Diastolic heart failure: diagnosis and therapy

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Purpose of review
This article focuses on the recent findings in the diagnosis and treatment of diastolic heart failure (DHF) or heart failure with preserved ejection fraction.

Recent findings
DHF has become the most common form of heart failure in the population. Although diastolic dysfunction still plays a central role, it is now understood that DHF is a very complex clinical entity with heterogeneous pathophysiology and significant contribution from extracardiac comorbidities. Alterations in ventricular-arterial coupling play a significant role in the impaired hemodynamic response to exercise seen in these patients. The absence of diastolic dysfunction at rest does not exclude the diagnosis of DHF. There has been little to no progress made in identifying evidence-based, effective, and specific treatments for patients with DHF. This may be because of the pathophysiological heterogeneity, incomplete understanding of DHF, and heterogeneity of patients included in clinical trials with variable inclusion criteria.

Summary
The understanding of the phenotypic heterogeneity and multifactorial pathophysiology of DHF may lead to novel therapeutic targets in the future. Currently, the key to the treatment of DHF is aggressive management of contributing factors.

Keywords
diagnosis, diastolic function, heart failure preserved ejection fraction, therapy

INTRODUCTION

Heart failure is a diagnosis associated with considerable morbidity and mortality. More than 5 million people in the USA carry this diagnosis with a sobering mortality rate of 50% at 5 years from diagnosis [1]. Although heart failure with reduced ejection fraction is a well understood, well studied entity in cardiovascular medicine, heart failure with preserved ejection fraction has only recently been identified as a clinical entity. It is considered to account for at least 50% of all heart failure cases and be responsible for the majority of heart failure hospital admissions. Its incidence will only increase in the coming years as the population ages [2]. Heart failure with preserved ejection fraction is defined by the American College of Cardiology and American Heart Association as the presence of clinical symptoms or signs of heart failure in a patient with a left ventricular ejection fraction (LVEF) greater than 50% with evidence of diastolic dysfunction by Doppler echocardiography or cardiac catheterization [3]. Several labels have been used to describe the same clinical entity such as heart failure with preserved ejection fraction, heart failure with normal ejection fraction, and diastolic heart failure (DHF). Although the term heart failure with preserved ejection fraction seems to be favored in the existing literature, for the purpose of this review, we will use the term DHF.

PATHOPHYSIOLOGY

Despite its importance, our understanding of the pathophysiology of DHF is still incomplete. Traditionally, it was assumed that the only pathology responsible for this disorder is impaired filling and diastolic dysfunction, hence the label of DHF. It is now understood that diastolic dysfunction plays a central role, but is not the solitary contributor to the diagnosis of DHF. Additional contributing pathophysiologic mechanisms include: abnormal

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KEY POINTS

- DHF is considered to account for at least 50% of all heart failure cases and be responsible for the majority of heart failure hospital admissions. Its incidence will only increase in the coming years as the population ages.
- The presence of normal LV geometry and normal diastolic function at rest does not exclude the diagnosis of DHF.
- There has been little to no progress made in identifying evidence-based, effective, and specific treatments for patients with DHF. Currently, the key to the treatment of DHF is aggressive management of contributing factors such as hypertension and atrial fibrillation.

ventricular-arterial coupling, systolic dysfunction, pulmonary hypertension, neuroendocrine dysfunction, chronotropic incompetence, inflammation, and multiple comorbidities such as obesity, hypertension, and atrial fibrillation. Understanding of some of these complex mechanisms may offer opportunities for developing diagnostic and therapeutic strategies [4].

Diastolic dysfunction

Increased left ventricle (LV) stiffness produces resistance to LV filling and it is a common finding in patients with DHF. Increased LV stiffness is linked to sarcomere structural alterations because of post-translational modifications of titin, a sarcomere protein responsible for myocardial stiffness [5▪▪,6]. Although increased myocardial stiffness may be present in the absence of LV hypertrophy and fibrosis, the presence of the aforementioned changes in the thickened myocardium further accentuates the increase in LV stiffness. Impaired LV relaxation is a universal finding in patients with DHF as a result of disturbances in adenosine triphosphate or calcium levels [7]. This phenomenon is independent of the presence of structural abnormalities such as LV hypertrophy or increased LV stiffness [5▪▪]. Several mechanisms responsible for impaired relaxation have been described including bioavailability of nitric oxide and proinflammatory cytokines [8,9].

Systolic dysfunction

Different cut-offs for the key criterion of DHF have been used during the past years across classifications, trials, and registries ranging for LVEF > 40% 40% to a LVEF > 50% [10▪▪], with the current definition using the 50% cut-off. However, using newer diagnostic techniques of myocardial deformation, several studies have shown subtle changes in systolic function including reduced longitudinal strain, impaired systolic twist, torsional dyssynchrony, and reduced myocardial systolic reserve [11]. Also, there is recent evidence that there is slow but progressive decline in ejection fraction in patients with DHF; therefore, these patients will eventually be diagnosed with heart failure with reduced ejection fraction [12,13]. Dunlay *et al.* showed that in patients with DHF, on an average, ejection fraction decreased by 5.8% over 5 years with greater declines in older individuals and in those with coronary artery disease. Overall, 39% of the patients initially diagnosed with DHF had a LVEF < 50% at some point after the diagnosis [12]. Recently, a third population of heart failure patients has been described, heart failure with recovered ejection fraction [14]. These patients have a distinct clinical phenotype, biology, and prognosis and may be misclassified as DHF. Although systolic function is seemingly normal or near-normal at rest, patients with DHF demonstrate a blunted hemodynamic response to exercise through the inability to increase accordingly LVEF, stroke volume, and cardiac output. Factors that are thought to contribute to this phenomenon include low stroke volumes because of a concentrically remodeled small LV cavity, β adrenergic receptor desensitization, chronotropic incompetence, mechanical dyssynchrony, and abnormal myocardial deformation.

Abnormal ventricular-arterial coupling

Ventricular-vascular coupling is defined as the ratio of arterial to ventricular elastance and reflects the interaction of the heart with the systemic vasculature. Increased arterial stiffness and an inadequate response to exercise through an inability to vasodilate can be seen in patients with DHF [15,16]. The attenuated reduction in mean vascular resistance together with the previously described limited systolic reserve lead to dynamic limitations in ventricular-arterial coupling with exercise seen in patients with DHF [17▪▪].

Right ventricle-pulmonary vascular unit dysfunction

Traditionally, chronic pulmonary venous hypertension and the resultant increase in right ventricle (RV) afterload have been considered the main causes of RV dysfunction in patients with DHF. In a recent community-based study, 64% of patients with DHF had a pulmonary artery systolic pressure greater than 40 mmHg. In the same study, 35% of patients

had some degree of RV dysfunction by tricuspid annulus systolic plane excursion. Compared with patients with normal RV function, patients with any RV dysfunction (mild and moderate to severe combined) were more likely to have atrial fibrillation, permanent pacing, and treatment with diuretics [18]. RV dysfunction was associated with clinical and echocardiographic evidence of more advanced heart failure and with poorer outcome [18]. More recently, it has been recognized that some patients develop RV dysfunction out of proportion to the degree of pulmonary hypertension and additional etiological factors may be involved [19] such as atrial fibrillation, moderate to severe tricuspid regurgitation, and RV pacing.

DIAGNOSIS

The diagnosis of DHF is based on the presence of heart failure symptoms, absence of LV systolic dysfunction, and the exclusion of other cardiac or noncardiac conditions which may be the cause of the clinical presentation. History and physical examination are instrumental in determining the presence of symptoms and signs of heart failure. However, the clinical presentation is similar in both systolic heart failure (SHF) and DHF, and therefore it is not helpful in discriminating the type of heart failure. The electrocardiogram may reveal LV hypertrophy and left atrial enlargement in patients with DHF, but the absence of these findings does not exclude the diagnosis. Chest radiography can exclude other cardiac or pulmonary pathology responsible for the presenting signs and symptoms. Brain natriuretic peptide (BNP) and pro-BNP levels tend to be lower in patients with DHF when compared with patients with SHF and may be within normal limits [5▪▪]. An algorithm of the diagnosis of DHF is presented in Fig. 1.

Echocardiography is a versatile tool in the diagnosis of DHF, and it is recommended as the primary noninvasive test in patients with new onset heart failure. Echocardiography is unique in its ability to provide information on LV systolic and diastolic function, volumes, RV function, hemodynamics, and valvular lesions.

Left ventricle structure and systolic function

Patients with DHF have a high prevalence of structural heart disease such as concentric LV remodeling and concentric hypertrophy. However, the presence of normal LV geometry does not exclude the diagnosis of DHF. Existing data from several clinical trials show significant heterogeneity in patients with DHF. Echocardiograms obtained in patients enrolled in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial before initiation of randomized therapy found that 14% had normal LV geometry, 34% concentric remodeling, 43% concentric hypertrophy, and 9% eccentric hypertrophy [20]. The echocardiographic substudy of the Irbesartan for Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial found that 46% of the patients enrolled had normal LV geometry [21]. These findings also have prognostic significance. The I-PRESERVE trial found LV mass and LV hypertrophy to be predictive of morbidity and mortality in patients with DHF [21]. The newer modalities of analyzing myocardial mechanics have challenged the concept of normal LV systolic function in patients with DHF. In a study assessing LV systolic function by speckle tracking analysis, Kraigher-Krainer *et al.* found that compared with both normal controls and hypertensive heart disease patients, patients with DHF demonstrated significantly lower longitudinal and circumferential strain. Reduced strain was associated with acute hospitalization and higher N-terminal pro-BNP levels [22]. In a similar fashion, mechanical dyssynchrony was assessed in patients with DHF enrolled in the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fraction Trial (PARAMOUNT). The investigators found that patients with DHF had greater LV dyssynchrony compared with healthy controls and that dyssynchrony was present even in patients with LVEF $\geq$ 55% and narrow QRS. Worse LV dyssynchrony was associated with a wider QRS interval, lower mitral annular relaxation velocity, and higher LV mass [23].

Left ventricle diastolic function

Assessment of diastolic function plays a key role in the diagnosis of DHF. Several review articles describe the echocardiographic modalities used to evaluate diastolic function, and it is not in the scope of this study to detail technical aspects of each technique [24]. One of the challenges in evaluating diastolic function is that patients with DHF are most often asymptomatic at rest but symptomatic with exercise, and therefore in some patients the indices of diastolic function may be within normal limits at rest. Several clinical trials have found that up to one-third of the patients enrolled had normal patterns of diastolic function as assessed at rest (TOPCAT – 34%, I-PRESERVE – 31%, PARAMOUNT – 8%) [20,21,23]. These findings emphasize the fact that normal diastolic function at rest does not exclude the diagnosis of DHF. In selected patients, diastolic

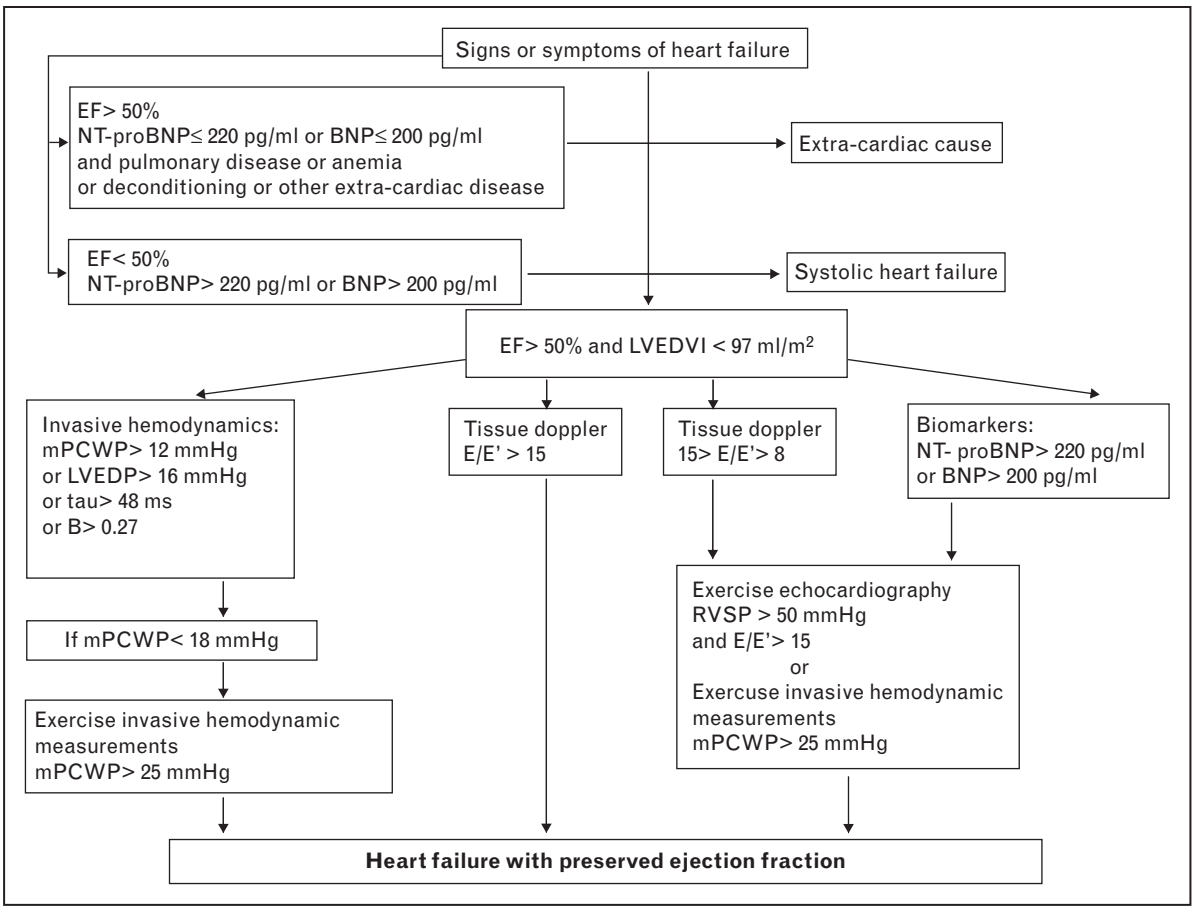

FIGURE 1. Proposed diagnostic algorithm for diastolic heart failure. B, constant of left ventricular chamber stiffness; BNP, B-type natriuretic peptide; E', mitral annulus early diastolic velocity as evaluated by tissue Doppler; E, transmitral early diastolic velocity; EF, ejection fraction; LVEDP, left ventricular end-diastolic pressure; LVEDVI, left ventricular end-diastolic volume index; mPCWP, mean pulmonary capillary wedge pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; RVSP, right ventricle systolic pressure. This figure is adapted with permission from [30] and from Wachter R, Edelman F. Diagnosis of heart failure with preserved ejection fraction. Heart Failure Clinics 2014; 10:399-406.

dysfunction can be unmasked by acquisition of echocardiographic data during or after provocative tests (exercise or dobutamine) [5▪▪,25▪▪]. Exercise stress echocardiography and cardiopulmonary exercise testing appear to be useful tests in this dynamic assessment of DHF. In a recent study, 87 patients with hypertension, exertional dyspnea, and normal resting LV systolic and diastolic function underwent exercise stress echocardiography and cardiopulmonary exercise testing. Increase of $E/e' > 15$ occurred in 8/87 patients (9.2%) during maximal workload. These patients had lower peak oxygen consumption (VO2), lower VO2 at anaerobic threshold, lower workload, lower peak partial pressure end tidal carbon dioxide, and higher minute ventilation-carbon dioxide production ratio (VE/VCO2) slope [26]. Detailed guidelines regarding performance of cardiopulmonary exercise testing in patients with heart failure have been described but are not specific for patients with DHF [27]. Among the many questions still unanswered regarding DHF is whether the current existing stages of diastolic function are optimal for clinical use, since some patients are difficult to categorize using the recommended algorithm for grading diastolic function [25▪▪]. A large observational study reported that patients frequently (17% of patients examined at a clinical echocardiography laboratory) had intermediate features between grades 1 and 2 (E/A ratio ≤ 0.75, deceleration time >140 ms, and E/e′ ratio ≥ 10) and had a worse prognosis than those with classic grade 1 dysfunction (differing in that E/e′ ratio ≤ 8) [28].

Left atrium size and function

Left atrial size and function assessment add incremental predictive information in the diagnosis of patients with DHF. Left atrial enlargement is present

in a majority of patients with DHF; 53% of patients enrolled in the TOPCAT trial and 66% of patients enrolled in the I-PRESERVE trial had some degree of left atrial enlargement [20,21]. Recently, left atrial reservoir, conduit, and pump function have been studied in a subset of patients enrolled in the PARAMOUNT trial using 2-dimensional volume indices and speckle tracking analysis and compared with healthy controls of similar age and sex. Compared with controls, DHF patients had worse left atrial reservoir, conduit, and pump function. Among DHF patients, lower systolic left atrial strain was associated with higher prevalence of prior heart failure hospitalization and history of atrial fibrillation, as well as worse LV systolic function, higher LV mass, and left atrial volume [29].

THERAPY

There has been little to no progress made in identifying evidence-based, effective, and specific treatments for patients with DHF. Drug classes, which have been shown to improve outcomes in patients with SHF, have proved ineffective in reducing mortality in DHF [30]. This may be because of the pathophysiological heterogeneity underlying DHF, incomplete understanding of DHF, heterogeneity of patients included in clinical trials with variable inclusion criteria, or contribution to DHF by extracardiac conditions [10▪▪]. Several drugs have been studied for the treatment of DHF: angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, aldosterone antagonists, β-blockers, digoxin, and sildenafil (Fig. 2).

Mineralocorticoid antagonists have been investigated for the treatment of DHF based on the participation of the renin–angiotensin–aldosterone system in the pathogenesis of DHF. In the recent TOPCAT trial, the effects of spironolactone have been studied in patients with DHF. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for management of heart failure. The results showed that spironolactone did not reduce the incidence of the primary composite endpoint [31]. It has also been hypothesized that a reduction in heart rate and therefore prolongation in diastolic filling time would result in more favorable LV filling and better coronary perfusion and would therefore mitigate DHF symptoms. The effect of heart rate reduction on exercise capacity has been studied in patients with DHF. Ivabradine, an If inhibitor of the sinoatrial pacemaker, devoid of effects on cardiac contractility has been compared with placebo in a recent randomized, crossover study. When compared with placebo, ivabradine significantly worsened the change in peak VO2 in the DHF cohort and significantly reduced submaximal exercise capacity

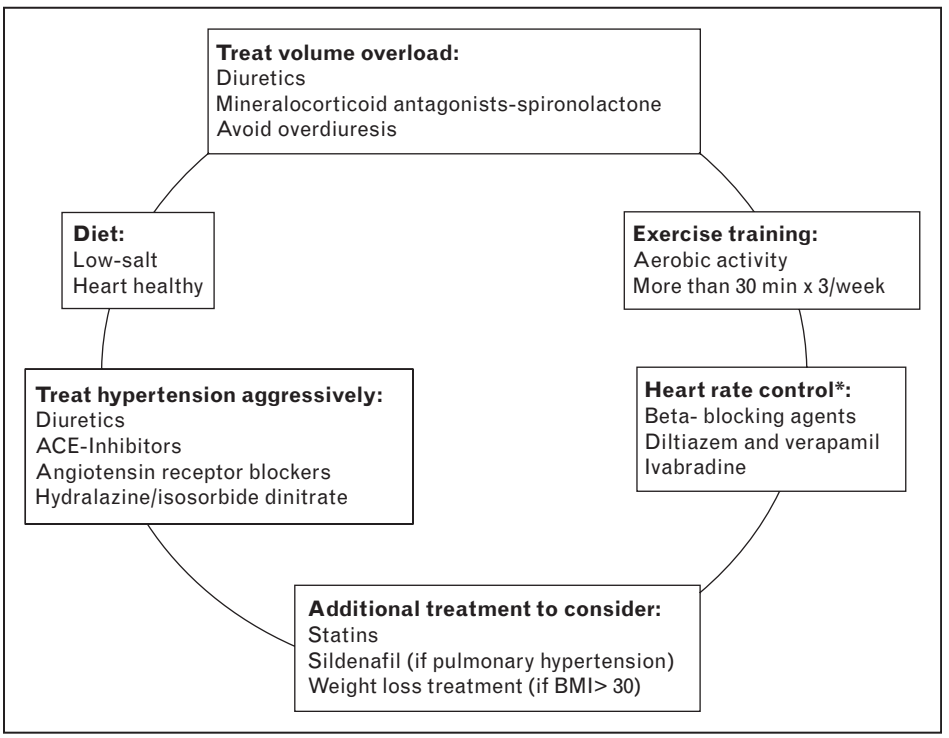

FIGURE 2. Therapeutic approach to diastolic heart failure. *Heart rate control is paramount in patients with atrial fibrillation. ACE, angiotensin converting enzyme. Adapted with permission from [5▪▪].

Table 1. Future therapies in diastolic heart failure

Therapy	Hypothesized mechanism
Sildenafil	Reduction in pulmonary pressure; reduction in cardiac fibrosis
Soluble guanylate cyclase antagonists	Pulmonary and systemic vasodilation; inhibition of smooth muscle proliferation
Endothelin receptor antagonists	Reduction in pulmonary pressure
Neprilysin inhibitors	RAAS and inhibition of breakdown of natriuretic peptides
Ivabradine	Increase time for diastolic filling
Iron supplements	Antioxidant
Ranolazine	Reduce intracellular calcium via reduction in late sodium current
Mitochondrial enhancement	Restoration of ATP production and energy deficit
Serelaxin	Pleiotropic effects
Statins	Endothelial redox balance restoration; effects on collagen turnover
Isosorbide dinitrate and hydralazine	Altered ventricular hemodynamics
Perhexiline	Correct myocardial energy deficiency

RAAS, renin-angiotensin-aldosterone system. Adapted with permission from [30].

as determined by the oxygen uptake efficiency slope [32]. Exercise training has been shown to improve cardiorespiratory fitness in patients with SHF. In a recent meta-analysis of randomized clinical trials that evaluated the efficacy of exercise training in patients with DHF, exercise training in patients with DHF was associated with an improvement in cardiorespiratory fitness and quality of life even if there were no significant changes in LV systolic or diastolic function [33]. A prospective randomized, multicenter study is underway with the objective of optimizing exercise training in prevention and treatment of DHF study (OptimEx-CLIN) and defining the optimal dose of exercise training the DHF [34]. A promising approach is targeting the treatment to a specific DHF phenotype [10▪▪]. In this vein, serelaxin, a recombinant form of human relaxin-2, has been studied comparatively in patients with DHF and patients with SHF in the RELAXin-Acute Heart Failure (RELAX-AHF) trial [35]. Serelaxin was well tolerated and effective in early dyspnea relief and in improving multiple outcomes including 180-day mortality irrespective of LVEF.

CONCLUSION

The prevalence of DHF is likely to continue to grow over the next several decades. Currently, the key to the treatment of DHF is aggressive management of contributing factors. The understanding of the phenotypic heterogeneity and multifactorial pathophysiology of DHF may lead to novel therapeutic targets in the future (Table 1). Gene therapy such as replacement of the cardiac isoform of sarco(endo)-plasmic reticulum Ca2+ATPase responsible for calcium handling has shown promising results in patients with SHF [36] and may have a role in the future treatment of DHF.

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Conflicts of interest

There are no conflicts of interest.

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