

# How to diagnose heart failure with preserved ejection fraction

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## Abstract

The current clinical and echocardiographic steps required for the recognition of heart failure with preserved ejection fraction (HFpEF) have contributed to the heterogeneity of this diagnostic group. There are three clinical manifestations—acute pulmonary edema, and exertional dyspnea with and without raised filling pressure. Additional steps in the characterization of HFpEF might include documentation of impaired functional capacity, the use of alternative systolic function parameters including global longitudinal strain, and new markers of left ventricular filling pressure and diastolic dysfunction. The diastolic stress test—performed invasively or noninvasively—may be particularly valuable for improving the attribution of dyspnea to raised left ventricular filling pressure in patients with normal filling pressure at rest. ■ *Heart Metab.* 2016;71:9-13

**Keywords:** diagnosis; diastolic dysfunction; heart failure with preserved ejection fraction

## Introduction

Heart failure with preserved ejection fraction (HFpEF) remains enigmatic. The combination of a clinical diagnosis of heart failure (itself inexact) with a rather inexact imaging measurement has engendered a heterogeneous entity. The variability of this disease goes some way to explain the failure of an effective therapeutic strategy.

## Clinical diagnosis

Although the presence of diastolic dysfunction (DD) in the absence of clinical symptoms may represent stage B heart failure (SBHF; discussed below), the recognition of HFpEF begins with clinical symptoms. There are two presentations—acute and chronic. The

acute clinical presentation of diastolic heart failure involves a presentation of acute pulmonary edema in a patient with a normal-sized heart.<sup>1</sup> If pulmonary edema resolves (or responds to therapy) within a short time interval, then HFpEF should be considered rather than other causes of pulmonary edema, such as myocardial ischemia and mitral valve disease.<sup>2</sup> HFpEF patients presenting in this way tend to have hypertensive heart disease with increased left ventricular (LV) mass.<sup>3</sup> However, such presentations are rare; probably around 5% of patients presenting with pulmonary edema have a preserved ejection fraction and remain stable after the presentation.

The second mode of presentation that is often labeled as HFpEF involves the patient with apparently normal systolic function who complains of exertional dyspnea. Few of these patients present with an

## Abbreviations

**BNP:** B-type natriuretic peptide; **DD:** diastolic dysfunction; **HFpEF:** heart failure with preserved ejection fraction; **LV:** left ventricular

acute episode of heart failure, and most have normal LV filling pressure at rest. They tend to be old, and have comorbidities that may also explain their symptoms, most commonly pulmonary disease, obesity, anemia, and/or deconditioning.<sup>4</sup> This is not a group well served by current definitions. An elderly patient presenting with exertional dyspnea and abnormal diastolic filling would have only one of the minor criteria for heart failure; so, according to this definition, patients in this situation should not be described as having heart failure. Indeed, there have been numerous efforts to create a specific definition for diastolic heart failure, which I now summarize:

*Standardized diagnosis.*<sup>5</sup> With standardized diagnosis, three groups are possible: those with definite, probable, or possible heart failure. A diagnosis of *definite* diastolic heart failure is based on proof of abnormal diastolic function upon left heart catheterization. Unfortunately, use of such a procedure is impractical for a community-based problem involving the elderly. *Probable* diastolic heart failure does not require left heart catheterization, but such diagnosis does require documentation of a normal ejection fraction within 72 hours of acute presentation. *Possible* diastolic heart failure requires a normal ejection fraction, although not at the time of the acute presentation.

*American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.*<sup>6</sup> These guidelines emphasize the shortcomings of a diagnosis of exclusion. They propose integration of clinical signs or symptoms of heart failure with evidence of preserved or normal LV ejection fraction (LVEF) and evidence of abnormal LV DD by Doppler echocardiography or cardiac catheterization, as proposed in the standardized diagnosis.

*European Diastolic Heart Failure Study group.*<sup>7</sup> This group's definition of diastolic heart failure combines signs/symptoms of heart failure (exertional dyspnea is admissible in the most recent update) with treatment response and either systolic dysfunction or echo Doppler criteria of diastolic abnormalities. However, of 27% of patients with confirmed heart failure who had preserved systolic function and no valvular

heart disease, only 43% were confirmed as having diastolic heart failure using the initial European criteria. Whereas these findings may have been partly due to imperfect recognition of pseudonormal LV filling patterns and/or a delay in acquiring these data after admission, in many cases, they reflect a problem with the diagnosis of heart failure.

*Current European Society of Cardiology guidelines.*<sup>8</sup> These guidelines emphasize the LV morphology associated with HFpEF (Table I), and they iden-

LV morphology and other properties	Patients with HFpEF	Patients with HFrEF
Systolic dysfunction (other than EF)	+	++
Diastolic dysfunction	++	++
LV remodeling	Concentric LVH Concentric remodeling	Eccentric remodeling
Aortic stiffness	++	+
Disturbances of LV relaxation or compliance	++	+

**Table I** Comparison of left ventricular morphology and other properties among patients with heart failure and preserved or reduced ejection fraction.

**Abbreviations:** EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; LVH, left ventricular hypertrophy.

tify most as having DD. They propose a “midrange” group (ejection fraction of 40% to 49%) as being separate from HFpEF, which is a step further than the ACC/AHA guidelines' recognition of this group as a subgroup of HFpEF.<sup>6</sup>

## Standard echocardiography

As HFpEF is most commonly a concern among elderly patients in the community, a widely available and noninvasive test is required for diagnosis, and echocardiography is generally the most suitable. The echocardiographic report involves three components—assessment of ejection fraction, estimation of filling pressure, and characterization of the stage of DD.

## Ejection fraction

The estimation of ejection fraction is inexact. A number of the problems of echocardiographic estimation of ejection fraction pertain to image quality, image orientation, and geometric assumptions, and these can be addressed by the use of echocardiographic

contrast agents and/or three-dimensional imaging.<sup>9</sup> However, ejection fraction obtained by any modality is susceptible to changes related to altered loading conditions. A 10% test-retest variation in ejection fraction is common, implying that an ejection fraction of 45% today could be under 35% or over 55% tomorrow, possibly with no change in myocardial performance. It is therefore not clear if the “intermediate” level of ejection fraction—between reduced and preserved—is a discreet group resulting from a true biologic variation or from variation in measurement.<sup>6,8</sup>

The entity of HFpEF has previously been interpreted to imply normal systolic function, but this is untrue. There is a gradation in not only diastolic, but also systolic, tissue velocity in normal individuals, in those with HFpEF and in those with HFrEF. Several new parameters of systolic function, especially global longitudinal strain (GLS), appear to offer more robust measurement and greater prognostic value than ejection fraction.<sup>10</sup> It is disappointing that the guidelines remain focused on ejection fraction because GLS may be a preferable parameter.

### Estimation of filling pressure

Although useful, the noninvasive evaluation of LV filling pressure remains approximate. The most widely available marker of LV diastolic pressure is the ratio of the passive mitral filling wave and the tissue Doppler wave corresponding to LV relaxation ( $E/e'$ ). Although this test forms one of the cornerstones of the diastolic function assessment guidelines,<sup>11</sup> it should be recognized that it is not feasible to carry out in many common scenarios (eg, the presence of mitral annular calcification)<sup>12</sup> and is not particularly accurate.<sup>13</sup>

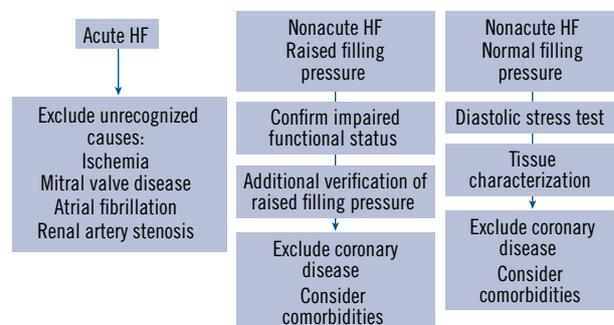
### Diastolic dysfunction (DD)

The three major categories of DD—delayed relaxation (mild), and pseudonormal (moderate) and restrictive filling (severe)—have differing prognostic implications. In the Olmsted County study, moderate or severe DD was present in 5% to 6% of the population, although even in these subjects fewer than half had a diagnosis of heart failure. Nonetheless, both mild and moderate-to-severe DD predicted all-cause mortality over a subsequent follow-up of 5 years, even in the absence of clinical heart failure.<sup>14</sup>

Although DD is prognostically relevant, it is also extremely common, especially with advancing age. The reported prevalence of DD in the population has varied between 11% and 36% in studies in the United States, Europe, and Australia. This variation corresponds to differing ages of the studied populations, as well as to different degrees of complexity of assessing transmitral flow. The Australian study examined the impact of age on transmitral flow: the prevalence of abnormal LV filling in the presence of normal ejection fraction varied from 1% to 4% in the 60–64-year age group, increasing to 10% or more in the over 80 age group.<sup>15</sup> Thus, although DD is prognostically sinister, it is common with increasing age, and there is a risk of overdiagnosis of HFpEF, especially if the symptoms attributed to heart failure are nonspecific.

### Additional steps

The traditional approach to diagnosis of HFpEF is based upon symptoms, estimated ejection fraction, and diastolic evaluation, all of which seem inexact. Further categorization will produce a more homogeneous diagnostic group (Figure 1).



**Fig. 1** Additional steps that might facilitate the characterization of patients with preserved ejection fraction and acute or chronic dyspnea.

Abbreviations: HF, heart failure.

### Symptoms

As in other conditions, symptoms may be misleading. Deconditioned individuals may express exercise intolerance in the presence of normal exercise capacity, and conversely, symptoms may be trivialized in patients who are inactive. Some form of functional testing is useful in order to objectify impaired exercise capacity.

Coronary artery disease remains common in the population, and significant disease may be associ-

ated with minimal or no angina. Atypical symptoms are most common in women, who are also prone to HFpEF. The exclusion of myocardial ischemia should be incorporated in the evaluation of HFpEF.

Comorbidities are common in HFpEF. Pulmonary disease, renal impairment, and anemia should be checked for as they may be the primary source of symptoms. Although these diagnoses do not exclude the coexistence of HFpEF, it would seem prudent to exclude them from intervention trials.

### **Ejection fraction**

The limitations of estimated ejection fraction have been discussed above. The results from evaluation of myocardial strain are often abnormal when ejection fraction is normal; perhaps this should form part of the diagnosis.

### **Diastolic function**

Both the filling pressure and diastolic class components of the HFpEF diagnosis have limitations. More specific markers of raised filling pressure together with more accurate tissue characterization may assist in the recognition of HFpEF. The use of a myocardial deformation (eg, strain or strain-rate),<sup>16</sup> rather than an annular measurement (eg,  $e'$ ) may improve diagnostic feasibility as it allows testing in patients with mitral annular calcification. Likewise, assessment of atrial strain may provide additional evidence about filling pressure.<sup>17</sup>

As discussed above, presentation of the HFpEF patient with pulmonary edema is uncommon and poses much less of a diagnostic challenge than the dyspneic patient with a small heart. In this setting, DD provides increased resistance to filling of the left ventricle under conditions of increased flow, leading to an inappropriate rise in the diastolic pressure-volume relationship and causing symptoms of pulmonary congestion during exercise. Provocative testing in this situation potentially distinguishes the HFpEF patient from one with “bystander” mild DD and nonspecific symptoms.

The value of measuring the B-type natriuretic peptide (BNP) level in this situation is questionable. The patients most likely to have elevated BNP levels are those with elevated LV filling pressure or a pseudo-normal filling pattern, who do not pose the greatest

diagnostic challenge. Nonetheless, about one-third of HFpEF patients do not have elevated BNP levels,<sup>18</sup> and this is associated with obesity. For those without elevated filling pressure, resting BNP is usually normal, but exercise intolerance related to increased LV filling pressure in response to exercise might be identifiable from the BNP response to stress.<sup>19</sup>

### **Other testing**

Tissue characterization using cardiac magnetic resonance imaging may help to distinguish patients according to their underlying disease. Such a process may help us to move away from the heterogeneity of the HFpEF construct and to instead characterize patients according to the contributions of disturbances in myocardial relaxation, interstitial fibrosis, chronotropic incompetence, increased pulmonary vascular resistance, and right ventricular dysfunction.<sup>20</sup>

### **Conclusion**

What used to be labeled as “diastolic heart failure” in elderly dyspneic patients was in many cases neither diastolic nor heart failure. DD is common with increasing age, which is associated with exercise intolerance and adverse outcome. However, its confusion with heart failure has led to mislabeling, inappropriate expectations about its epidemiology and outcome, and the obscuring of underlying treatable etiologies. The additional testing for functional capacity, comorbidity, and diastolic responses to exercise, and the introduction of new measures to characterize myocardial function may reduce the heterogeneity of the diastolic heart failure diagnosis. ■

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