

Advances in diastolic heart failure

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Abstract

More than 50% of people living with congestive heart failure have diastolic heart failure (DHF). Most of them are older than 70 years, and female. The prevalence of DHF has increased with time. DHF is caused by left ventricular (LV) diastolic dysfunction (DD) which is induced by diastolic dyssynchrony. Cardiac and extra-cardiac factors play important roles in the development of heart failure (HF) symptoms. The diagnosis of DHF is generally based on typical symptoms and signs of HF, preserved or normal LV ejection fraction, DD and no valvular abnormalities on examination, using non-invasive and invasive methodologies. The outcomes with pharmacological therapy in patients with DHF are frequently neutral in clinical trials, and prognosis still remains poor with a 5-year mortality of 42.3% after hospitalization for HF. Further trials are necessary.

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Key words: B-type natriuretic peptide; Diastolic dysfunction; Diastolic dyssynchrony normal ejection fraction; Diastolic heart failure; Echocardiography; Heart failure

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INTRODUCTION

The terms, systolic and diastolic heart failure (DHF), have been routinely used in clinical practice to establish categories of congestive heart failure (CHF). Ejection fraction (EF) as the preferred index of left ventricular (LV) systolic performance has been recognized. In addition, LVEF as an indicator of the LV pumping function allows the separation of patients with heart failure (HF) into grades of severity associated with different prognoses. In clinical practice, a group of patients with CHF characterized by normal or near-normal LVEF and absence of progressive LV dilatation, were classified as DHF by Kessler^[1]. This review highlights advances in the clinical and diagnostic aspects of DHF.

PREVALENCE OF DHF

CHF affects approximately six million people, and more than 550 000 new cases are diagnosed each year in the USA^[2,3]. Studies have demonstrated that more than 50% of people living with CHF have DHF^[3,4]. Most patients with DHF are older than 70 years, and are female. Patients with DHF are usually overweight and quite often are smokers^[5]. In another study, 69% of men and 90% of women with CHF had DHF, based on current HF symptoms and an LVEF > 45%^[6]. In the CHARM preserved trial of DHF, a total of 3025 patients with a mean age of 67 years and a mean LVEF of 54% were included, 40%

were women^[7]. In the PEP-CHF multicenter, randomized, placebo-controlled trial, 850 patients with DHF and a mean age of 76 years and a mean LVEF of 65% were enrolled, 55% were women^[8]. It is recognized that the prevalence of DHF has increased in accordance with a combination of factors, including an increase in the elderly population, the development of non-invasive diagnostic techniques for detecting heart function, such as echocardiography, cardiac magnetic resonance (CMR), positron emission tomography and single-photon emission computed tomography, as well as improvements in the treatment of coronary artery disease (CAD) and other cardiovascular diseases resulting in the preservation of LVEF. However, the prognosis of DHF still remains poor with a 5-year mortality of 42.3% after hospitalization for HF^[2].

PATHOPHYSIOLOGY OF DHF

DHF is caused by LV diastolic dysfunction (DD), leading to increased resistance to LV filling and finally resulting in HF syndrome. Diastolic dyssynchrony leading to DD is well supported by a number of studies^[9]. The pathophysiology of DHF is still not completely known, evidence suggests that cardiac and extracardiac factors play important roles in the development of HF symptoms. Elderly patients with DHF usually have systolic hypertension with a wide pulse pressure^[5] and have evidence of concentric LV hypertrophy or normal mass with increased wall thickness to cavity radius. Patients may also have complicating disorders, such as atrial fibrillation, CAD, anemia, diabetes, and renal failure.

Patients with DHF have normal or near-normal end-diastolic volumes with demonstrable DD that impairs primarily LV relaxation, followed by the development of an increased chamber stiffness^[9]. Cardiac relaxation is altered due to aging, pathological hypertrophy, increased afterload, ischemia and some neuro-hormonal factors such as the renin-angiotensin system. LV stiffness is mainly influenced by myocardial stiffness, which is altered by wall thickness, interstitial fibrosis, and incomplete relaxation, biventricular interaction, LV geometry, and pericardial constraint^[10]. In elderly and/or hypertensive patients, abnormalities of relaxation and stiffness are more common even without clinical findings of HF, which influence the effect of volume loading. What effect does left atrial (LA) function have in patients with DHF? A study showed that LA stiffness is the most accurate parameter in identifying patients with DHF^[11], and revealed that although asymptomatic hypertensive patients with LV hypertrophy and patients with normal LVEF and DHF had no differences in LV mass, LA volumes, or LA contraction function, DHF patients did have reduced LA strain and strain rate during LV systole, and increased LA stiffness index.

Diastole of the heart starts with isovolemic relaxation, which is an energy-dependent process, followed by

rapid ventricular filling, and eventually atrial contraction. Impairment in diastolic filling caused by DD leads to the development of an increase in pulmonary pressures and sequentially pulmonary congestion or edema, followed by the development of clinical symptoms and signs of DHF. DD can be induced by intrinsic or extrinsic factors, and intrinsic factors include impaired relaxation and/or increased stiffness. Active relaxation depends on the integrated process of the regulation of diastolic intracellular calcium levels and the uncoupling of the myofilament protein responsible for cellular contraction: Intracellular calcium control during diastole is mainly dependent on calcium uptake into the sarcoplasmic reticulum, mediated by the sarcoplasmic/endoplasmic reticulum calcium adenosine triphosphate (ATP)ase type 2^[12], and low sarcoplasmic/endoplasmic reticulum calcium ATPase type 2 is related to impaired relaxation^[13]. Activity of sarcoplasmic/endoplasmic reticulum calcium ATPase type 2 is regulated by the interacting protein, phospholamban, and is further controlled by phosphorylation^[12]. Extrinsic factors, such as pericardial restriction, can also induce DD^[14]. Pathological hypertrophy in the ventricle can increase ventricular stiffness and impair diastolic function. Concentric LV hypertrophy is common secondary to hypertension or aortic stenosis, resulting in disproportionate growth of the nonmyocardial extracellular matrix, which can also increase ventricular stiffness^[15], this change in the extracellular matrix, particularly in fibrillar collagen- α key component of the extracellular matrix, leads to ventricular hypertrophy and DD. This concentric LV hypertrophy may also decrease activity of the sarcoplasmic reticulum calcium ATPase and increase phospholamban which are caused by calcium removal from the cytosol due to ischemia^[16]. The hypertrophied heart can not completely relax, and thereby increases LV filling pressure^[17], influencing diastolic filling. Activation of the renin-angiotensin-aldosterone system is the key in developing myocardial fibrosis and stiffness, stimulating vasoconstriction, and maintaining sodium and water. Angiotensin II and aldosterone both stimulate collagen deposition, and aldosterone can also act in salt retention^[18].

LV rotation, twist, and torsion are important aspects of cardiac mechanics. The term "rotation" refers to rotation of the short-axis section of LV^[19]. LV twist is the net difference at isochronal time points between the apex and base in the rotation angle along the LV longitudinal axis, therefore LV torsion is LV twist indexed to the distance between LV apex and LV base (LV length)^[20]. The LV twist increases gradually from infancy to adulthood, increasing LV torsion and untwisting (clock-wise rotation) velocity with age. Untwisting normally starts in late systole and is complete before mitral valve opening. The LV untwisting rate has been evaluated as an index of myocardial relaxation. The LV untwisting rate correlates well with LV twist and with negative end-systolic volume regardless of LVEF.

Patients with DHF have delayed onset and delayed peak of untwisting, these patients have larger LA volumes and higher pulmonary artery pressure^[21]. One study has proposed that endocardial function is more likely to reduce with age due to greater susceptibility of the subendocardium to fibrosis and/or subclinical reduction in perfusion^[19]. The finding of increased torsion and reduced subendocardial function in the elderly results in the preservation of LVEF, and may explain why DHF is seen more often in elderly people. Studies have reported a significant correlation between LV twist and LVEF, or between dp/dt_{max} (an invasive unit for measuring LV contractility) and LV twist ($R^2 = 0.747$, $P < 0.001$). It is suggested that LV twist may be an index of systolic myocardial deformation, while LVEF simply reflects LV volume reduction during systole^[22].

DIAGNOSIS OF DHF

The diagnosis of DHF is generally based on the typical symptoms and signs of HF, preserved or normal LVEF, DD and no valvular abnormalities on examination (named HFNEF). The revised criteria for the diagnosis of HFNEF published by the European Society of Cardiology has to include all of the 3 following items: (1) Clinical symptoms or signs of HF; (2) Normal or mildly reduced LV systolic function and normal LV chamber size (LVEF $> 50\%$ and LVEDVI $< 97 \text{ mL/m}^2$); and (3) Evidence of abnormal LV relaxation, filling, diastolic distensibility and diastolic stiffness (including the following measurements: (a) PCWP $> 12 \text{ mmHg}$ or LVEDP $> 16 \text{ mmHg}$; (b) time constant of LV relaxation (τ) $> 48 \text{ msc}$; or (c) diastolic LV stiffness modulus > 0.27 , or (d) echocardiographic data alone or combined with biomarkers^[23]. The criteria of the National Heart, Lung, and Blood Institute's Framingham Heart Study, require all 3 of the following for the diagnosis of HFNEF: (1) Definite evidence of HF; (2) Normal LV systolic function (LVEF ≥ 0.50 within 72 h of the HF event); and (3) Evidence of abnormal LV relaxation, filling, distensibility indices on cardiac catheterization^[24]. Invasive criteria [as described in (a) of the European criteria] are more difficult to apply in the majority of patients, noninvasive modalities have recently had widespread clinical application.

Echocardiography can be used to reliably measure LV volumes, mass and EF. Tissue Doppler imaging of mitral annulus velocities is the most sensitive and reliable method for assessing LV relaxation and filling pressures in patients with DHF. Mitral annulus e' velocity relates significantly with the time constant of LV relaxation, and the ratio of mitral E velocity to mitral annulus e' velocity (E/e') correlates with LV filling pressure^[25]. The E/e' ratio also seems to reflect LV filling pressure during exercise. E/e' measured at the medial annulus was related to LVEDP both at rest and during exercise, but the r value during exercise ($= 0.570$) was worse than at rest ($= 0.67$)^[26]. Ommen *et al.*^[27] showed that the correlations between the E/e' ratio (e' measured at the medial mitral

annulus) and the mean LV diastolic pressure was 0.60 for patients with LVEF $< 50\%$ but only 0.47 for patients with LVEF $> 50\%$. All patients with an E/e' ratio > 15 had a mean diastolic LV pressure $> 12 \text{ mmHg}$. If the average of septal and lateral e' is used, an E/e' ratio < 8 identifies patients with normal filling pressure, a ratio > 13 identifies patients with elevated LV filling pressure^[28]. Therefore an E/e' ratio > 15 has been suggested for the diagnosis of HFNEF in patients with typical findings of HF and an LVEF $> 50\%$. An E/e' ratio between 8 and 15 was associated with a very wide range of mean LV diastolic pressure^[27]. CMR may be considered as the gold standard for LV and LA volume and LV mass measurements. In patients with suspected HFNEF, CMR can demonstrate preserved LV systolic function, normal LV volume, LV hypertrophy, and an enlarged LA volume^[29].

B-type natriuretic peptide (BNP), a cardiac neuro-hormone released by the ventricles in response to volume expansion and pressure overload, has a half-life of about 20 min, and the N-terminal part of its precursor peptide (NT-proBNP) has a longer half-life of approximately 1 to 2 h, leading to higher circulating levels and slower fluctuations compared with BNP, despite the 1:1 secretion. BNP and NT-proBNP levels were elevated in patients with LV DD and correlated with the severity of LV DD and LV filling pressure^[30]. Both BNP levels have been shown to correlate with invasive indices of LV DD, the time constant of relaxation, LV end-diastolic pressure, and LV stiffness^[31]. Investigators have suggested using NT-proBNP to distinguish a normal from a "pseudonormal" (elevated LVEDP) LV filling pattern^[30]. BNP levels are elevated in DHF and systolic heart failure (SHF), and mean BNP levels are 20 times greater in patients with DHF than in matched control normal subjects^[32]. Natriuretic peptide levels are clearly age- and gender-specific, the normal value in 90% of young, healthy adults is BNP $< 25 \text{ pg/mL}$ and NT-proBNP $\leq 70 \text{ pg/mL}$ ^[33]. The European criteria recommend that natriuretic peptide, when used for diagnostic purposes, should be implemented with echocardiographic indices of LV DD, but they can also be used for exclusion based on the high negative predictive value, which is 96% and 93% when using a cut-off value of 100 pg/mL for BNP and 120 pg/mL for NT-proBNP, respectively^[23].

TREATMENT OF DHF

Table 1 depicts the benefits of drugs in patients with DHF on the different studies. β blockers and slow-releasing calcium channel blockers are generally used in patients with DHF. These drugs can decrease blood pressure, afterload and increase the diastolic filling period. However, they may have an adverse effect on LV relaxation and negative chronotropic properties. Cardiac output will be reduced despite better filling when the heart rate is decreased significantly. An initial goal might be a heart rate of approximately 60 beats/min at rest. These drugs increase LV filling time to keep pulmonary

Table 1 The benefits of drugs in patients with DHF in different studies

	Diuretic	D + irbes	D + Ram	Digoxin	Candes	Perindo	Nebivo	irbes
n	50	56	45	492	3022	850	2128	4128
mean age (yr)	70	75	74	67	67	65	76	72
Female (%)	58	66	60	42	40	54	36	60
Mean LVEF (%)	69	66	65	50-71	54	65	36	59
Results								
(52 wk) LV mass (g)	-11	-8	-7					
QoL score	20.0-10.9	19.0-9.4	23.0-11.4					
6 MWT (meter)	1011-1048	950-1007	962-1028					
Benefits				No		No	No	
Death					No			No
CV or CHF hospital					Yes			No
Ref.	[36]	[36]	[36]	[35]	[7]	[8]	[34]	[42]

D: Diuretic; irbes: Irbesartan; Ram: Ramipril; Candes: Candesartan; Perindo: Perindopril; Nebivo: Nebivolol; QoL: Quality of life; 6 MWT: 6 min walk test.

artery pressure lower, but they also directly reduce the heart's ability to relax due to their effects at the cell level. Therefore, patients with DHF need very individualized treatment, and the final balance among all these effects determines the clinical response in a given patient. A new β blocker-Nebivolol has been investigated in an initial study^[34], and the main benefit of this agent is the blocking of β -1 without β -2 blocking as well as relaxing the arteries without the side effects of vasodilatation. Nebivolol also helps endothelial function and is a powerful anti-oxidant. The study showed that 43 HF patients (total 104 cases) with an LVEF < 36%, had reduced heart size and improved EF (5%), but no changes in patients with near-normal or normal LVEF (DHF) were observed after 1 year. In patients with HF and advanced systolic LV dysfunction, nebivolol reduces ventricular size and improves EF^[34]. A study revealed that digoxin is not helpful in treating patients with mild to moderate chronic DHF and normal sinus rhythm^[35]. In patients with signs of volume overload, diuretics are needed and appear to reduce symptoms and improve quality of life^[36], however, it is necessary to avoid an acute drop in LV stroke volume. Diuretic dose for DHF is usually much smaller than for SHF, whereas β blockers are titrated much more rapidly to moderate or high doses in DHF patients based on the clinical response^[37].

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers can lead to regression of LV mass and interstitial fibrosis due partially to their favorable effect on LV stiffness^[38]. Initial therapy should begin with an ACEI when indicated. Studies have demonstrated that ACEIs can decrease LV hypertrophy, increase LV relaxation^[39], and significantly improve diastolic filling, exercise tolerance, LVEF and HF functional class^[40]. Losartan induced a greater reduction in LV mass from baseline than the β blocker atenolol in a study of patients with hypertensive LV hypertrophy^[41]. A multicenter, randomized, controlled trial^[36] indicated that irbesartan and ramipril in combination with diuretics could reduce LV mass, which become statistically significant only for irbesartan at 24 wk, with no differences

among the three groups at 1 year. A large multicenter placebo-controlled study of 4128 patients with a mean age of 72 years, of which 60% were female, showed the morbidity-mortality of DHF patients enrolled in the I (irbesartan)-PRESERVE trial, and demonstrated that irbesartan did not improve the outcomes of patients with HFNEF^[42]. Despite the use of similar drugs, outcomes in recent HF trials were frequently neutral in patients with HFNEF and positive in HF patients with reduced LVEF (HFREF). The neutral outcomes in HFNEF trials were often attributed to reduced HFNEF patient recruitment with inclusion of many HFREF or noncardiac patients^[43]. Further clinical trials are required to control the criteria and various cutoff points of the results.

CONCLUSION

More than 50% of people living with CHF have DHF. The prevalence of DHF has increased with time. The diagnosis of DHF is generally based on typical symptoms and signs of HF, preserved or normal LVEF, DD and no valvular abnormalities. The outcomes of pharmacological therapy in patients with DHF are frequently neutral in clinical trials. Further trials are necessary.

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