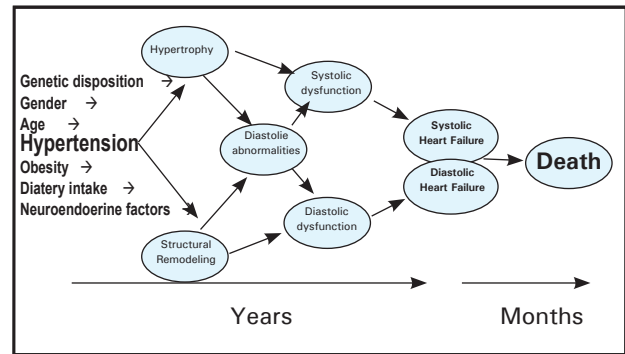
for several reasons.<sup>6-8</sup> Firstly, investigators have questioned whether these patients truly have heart failure or if they actually have conditions such as obesity or pulmonary disease that can mimic heart failure.<sup>9</sup> In a study of a direct access echocardiography service, Caruana et al concluded that most patients with suspected heart failure and preserved systolic function were inappropriately labeled as having diastolic heart failure, and in fact had other factors including lung disease causing their symptoms.<sup>10</sup>

Doubts regarding diastolic heart failure are cast especially because the diagnosis of heart failure is partly clinical and prone to error. When the left ventricular ejection fraction is low the diagnosis of heart failure is seldom questioned—clinicians seem more willing to accept a diagnosis of systolic heart failure. Fortunately the advent of biomarkers such as plasma B-type natriuretic peptides should help confirm the presence of heart failure in patients with suspected diastolic heart failure.

A second area of controversy is that while investigators may agree that some patients with heart failure do have a normal ejection fraction, they doubt if the underlying mechanism is truly left ventricular diastolic dysfunction, as implied by the term diastolic heart failure. Some of these patients have subtle abnormalities of systolic function (although the ventricular ejection fraction is normal). In some case series the relations between left ventricular pressure and volume on cardiac catheterization do not conform to a classical pattern of diastolic dysfunction.<sup>11</sup> The evidence base for the diagnosis and treatment of diastolic heart failure has lagged behind systolic heart failure mainly secondary to the foregoing points.

**Patho-physiology of Diastolic Heart Failure:** The patho-physiology of diastolic heart failure is characterized by a low cardiac output that results typically from a ventricle that has thick walls but a small cavity (Increased Left Ventricular Mass/Volume Ratio).<sup>12</sup> When the left ventricle is stiff, it relaxes slowly in early diastole and offers greater resistance to filling in late diastole, so the diastolic pressures are elevated. The low cardiac output manifests as fatigue, while the higher end diastolic pressure is transmitted backwards through the valve-less pulmonary veins to the pulmonary capillaries, resulting in exertional dyspnea. These patho-physiological abnormalities trigger neurohormonal activation as happens in systolic heart failure. Symptoms may be unmasked by exercise because, unlike normal people, patients with diastolic heart failure are unable to augment their stroke volume by increasing their left ventricular end diastolic volume (Frank-Starling mechanism). These patients often have an exaggerated response of systolic

blood pressure to exercise. Mechanisms contributing to abnormal left ventricular diastolic properties include stiff large arteries, hypertension, myocardial ischemia, diabetes, and intrinsic myocardial changes with or without associated hypertrophy<sup>12</sup> (Figure 1).



**Figure 1. Progression from hypertrophy to diastolic heart failure.** Several cardiovascular risk factors are associated with the occurrence of LV hypertrophy and structural remodeling. At the initial stage diastolic abnormalities are present with maintained systolic and diastolic function. During follow-up, systolic and diastolic dysfunction occur and are associated either systolic pump or diastolic filling failure. In the presence of congestive symptoms the time course of heart failure may become progressive and may end with sudden cardiac death or intractable end-stage failure.

**Specificity of Symptoms and Signs:** The symptoms (dyspnea, fatigue, exercise intolerance), signs (jugular venous distension, pulmonary rales, peripheral edema), and radiographic evidence (pulmonary vascular redistribution, interstitial edema, pleural effusions) of Heart Failure (HF) occur with equal frequency in patients with diastolic heart failure when compared with patients with systolic heart failure.<sup>13</sup> Therefore, the history, physical exam, and chest X-ray are not specific enough to differentiate the two entities. Taken together, however, they are specific enough to detect the presence of HF. The clinician's ability to use this clinical evidence in diagnosing HF has been questioned.<sup>14,15</sup> Curiously, this uncertainty has only been discussed with reference to DHF and has not been questioned in patients with SHF. Characteristics of SHF and DHF are compared in Table 1. It has been argued that some patients with DHF have symptoms and signs for which an explanation other than HF can be identified.<sup>14,15</sup> For example, older patients who are significantly de-conditioned may have symptoms of fatigue that may not be caused by HF. Likewise, patients with chronic lung disease may have dyspnea that is not caused by HF. The advent of widely available assays of brain natriuretic peptide

and other new noninvasive techniques may make this problem of accurately diagnosing HF less challenging. This challenge can also be overcome by using the strict, predefined, and validated criteria that include symptoms and signs of HF such as those used by Smith et al.<sup>16</sup> and others.<sup>17</sup>

<b>Table 1. Characteristics of Systolic Vs Diastolic Heart failure.</b>		
<b>Characteristics</b>	<b>Systolic heart failure</b>	<b>Diastolic heart Failure</b>
<b>Systolic function</b>		
2. Stroke volume	↓	N or ↓
3. Contractility	↓↓	↓
<b>Diastolic Function</b>		
1. LV end diastolic pressure	or ↑↑	↑ or ↑
2. Relaxing time constant	or ↑↑	↑ or ↑
3. Filling Rate	– or ↑ or N	– or ↑ or N
4. Chamber stiffness	↓	↑↑
5. Myocardial Stiffness	N or ↑	↑
<b>Mortality</b>		
1. At 6 months	↑↑	↑
2. At 5 years	↑↑	↑

**Co-existence of Systolic and Diastolic Dysfunction:** It is now clearly recognized that all patients with HF have abnormalities in both systolic and diastolic function. However, the coexistence of these functional abnormalities does not necessarily mean that SHF and DHF are part of a single continuum. There are significant differences between SHF and DHF that justify their separation into two different groups.

There is no doubt that a normal EF does not necessarily indicate the presence of normal myocardial or even ventricular contractility.<sup>18,19</sup> Therefore, patients with HF and preserved EF may have relatively small but detectable abnormalities in systolic function. For this reason the terms HF with preserved systolic function should not be used. However, there are no convincing data to support the idea that abnormalities in contractility are responsible for the symptoms and signs of HF, or the patho-physiologic remodeling that is seen in patients with DHF. Patients with DHF commonly have concentric remodeling characterized by normal LV volume, increased LV mass, increased wall thickness, decreased volume-to-mass ratio, and increased chamber and myocardial stiffness. There is no conceptual framework to support the notion that abnormal contractility contributes causally to this concentric remodeling. Therefore, the presence of abnormal indices of contractility in patients with DHF does not negate

the fact that the predominant abnormality is diastolic dysfunction, nor does it support the idea that this abnormal contractility is the mechanism responsible for the development of DHF. Thus, HF in patients with DHF is caused by a predominate (although not isolated) abnormality in diastolic function.

**Diagnosis of Diastolic Heart Failure:** The diagnosis of diastolic heart failure requires three conditions to be simultaneously satisfied.<sup>20</sup>

(1) Presence of signs and symptoms of heart failure

(2) Presence of normal or only slightly reduced LV Ejection Fraction (EF 50%)

(3) Presence of increased diastolic pressure or impaired filling caused by delayed iso-volumic relaxation or elevated stiffness.

Patients with shortness of breath on exertion, pulmonary rales, or gallop sound but with near normal systolic function are usually diagnosed with DHF.<sup>21</sup>

#### A. Non-invasive assessment of diastolic function

Several non-invasive techniques have been used for assessing diastolic function in patients with coronary, valvular or myocardial heart disease. The most commonly used methods are 2D and Doppler-echocardiography, Doppler-tissue imaging, radionuclide ventriculography, MR myocardial tagging and MR imaging.<sup>22</sup>

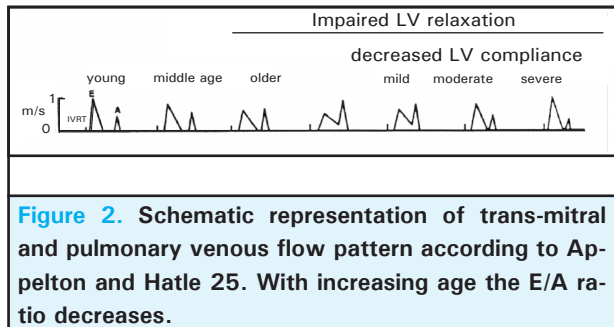
#### 1. Echocardiography

M-mode echocardiography has been used to assess the dimensional changes and its first derivatives during diastolic filling. The presence of LV myocardial fibers oriented in the longitudinal direction and located in the trabecular, subendocardial, and papillary muscle regions has led to an increasing interest in echocardiographic assessment of the LV long axis function. As displacement of the atrioventricular plane towards the apex is a direct reflection of longitudinal fiber contraction, its measurement by M-mode echocardiography provides additional information regarding global and regional systolic and diastolic function. As shown by Henein and Gibson, delayed onset of lengthening can effectively suppress early diastolic trans-mitral flow, even though the minor axis increases and mitral cusps separate normally.<sup>23</sup>

During the last two decades, Doppler-echocardiography has emerged as an important clinical tool providing reliable and useful data on diastolic performance. Three different approaches are routinely used in the assessment of diastolic dysfunction:

measurement of trans-mitral and pulmonary venous flow as well as intra-ventricular filling patterns (Doppler flow propagation).<sup>22</sup>

The trans-mitral velocity pattern remains the starting point of echocardiographic assessment of LV diastolic function, since it is easy to acquire and can rapidly categorize patients with normal or abnormal diastolic function by E/A ratio (early to late filling velocity).<sup>23,24</sup> In healthy young individuals, most diastolic filling occurs in early diastole so that the E/A ratio is  $>1$  (Figure 2).



When relaxation is impaired, early diastolic filling decreases progressively and a vigorous compensatory atrial contraction (atrial kick) occurs. This results in a reversed E/A ratio, increased deceleration time, and increased iso-volumic relaxation time.<sup>24</sup> With disease progression LV compliance becomes reduced and filling pressures begin to increase leading to compensatory augmentation of left atrial pressure with increase in early filling despite impaired relaxation, so that filling pattern looks relatively normal ('pseudo-normalization' pattern =  $E/A > 1$ ).<sup>24</sup> Finally, in patients with severe decrease in LV compliance, left atrial pressure is markedly elevated and compensates with vigorous early diastolic filling for impaired relaxation. This 'restrictive' filling pattern ( $E/A > 1$ ) is consistent with an abnormal rise in LV pressure and an abrupt deceleration of flow with little additional filling during mid-diastole and atrial contraction. In extreme cases the LV pressure rise overshoots left atrial pressure so that diastolic mitral regurgitation in mid diastole may be seen.

**Color Doppler M-mode** provides a unique window into the fluid dynamics of flow across the mitral valve. The speed of propagation is enhanced with rapid relaxation and LV suction. Clinical and experimental studies have demonstrated that the inverse correlation to  $t$  is relatively independent of left atrial pressure.<sup>25</sup> Furthermore, combined evaluation of flow propagation velocity and early diastolic annular velocity can be used for estimation of filling pressure.<sup>26</sup>

**Doppler tissue imaging** yields information on intra-myocardial velocity, providing a unique insight into LV mechanics during iso-volumic contraction and

relaxation. In normal persons the mitral annular motion is almost a mirror image of the trans-mitral flow pattern, but in patients with pseudo normal or restrictive filling pattern, annular motion is abnormally low, implying that it is relatively independent of preload.<sup>27,28</sup>

It has been shown that relaxation velocities in the myocardium are inversely correlated with  $t$ , so that a non-invasively calculation of the time constant of relaxation seems to be possible.<sup>29,30</sup> Through the integrated use of Doppler echocardiography and Doppler tissue imaging, it is possible to obtain a fairly precise picture of LV diastolic function.<sup>31</sup> However, atrial fibrillation or frequent ectopic beats are the major limitation of these techniques. To overcome this problem, averaging of several heart cycles with similar RR intervals has been proposed.

## 2. Magnetic resonance imaging

This technique has been shown to be of considerable use in the morphologic assessment of the heart, but functional assessment can also be obtained. However, their clinical relevance remains to be demonstrated.<sup>32</sup> Additional information may be gained from newer techniques such as magnetic resonance myocardial tagging, which allows the labeling of specific myocardial regions.<sup>33</sup> From these tags the rotational and translational motion of the left ventricle can be determined, which is characterized by a systolic wringing motion followed by a rapid diastolic untwisting.<sup>34</sup> This untwisting motion is directly related to relaxation and may be used as a measure of the rate and completeness of relaxation as well as an estimate of early diastolic filling.

## 3. Radionuclide angiography

This technique may be used to study the rapid filling phase of diastole, the duration of the iso-volumic relaxation phase, the relative contribution of rapid filling to total diastolic filling, and the relation between regional non-uniformity of left ventricular function and global filling properties.<sup>35-37</sup> However, radionuclide angiography does not permit assessment of the left atrial-left ventricular pressure gradient or the simultaneous evaluation of changes in left ventricular pressure and volume during relaxation and filling. Therefore, complete clinical interpretation of 'abnormal' left ventricular filling indexes, or changes in these indexes after interventions, is not possible. Despite the inherent limitations of noninvasive assessment of left ventricular diastolic function, radionuclide evaluation of left ventricular filling may provide clinically useful insights.<sup>38</sup>

## B. Invasive assessment of diastolic function

**Cardiac catheterization** with simultaneous pressure and volume measurements is the 'gold' standard for assessing LV diastolic function. Prerequisites are high-fidelity pressure recordings with simultaneous angio or echocardiography or the use of the conductance technique. The rate of LV relaxation, rate and timing of diastolic filling as well as myocardial and chamber stiffness can be determined.<sup>39</sup>

## Management of diastolic dysfunction

Despite the large number of individuals suffering from diastolic dysfunction, there is a paucity of recommendations available to help guide medical therapy in these patients. The guidelines for the European Society of Hypertension (ESH) only briefly touch on the subject of diastolic dysfunction and offer no specific recommendations for its management, commenting that little information is available comparing the effects of different antihypertensive agents on diastolic dysfunction.<sup>40</sup> The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure also discussed the high prevalence of impaired LV relaxation in hypertensive patients, but had no specific recommendations on its management.<sup>41</sup> Thus, for the moment, there are no definitive guidelines for treating diastolic dysfunction.

Diastolic dysfunction may be present for several years before any symptoms occur and may represent the first phase of diastolic heart failure. Thus, it is important to detect diastolic dysfunction early and to start treatment before irreversible structural alterations and systolic dysfunction have occurred.

**Four treatment goals** have been advocated for the therapy of diastolic dysfunction:

1. Reduction of central blood volume (diuretics)
2. Improvement of LV relaxation (calcium channel blockers or ACE inhibitors)
3. Regression of LV hypertrophy (decrease in wall thickness and removal of excess collagen by ACE inhibitors, ARB)
4. Maintenance of atrial contraction and control of heart rate (beta-blockers & antiarrhythmic)

**1. Diuretics:** Diuretics are effective in reducing pulmonary congestion in patients with diastolic dysfunction, shifting the pressure-volume relation downwards. However, their positive effect on LV chamber stiffness is indirect, caused particularly by a reduction in systemic blood

volume and the lowering of right atrial blood volume with a decrease in pericardial constraint. However, they must be used judiciously because the volume sensitivity of patients with diastolic dysfunction bears the risk that excessive diuresis results in sudden drop of stroke volume.<sup>42</sup> The steep pressure-volume relationship, has explained volume sensitivity when stroke volume can be maintained only with a high filling pressure. A small decrease in diastolic filling pressure results in a drop in stroke volume, thus, cardiac output.

**2. Beta-blockers:** Beta-blockers have long been theorized to provide benefit to patients with diastolic dysfunction. By slowing the heart rate to allow more time for LV filling and lowering blood pressure to improve LV compliance, beta-blockers can improve diastolic function.<sup>43</sup> Tachycardia has also been shown to be detrimental to patients with diastolic dysfunction because the increased heart rate shortens the diastolic filling period resulting in less time for LV relaxation and worse compliance.<sup>44</sup> These concepts have been validated in the SILVHIA trial, which found that after 48 weeks of treatment with Atenolol, patients with diastolic dysfunction and hypertension had improvements in indices of diastolic function.<sup>45</sup> Another smaller study also showed that after six months of treatment with Atenolol or Nebivolol, hypertensive patients with diastolic dysfunction had decreased LV mass and an improved E/A ratio.<sup>46</sup> There is conflicting data regarding the clinical benefits of these improved diastolic filling parameters. In subgroup analysis of the patients with DHF, Nebivolol did not show a reduction in all-cause mortality or cardiovascular hospital admissions at 21 months.<sup>47</sup> Two small studies showed clinical benefits with beta-blockers in DHF. The first examined the impact of Propranolol on 158 patients with heart failure and ejection fraction(40%).<sup>48</sup> At 32 months, patients receiving Propranolol had a 35% reduction in total mortality and a 37% reduction in the composite of total mortality or nonfatal myocardial infarction. The second trial showing the benefit of beta blockade in DHF consisted of 40 patients with mild or moderate heart failure and EF (>45%).<sup>49</sup>

**3. Calcium channel blockers:** Calcium channel blockade is thought to improve diastolic function by several mechanisms, including attenuating calcium homeostasis, reducing blood pressure, promoting LV hypertrophy regression, and slowing the heart rate.<sup>50</sup> Benefits of calcium channel blockade on diastolic function have been examined in a few studies. In the ELVERA trial, the use of Amlodipine in hypertensive patients led to a reduction in LV mass and improved diastolic function at two year follow up.<sup>51</sup> In a sub-study of the Anglo- Scandinavian Cardiac Outcomes Trial (ASCOT), hypertensive patients with diastolic



dysfunction were treated with Amlodipine and had improved diastolic filling parameters at 1-year follow-up.<sup>52</sup> Calcium blockers of the verapamil type are first line drugs in patients with hypertrophic cardiomyopathy due to their beneficial effect on relaxation and diastolic filling, which are often severely abnormal in these patients.<sup>53</sup>

**4. ACE-inhibitors and ARB:** ACE inhibitors and ARB's show not only an effect on blood pressure but elicit a direct effect on the myocardium via the local renin-angiotensin system. These effects are essential for the regression of LV hypertrophy, and the improvement in the elastic properties of the myocardium.<sup>54,55</sup> Several trials have documented that LV hypertrophy is more effectively reduced by ACE inhibitors than by any other antihypertensive drugs, suggesting an effect

on myocardial structure beyond that provided by the reduction of pressure overload. Recent data suggest that ARBs have similar effects on LV mass and structure such as ACE inhibitors. In a direct comparative trial of ARBs and beta-blockers, it was demonstrated that despite similar reductions in blood pressure, regression of LV hypertrophy with Irbesartan was greater than those attained with Atenolol.<sup>56</sup>

**5. Digitalis:** Digitalis should not be used in patients with diastolic dysfunction, except in those with atrial fibrillation. When atrial fibrillation occurs, restoration of sinus rhythm is mandatory and is best achieved with electric conversion. For prophylaxis of recurrence, beta-blockers, especially sotalol, which exerts a class III antiarrhythmic effect and amiodarone are the most suitable.

## REFERENCES

1. Bonow RO, Udelson JE. Left ventricular diastolic dysfunction as a cause of congestive heart failure. Mechanisms and management. *Ann Intern Med.* 1992;117:502-10.
2. Cregler LL, Georgiou D, Sosa I. Left ventricular diastolic dysfunction in patients with congestive heart failure. *J Natl Med Assoc.* 1991;83:49-52.
3. Fagerberg B. National and international guidelines ignore significant cause of heart failure. Diastolic dysfunction is often the cause of heart failure in the elderly and in women. *Lakartidningen.* 1998;95:5305-8.
4. Marantz PR, Tobin JN, Derby CA, Cohen MV. Age-associated changes in diastolic filling: Doppler E/A ratio is not associated with congestive heart failure in the elderly. *South Med J.* 1994;87:728-35.
5. Lindroos M, Iivanainen AM, Heikkilä J, Tilvis R. Congestive heart failure in old age: prevalence, mechanisms and 4-year prognosis in the Helsinki Ageing Study. *J Intern Med.* 1997;241:387-94.
6. Ibrahim BS. The frequency of systolic versus diastolic heart failure in an Egyptian cohort. *Eur J Heart Fail.* 2003;5:41-5.
7. Sanderson JE, Chan SK, Chan WW, Hung YT, Woo KS. The aetiology of heart failure in the Chinese population of Hong Kong-a prospective study of 730 consecutive patients. *Int J Cardiol.* 1995;51:29-35.
8. 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.
9. Caruana L, Petrie MC, Davies AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. *BMJ.* 2000;321:215-8.
10. Caruana L, Petrie MC, Davies AP, McMurray JJV. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. *Br Med J.* 2000;321:215-8.
11. Burkhoff D, Maurer MS, Packer M. Heart failure with a normal ejection fraction: is it really a disorder of diastolic function? *Circulation.* 2003;107:656-8.
12. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA.* 2002;288:2144-50.
13. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure. Part I: diagnosis, prognosis, measurements of diastolic function. *Circulation.* 2002;105:1387-93.
14. Caruana L, Petrie MC, Davies AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. *BMJ.* 2000;321:215-8.
15. Banerjee P, Banerjee T, Khand A, Clark AL, Cleland JG. Diastolic heart failure: neglected or misdiagnosed? *J Am Coll Cardiol.* 2002;39:138-41.
16. Smith GL, Masoudi FA, Vaccarino V, Radford MJ, Krumholz HM. Outcomes in heart failure patients with preserved ejection fraction: mortality, readmission, and functional decline. *J Am Coll Cardiol.* 2003;41:1510-8.
17. 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.
18. Shimizu G, Zile MR, Blaustein AS, Gaasch WH. Left ventricular chamber filling and midwall fiber lengthening in left ventricular hypertrophy: conventional midwall measurements overestimates fiber velocities. *Circulation.* 1985;71:266-72.

19. Aurigemma GP, Silver KH, Priest MA, Gaasch WH. Geometric changes allow normal ejection fraction despite depressed myocardial shortening in hypertensive left ventricular hypertrophy. *J Am CollCardiol*. 1995;26:195-202.
20. European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. *Eur Heart J*. 1998;19:990-1003.
21. Packer M. Abnormalities of diastolic function as a potential cause of exercise intolerance in chronic heart failure. *Circulation*. 1990 Feb;81(2 suppl):III78-86.
22. 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 SocEchocardiogr*. 1996;9:736-60.
23. Henein MY, Gibson DG. Suppression of left ventricular early diastolic filling by long axis asynchrony. *Br Heart J*. 1995;73:151-7.
24. Giannuzzi P, Imparato A, Temporelli PL et al. Doppler-derived mitral deceleration time of early filling as a strong predictor of pulmonary capillary wedge pressure in postinfarction patients with left ventricular systolic dysfunction. *J Am CollCardiol*. 1994;23:1630-7.
25. Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. *J Am CollCardiol*. 1988;12:426-40.
26. Takatsuji H, Mikami T, Urasawa K et al. A new approach for evaluation of left ventricular diastolic function: spatial and temporal analysis of left ventricular filling flow propagation by color M-mode Doppler echocardiography [see comments]. *J Am CollCardiol*. 1996;27:365-71.
27. Nagueh SF, Middleton KJ, Spencer WH, Zoghbi WA, Quinones MA. Doppler estimation of left ventricular filling pressure in patients with hypertrophic cardiomyopathy. *Circulation*. 1999;99:254-61.
28. Sohn DW, Chai IH, Lee DJ et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol*. 1997;30:474-80.
29. Lindstrom L, Wranne B. Pulsed tissue Doppler evaluation of mitral annulus motion: a new window to assessment of diastolic function. *Clin Physiol*. 1999;19:1-10.
30. Sohn DW, Kim YJ, Kim HC, Chun HG, Park YB, Choi YS. Evaluation of left ventricular diastolic function when mitral E and A waves are completely fused: role of assessing mitral annulus velocity. *J Am SocEchocardiogr*. 1999;12:203-8.
31. Oki T, Tabata T, Yamada H et al. Clinical application of pulsed Doppler tissue imaging for assessing abnormal left ventricular relaxation [see comments]. *Am J Cardiol*. 1997;79:921-8.
32. Blomstrand P, Kongstad O, Broqvist M, Dahlstrom U, Wranne B. Assessment of left ventricular diastolic function from mitral annulus motion, a comparison with pulsed Doppler measurements in patients with heart failure. *Clin Physiol*. 1996;16:483-93.
33. Kudelka AM, Turner DA, Liebson PR, Macioch JE, Wang JZ, Barron JT. Comparison of cine magnetic resonance imaging and Doppler echocardiography for evaluation of left ventricular diastolic function. *Am J Cardiol*. 1997;80:384-6.
34. Zerhouni EA, Parish DM, Rogers WJ, Yang A, Shapiro EP. Human heart: tagging with MR imaging – a method for noninvasive assessment of myocardial motion. *Radiology*. 1988;169:59-63.
35. Stuber M, Schedegger MB, Fischer SE et al. Alterations in the local myocardial motion pattern in patients suffering from pressure overload due to aortic stenosis. *Circulation*. 1999;100:361-8.
36. Chen YT, Chang KC, Hu WS, Wang SJ, Chiang BN. Left ventricular diastolic function in hypertrophic cardiomyopathy: assessment by radionuclide angiography. *Int J Cardiol*. 1987;15:185-93.
37. Briguori C, Betocchi S, Losi MA et al. Noninvasive evaluation of left ventricular diastolic function in hypertrophic cardiomyopathy. *Am J Cardiol*. 1998;81:180-7.
38. Bonow RO. Radionuclide angiographic evaluation of left ventricular diastolic function. *Circulation*. 1991;84:1208-15.
39. Little WC, Downes TR, Applegate RJ. Invasive evaluation of left ventricular diastolic performance. *Herz*. 1990;15:362-76.
40. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European society of hypertension (esh) and of the European society of cardiology (ESC). *Eur Heart J*. 2007 Jun 28;28(12):1462-536.
41. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo J, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *J Am Med Assoc*. 2003 May 21;289(19):2560-72.
42. Dumesnil JG, Gaudreault G, Honos GN, Kingma Jr. JG. Use of Valsalva maneuver to unmask left ventricular diastolic function abnormalities by Doppler echocardiography in patients with coronary artery disease or systemic hypertension. *Am J Cardiol*. 1991;68:515-9.
43. Bonow RO, Udelson JE. Left ventricular diastolic dysfunction as a cause of congestive heart failure. Mechanisms and management. *Ann Intern Med*. 1992 Sep;117(6):502-10.
44. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: part II: causal mechanisms and treatment. *Circulation*. 2002 Mar 26;105(12):1503-8.

45. Muller-Brunotte R, Kahan T, Malmqvist K, Ring M, Edner M. Tissue velocity echocardiography shows early improvement in diastolic function with irbesartan and atenolol therapy in patients with hypertensive left ventricular hypertrophy. Results from the Swedish irbesartan left ventricular hypertrophy investigation vs atenolol (SILVHIA). *Am J Hypertens*. 2006 Sep;19(9):927-36.
46. Nodari S, Metra M, Dei Cas L. Beta-blocker treatment of patients with diastolic heart failure and arterial hypertension. A prospective, randomized, comparison of the long-term effects of atenolol vs. nebivolol. *Eur J Heart Fail*. 2003 Oct; 5(5):621-7.
47. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, 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 Feb;26(3):215-25.
48. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or Z40% treated with diuretics plus angiotensin-converting enzyme inhibitors. *Am J Cardiol*. 1997 Jul 15;80(2):207-9.
49. Takeda Y, Fukutomi T, Suzuki S, Yamamoto K, Ogata M, Kondo H, et al. Effects of carvedilol on plasma B-type natriuretic peptide concentration and symptoms in patients with heart failure and preserved ejection fraction. *Am J Cardiol*. 2004 Aug 15;94(4):448-53.
50. Ventura H, Loyalka P, Smart FW. Treatment of the hypertensive patient with microvascular angina. *Curr Opin Cardiol*. 1999 Sep;14(5):370-4.
51. Terpstra WF, May JF, Smit AJ, de Graeff PA, Havinga TK, van den Veur E, et al. Long-term effects of amlodipine and lisinopril on left ventricular mass and diastolic function in elderly, previously untreated hypertensive patients: the ELVERA trial. *J Hypertens*. 2001 Feb;19(2):303-9.
52. Tapp RJ, Sharp A, Stanton AV, O'Brien E, Chaturvedi N, Poulter NR, et al. Differential effects of antihypertensive treatment on left ventricular diastolic function: an ASCOT (anglo-scandinavian cardiac outcomes trial) substudy. *J Am Coll Cardiol*. 2010 Apr 27;55(17):1875-81.
53. Rosing DR, Idanpaan-Heikkilä U, Maron BJ, Bonow RO, Epstein SE. Use of calcium-channel blocking drugs in hypertrophic cardiomyopathy. *Am J Cardiol*. 1985;55:185b-95b.
54. Mitsunami K, Inoue S, Maeda K et al. Three-month effects of candesartan cilexetil, an angiotensin II type 1 (AT1) receptor antagonist, on left ventricular mass and hemodynamics in patients with essential hypertension. *Cardiovasc Drugs Ther*. 1998 Oct;12(5):469-74.
55. Angomachalelis N, Hourzamanis AI, Sideri S, Serasli E, Vamvalis C. Improvement of left ventricular diastolic dysfunction in hypertensive patients 1 month after ACE inhibition therapy: evaluation by ultrasonic automated boundary detection. *Heart Vessels*. 1996;11:303-9.
56. Kahan T. The importance of left ventricular hypertrophy in human hypertension. *J Hypertens Suppl*. 1998;16:S23-9.