**EDITORIAL COMMENT**

Heart Failure With Preserved Ejection Fraction: Is This Diastolic Heart Failure?*

Michael R. Zile, MD, FACC
Charleston, South Carolina

As described in the study by Smith et al. (1) published in this issue of the *Journal,* the syndrome of “heart failure with a preserved ejection fraction” includes patients admitted to the hospital with symptoms and signs of heart failure (HF), radiographic evidence of HF, and an ejection fraction (EF) >40%. Approximately one-half of the consecutively enrolled patients with HF had an EF >40%, indicating a prevalence of 50%. Mortality, hospital readmission, and functional status in this group of patients were compared to patients with HF and a depressed EF. This comparison revealed that these two groups of patients with HF have unique, statistically significant, and clinically important differences. Patients with HF and a preserved EF tended to be older, were more often women, more frequently had hypertension, and less frequently had coronary artery disease. The mortality rate in these patients was significantly less than in patients with HF and a depressed EF, but was significantly greater than age-matched control patients without HF. Therefore, these important differences in demographics and mortality justify the classification of patients with HF into two groups.

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**WHAT IS DIASTOLIC HEART FAILURE (DHF)?**

Smith et al. (1) did not mention the terms “diastolic heart failure” or “diastolic dysfunction” in their paper and they did not measure diastolic function in their patients. The division of patients with HF into two groups has evolved over the past 50 years and has included forward versus backward failure, systolic heart failure (SHF) versus DHF, and more recently, HF with depressed versus preserved EF. Which terminology is most appropriate? What rationale should be used to guide our choice of terminology? Does the choice of terminology matter? These three sets of terms are equivalent and describe the same two groups of patients with HF. Thus, patients with HF and a preserved EF in fact have DHF. However, the terminology “DHF versus SHF” is the most appropriate because it underscores the fundamental differences in the pathophysiologic mechanisms that cause HF in these two groups of patients. Patients with DHF have a predominant (although not isolated) abnormality in diastolic function. Patients with SHF have a predominant (although not isolated) abnormality in systolic function. These specific differences in left ventricular (LV) function are associated with distinctly different cardiac and myocardial remodeling in the two groups of patients with HF. The differences in pathophysiologic mechanisms, function, and remodeling result in the clinically significant differences in demographics and mortality described by Smith et al. (1).

What are the issues that have created a reluctance to use the term “DHF” and caused the emergence of the term “HF with preserved EF”? The issues include the assertions that: 1) it is difficult to measure diastolic function; 2) there are no clear diagnostic criteria for DHF; 3) EF measurements are not representative of the causal physiology; 4) patients with DHF also have coexistent abnormalities in systolic function; 5) some patients diagnosed as having DHF do not have HF; and 6) some patients diagnosed as having DHF do not have abnormal diastolic function. Each of these concerns has been or is being addressed by new technical developments and recently published studies. None of these issues should invalidate the use of the term DHF.

**MEASUREMENTS OF DIASTOLIC FUNCTION**

To fully characterize diastolic function, measurement of LV pressure, volume, wall thickness, and calculations that reflect the process of active relaxation (the rate of isovolumic LV pressure and LV filling) and those that reflect passive stiffness (chamber compliance and myocardial viscoelastic stiffness) must be made (2). Because this requires invasive methods and detailed analysis, these methods are difficult to use in patient screening or to perform in large clinical trials. Noninvasive measurements of diastolic function have a low sensitivity, specificity, and predictive accuracy (2). This is caused, at least in part, because all indices of diastolic function are altered by changes in load, heterogeneity, remodeling, and other factors that make their interpretation difficult. However, new approaches to data interpretation, new noninvasive techniques (such as tissue Doppler), and new serum markers of increased LV diastolic pressure (such as brain natriuretic peptide) hold promise. In addition, recent studies have shown that it may not be necessary to directly measure diastolic function in every patient to prove that they have HF caused by a predominant abnormality in diastolic function (3). Therefore, the absence of a simple, noninvasive, load-independent measure of diastolic dysfunction does not justify avoiding an assessment of diastolic function when necessary, nor does it justify the use the more descriptive terminology “HF with a preserved EF.” In patients with HF and a preserved EF, diastolic dysfunction is the predominant cause of HF, just as systolic dysfunction.
is the predominant cause of HF in patients with HF and a depressed EF.

**DIASTOLIC DYSFUNCTION VERSUS DHF**

If diastolic function is examined and indices of diastolic function are found to be abnormal, does this alone indicate the presence of DHF? Diastolic dysfunction refers to a condition in which abnormalities in mechanical function are present during diastole. Abnormal diastolic function can occur in the presence or absence of a clinical syndrome of HF and can occur with or without coexistent abnormalities in systolic function. Therefore, whereas diastolic dysfunction describes an abnormal mechanical property, DHF describes a clinical syndrome. In other words, patients can have abnormal diastolic function without symptoms or signs of HF (asymptomatic diastolic dysfunction), or patients can have abnormal diastolic function with both symptoms and signs of HF and DHF.

**DIAGNOSTIC CRITERIA FOR DHF**

How do you make the diagnosis of DHF? There is an emerging consensus that DHF can be diagnosed based on the presence of two criteria: 1) symptoms and signs of HF, and 2) a normal ejection fraction (>50%). The measurement of diastolic function is not mandatory but may be confirmatory.

The development of these criteria began when the Working Group for the European Society of Cardiology proposed three criteria: 1) the presence of signs or symptoms of HF, 2) the presence of normal LV systolic function, and 3) evidence of abnormal LV relaxation, filling, or diastolic stiffness (4). Among the weaknesses of these criteria is the wording “signs or symptoms” and “systolic function.” In part to address these weaknesses, the European proposal was revised and refined by Vasan and Levy (5), who suggested specific criteria for definite, probable, and possible DHF. Each of these three categories required the presence of symptoms and signs of HF and a normal EF (>50%). In addition, there were requirements related to the timing of EF determination and evidence of diastolic dysfunction measured using invasive techniques. The clinical application of the guidelines proposed by the European working group and Vasan and Levy (5) has been limited because they are complex and because they are empiric. However, recent studies have suggested methods to simplify the diagnostic criteria and have provided objective data to validate them (3,6).

**Timing and threshold value for EF measurements.** Vasan and Levy (5) proposed that the EF must be determined coincident with (or at least close to) the time a patient presents with acute decompensated HF. They reasoned that, if there were a transient decrease in EF at the time a patient was acutely decompensated, the measurement of an EF >50% at a time remote from the acute event may not reflect the pathophysiologic events causing the HF.

This proposal can now be modified on the basis of studies by Gandi et al. (6) and Smith et al. (1). Gandi et al. (6) showed that there were no significant changes in EF in patients with either SHF or DHF between the times they had acute decompensated HF and a later time when they were compensated and their symptoms were resolved. This conclusion was supported by Smith et al. (1), who showed that their results were independent of the time at which the EF was measured, and that their major conclusions would not be changed if only those patients with concurrently assessed EF were included. Therefore, as long as there have been no intervening events that would potentially modify LV EF, an EF >50% measured at a time remote from the acute presentation of decompensated HF can be used to make the diagnosis of DHF.

The EF threshold (or “cutoff”) value used to differentiate SHF from DHF has ranged from 40% to 50% in a variety of studies. What is the ideal threshold value? The number of patients with HF and an EF between 40% and 50% in the study of Smith et al. (1) was quite small (8%) and similar to previous studies (7). Data indicate that patients with an EF between 40% and 50% behave more like patients with EF <40%. The major conclusions of Smith et al. (1) would not be changed if the EF cutoff was >50% instead of >40%. Therefore, it is reasonable to conclude that the ideal cutoff to differentiate SHF from DHF is EF >50%.

**Necessity of obtaining objective evidence of diastolic dysfunction.** A recent study examined the necessity of obtaining objective evidence of diastolic dysfunction (3). In this study, patients with symptoms and signs of HF (fulfilling the Framingham criteria) and an EF >50% underwent diagnostic left heart catheterization and simultaneous Doppler echocardiography. In this group of patients, 92% had at least one pressure derived abnormality in diastolic function, 94% had at least one Doppler echocardiography derived abnormality in diastolic function, and 100% had at least one pressure or Doppler abnormality in diastolic function. Therefore, objective measurements of LV diastolic function serve to confirm rather than establish the diagnosis of DHF. Thus, the diagnosis of DHF can be made without measurement of diastolic function, if two criteria are present: 1) symptoms and signs of HF, and 2) normal EF.

**SPECIFICITY OF SYMPTOMS AND SIGNS OF HF**

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 HF occur with equal frequency in patients with SHF versus DHF (2). Therefore, the history, physical exam, and chest X-ray are not specific enough to differentiate systolic from DHF. Taken together, however, they are specific enough to detect the presence of HF. Recently, the clinician’s ability to use this clinical evidence in diagnosing HF has been questioned (8,9). Curiously, this uncertainty has only been discussed
Systolic function

However, the coexistence of these functional abnormalities in both systolic and diastolic function (Table 1). It is now clearly recognized that all patients with HF have diastolic dysfunction in both SHF and DHF. Coexistence of systolic and diastolic function (11,12). Therefore, patients with HF and preserved EF may have relatively small but detectable abnormalities in systolic function. For this reason the terms HF and 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 pathophysiologic 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.

Table 1. Features That Differentiate SHF From DHF

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SHF</th>
<th>DHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction</td>
<td>↓ ↓</td>
<td>N (or ↑)</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>↓ (or N)</td>
<td>N (or ↓)</td>
</tr>
<tr>
<td>Contractility</td>
<td>↓ ↓</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>LV end-diastolic pressure</td>
<td>↑ (or ↑ ↑)</td>
<td>↑ ↑ (or ↑)</td>
</tr>
<tr>
<td>Relaxation time constant</td>
<td>↑ (or ↑ ↑)</td>
<td>↑ ↑ (or ↑)</td>
</tr>
<tr>
<td>Filling rate</td>
<td>↓ (or ↑ or N)</td>
<td>↓ (or ↑ or N)</td>
</tr>
<tr>
<td>Chamber stiffness</td>
<td>↓ ↑</td>
<td>↑ ↑</td>
</tr>
<tr>
<td>Myocardial stiffness</td>
<td>N (or ↑)</td>
<td>↑</td>
</tr>
<tr>
<td>LV volume</td>
<td>↑ ↑</td>
<td>N (or ↓)</td>
</tr>
<tr>
<td>LV mass</td>
<td>↑ ↑</td>
<td>↑</td>
</tr>
<tr>
<td>LV geometry</td>
<td>Eccentric</td>
<td>Concentric</td>
</tr>
<tr>
<td>Cardiomyocyte</td>
<td>↑ Length</td>
<td>↑ Diameter</td>
</tr>
<tr>
<td>Extracellular matrix</td>
<td>↓ (or ↑ or N)</td>
<td>↑ ↑ Collagen</td>
</tr>
<tr>
<td>Mortality (6 months)</td>
<td>↑ (5 yrs)</td>
<td>↑</td>
</tr>
<tr>
<td>Morbidity (hosp, 6 months)</td>
<td>↑ ↑</td>
<td>↑ ↑</td>
</tr>
<tr>
<td>(CHF hosp, 6 months)</td>
<td>↑ ↑</td>
<td>↑ ↑</td>
</tr>
</tbody>
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CHF = congestive heart failure; DHF = diastolic heart failure; LV = left ventricular; N = normal; SHF = systolic heart failure; ↓ = decreased; ↑ = increased.

with reference to DHF and has not been questioned in patients with SHF. It has been argued that some patients with DHF have symptoms and signs for which an explanation other than HF can be identified (8,9). For example, older patients who are significantly deconditioned 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. Signs of peripheral edema may be caused by vascular insufficiency and not indicate the presence of HF. Although age and coexistent disease may make accurate diagnosis of HF more difficult, this difficulty exists with both SHF as well as DHF and exists whether the term DHF or HF with preserved EF is used. 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. (1) and others (10).

COEXISTENCE OF SYSTOLIC AND DIASTOLIC DYSFUNCTION IN BOTH SHF AND DHF

It is now clearly recognized that all patients with HF have abnormalities in both systolic and diastolic function (Table 1). 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 groups.

There is no doubt that a normal EF does not necessarily indicate the presence of normal myocardial or even ventricular contractility (11,12). Therefore, patients with HF and preserved EF may have relatively small but detectable abnormalities in systolic function. For this reason the terms HF and 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 pathophysiologic 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.

TREATMENT OF DHF: CURRENT GUIDELINES, FUTURE DIRECTIONS

The ultimate importance of distinguishing between patients with SHF versus DHF will depend on defining effective treatment of DHF and defining differences in therapeutic approaches between SHF versus DHF using randomized clinical trials. There are already some significant differences in treatment strategy between DHF and SHF. For example, dihydropyridine calcium channel blockers are not used in SHF but may be useful in DHF. The doses of diuretics used in DHF are generally smaller than in SHF. Slow titration of beta-blockers is mandatory in SHF but unnecessary in DHF. Current guidelines for the treatment of DHF are empiric and are based on treating presenting symptoms and causal disease processes (13,14). In addition to symptom- and disease-targeted therapy, effective new treatment strategies will depend on targeting the underlying cardiomyocyte, extracellular matrix, and neurohormonal mechanisms (15). Because there are significant differences in these underlying mechanisms between patients with SHF and DHF (Table 1), it is likely that effective mechanism-targeted therapy for DHF will differ significantly from SHF.

To date, no randomized clinical trials designed to directly target the treatment of DHF have been completed; however, a number of randomized clinical trials have been initiated, including Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) and Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE). The academic discourse surrounding the choice of terminology and the distinction between SHF and DHF has been and may continue to be an impediment decreasing the enthusiasm of the pharmaceutical industry, government, and other agencies to fund randomized clinical trials in DHF. Consensus on pathophysiology-based termi-
nology of SHF versus DHF and clear acknowledgement of distinct groups of patients with HF are critical if we are to define the optimal treatment of all patients with HF, especially those with DHF.

CONCLUSIONS

On the basis of the discussion here and the data presented by Smith et al. (1), the following conclusions appear justified. Patients with HF should be separated into two groups. The most appropriate terms to describe these groups are SHF and DHF. The term “DHF” should not be replaced with the term “HF with preserved EF.” The separation of patients with HF into two groups and the choice of terminology to describe them have pragmatic, clinical, and scientific importance. Choosing simple, pathophysiology-based terminology provides the rationale for the existing differences in treatment strategy, focuses research aimed at developing more specific therapeutic targets, and promotes sponsorship of randomized clinical trials. Although the choice of terminology may be controversial in the halls of academia, the general community of health care providers already accepts, embraces, and has overwhelmingly chosen the term SHF. Thus, if we are willing to use the term SHF (13,14), we should stop the discrimination against the term DHF.

Reprint requests and correspondence: Dr. Michael R. Zile, Cardiology/Medicine, Medical University of South Carolina, 135 Rutledge Avenue, Suite 1201, P.O. Box 250592, Charleston, South Carolina 29425. E-mail: zilem@musc.edu.

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