Diastolic Heart Failure: Definitions and Terminology

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Patients with chronic heart failure can be divided into 2 broad categories: systolic heart failure and diastolic heart failure. There are significant differences in demographics, prognosis, left ventricular structure, as well as systolic and diastolic function between these 2 groups of patients. The purpose of this presentation is to define the terminology used to describe these 2 broad categories of heart failure and to characterize the functional measurements that constitute their pathophysiological mechanisms.

Epidemiological studies have clearly shown that diastolic heart failure (DHF) is a common cause of chronic heart failure (CHF) and causes a significant increase in cardiovascular morbidity and mortality.[1-4] However, there is continued controversy surrounding the terminology used to describe patients with DHF, the methods used to assess diastolic function, the criteria used to make the diagnosis, the precise prognosis, and the underlying pathophysiology.[5-7] As a result, clinical therapeutic trials have been slow to develop and difficult to design. Recent clinical studies have provided new data that should improve our ability to develop standardized diagnostic criteria, to measure diastolic function, and to define the underlying pathophysiology.[8-13] Experimental studies have provided new insights into the cellular, extracellular, and neurohumoral mechanisms causing DHF. [14-16] Together, these clinical and experimental studies are being used to design targeted clinical trials to test effective treatments for DHF.[17,18]

The purposes of this issue of the *Progress in Cardiovascular Diseases* are to define (1) the terms diastolic dysfunction and DHF (Zile), (2) the diagnostic criteria (Gaasch), (3) the epidemiology (Redfield), (4) the effects of DHF on prognosis (Aurigemma), (5) the methods used to assess diastolic function (Quinones), (6) the changes in neurohormonal activation that occur in DHF (McMurray), (7) the effects of DHF on exercise tolerance (Kitzman), (8) the cellular and extracellular mechanisms that cause DHF (Paulus), (9) the current strategies for treatment of DHF (Little), and (10) the ongoing randomized clinical trials in DHF (Massie).

Definitions and Terminology

Comparison Between SHF and DHF

Patients with CHF can be divided into 2 broad categories: systolic heart failure (SHF) and DHF. There are significant differences in demographics, prognosis, left ventricular (LV) structure, and function between these 2 groups of patients (Tables 1 and 2).[2,4,5,19]

Patients with SHF have eccentric remodeling, increased LV diastolic volume, and predominant abnormalities in LV systolic properties including decreased systolic performance, function, and contractility.[5,20,21] Effective arterial elastance is decreased and the arterial-vascular coupling is abnormal. In symptomatic patients with SHF, LV diastolic pressures are increased but LV passive

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Table 1. Comparison Between SHF and DHF: Demographic and Prognostic Features

Characteristic	SHF	DHF
Demographics		
Age (y) (mean)	61	72
Sex (% female)	35	66
Hypertension (%)	62	85
CAD (%)	86	45
Symptoms and signs		
Exercise duration	↓	↓
Systolic BP	N-↓	↑
Pulse pressure	↓	↑
$\dot{V}O_2$	↓	↓
BNP	↑ ↑	↑
Morbidity	↑ ↑	↑ ↑
Mortality	↑ ↑	↑

Abbreviations: CAD, coronary artery disease; BP, blood pressure; $\dot{V}O_2$, maximum oxygen consumption; BNP, brain natriuretic peptide; N, no change; ↓, decreased; ↑, increased.

stiffness is decreased. The pathophysiology underlying SHF is dependent on progressive LV dilation and systolic dysfunction.[22]

The term *diastolic heart failure*, first introduced by Kessler[23] in 1988, is used to describe a group of CHF patients characterized by concentric remodeling, normal LV diastolic volume, and predominant abnormalities in LV diastolic properties including slow and delayed active relaxation and increased passive stiffness.[11-13] In DHF, LV systolic properties including systolic performance, function, and contractility are normal.[13] Although effective arterial elastance is increased, arterial-vascular coupling is normal.[13] The pathophysiology underlying DHF is dependent on concentric remodeling and abnormal diastolic function.

Thus, it is essential to recognize that the terms SHF and DHF refer to 2 groups of CHF patients distinguished not just by ejection fraction but rather by a constellation of features including differential LV remodeling, differences in LV structure, and differences in the predominant nature of their functional abnormalities.

Differentiating Dysfunction From Heart Failure

Systolic dysfunction refers to a defect in the ability of the myofibrils to shorten against a load; the ventricle loses its ability to eject blood into a high-pressure aorta and the LV systolic properties become abnormal. Left ventricular systolic properties can be examined by measuring LV systolic performance, function, and contractility. As shown in Fig 1, systolic dysfunction is characterized by decreased performance (decreased stroke work [ie, decreased area inside the pressure-volume loop]), decreased function (decreased ejection fraction), and decreased contractility (decreased end-systolic elastance [ie, decreased slope of the end-systolic pressure-volume relationship]). Abnormalities in systolic properties can occur in the presence or absence of a clinical syndrome of heart failure and with normal or abnormal diastolic function. Therefore, systolic dysfunction

Table 2. Comparison Between SHF and DHF: LV Structural and Functional Features

Characteristic	SHF	DHF
Remodeling		
LV end-diastolic volume	↑	N
LV end-systolic volume	↑	N
LV mass	↑ eccentric LVH	↑ concentric LVH
Relative wall thickness	↓	↑
Cardiomyocyte	↑ length	↑ diameter
Extracellular matrix collagen	↓	↑
Diastolic properties		
LV end-diastolic pressure	↑ ↑	↑ ↑
Relaxation time constant	↑	↑ ↑
Filling rate	↓	↓↓
Chamber stiffness	N-↓	↑
Myocardial stiffness	N-↑	↑
Systolic properties		
Performance		
Stroke volume	↓	N-↓
Stroke work	↓	N
Function		
Ejection fraction	↓	N
Ejection rate	↓	N
PRSW	↓	N
Contractility		
(+)d*P*/d*t*	↓	N
Ees	↓	N-↑
FS vs stress	↓	N
Preload reserve	Exhausted	Limited
Ea	↓	↑
Arterial-ventricular coupling (Ea/Ees)	↓	N

Abbreviations: PRSW, preload-recruitable stroke work; Ees, end-systolic elastance; FS, fractional shortening; Ea, Effective arterial elastance.

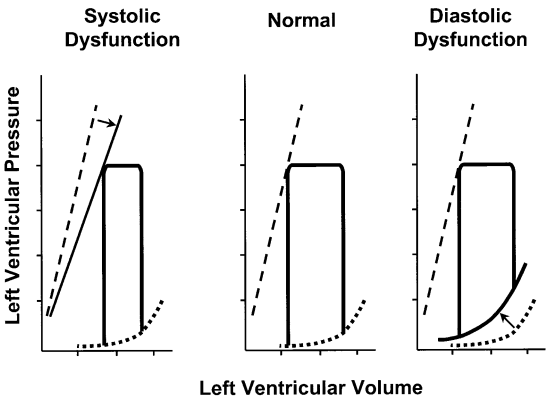

Fig 1. Diagram of LV pressure-volume loops in systolic dysfunction (left panel), normal (center panel), and diastolic dysfunction (right panel). On the left panel, systolic dysfunction is characterized by decreased performance (decreased stroke work [ie, decreased area inside the pressure-volume loop]), decreased function (decreased ejection fraction), and decreased contractility (decreased end-systolic elastance [ie, decreased slope of the end-systolic pressure-volume relationship], the end-systolic pressure-volume line is displaced downward and to the right). Diastolic properties are normal. On the right panel, diastolic dysfunction is characterized by increased chamber stiffness (the diastolic pressure-volume relation is displaced upward and to the left). Systolic properties are normal.

describes an abnormal mechanical property, not a clinical syndrome.

Diastolic dysfunction refers to the inability of the myofibrils to rapidly or completely return to their resting length; the ventricle cannot accept blood at low pressures and ventricular filling is slow or incomplete unless atrial pressure rises. Diastolic dysfunction can be detected by examining measurements of active relaxation (rate and extent of isovolumic pressure decline and LV filling) and passive stiffness. As shown in Fig 1, diastolic dysfunction is characterized by increased LV chamber stiffness (left and upward shift of the diastolic pressure-volume relationship). Abnormalities in diastolic properties can occur in the presence or absence of a clinical syndrome of heart failure and with normal or abnormal LV systolic properties. Therefore, diastolic dysfunction describes an abnormal mechanical property, not a clinical syndrome.

Chronic heart failure is a clinical syndrome characterized by symptoms and signs of increased tissue/organ water and decreased tissue/organ perfusion. Standardized criteria to diagnose heart failure have been developed, perhaps the best validated of which come from the Framingham Study.[24] Defining the pathophysiological mechanisms that cause this clinical syndrome requires measurement of both systolic and diastolic function and definition of the type and extent of LV remodeling. When heart failure is accompanied by concentric remodeling and a predominant abnormality in diastolic properties, this clinical syndrome is called DHF (Fig 2). When heart failure is accompanied by eccentric remodeling, progressive LV dilation, and a predominant abnormality in systolic properties, this clinical syndrome is called SHF (Fig 2).

Structural Remodeling in DHF: Changes in LV Volume, Mass, and Geometry

To date, at least 4 studies have examined LV diastolic volume in patients with DHF.[12,13,25-28] In each study, using either 2-dimensional echocardiography or 3-dimensional magnetic resonance imaging, LV end-diastolic volume in patients with DHF was either the same as or less than the LV end-diastolic volume of age- and sex-matched control subjects with no evidence of cardiovascular disease.

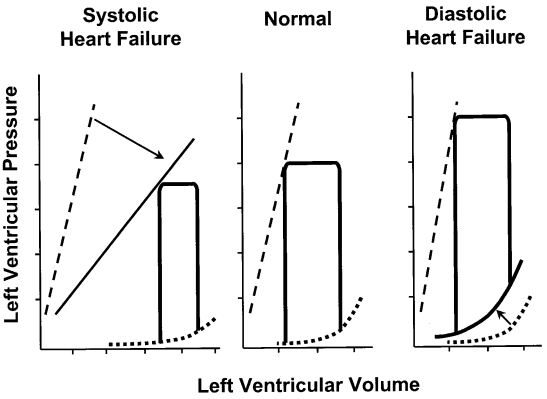

Fig 2. Diagram of LV pressure-volume loops in SHF (left panel), normal (center panel), and DHF (right panel). In SHF, eccentric remodeling results in increased volumes, the pressure-volume loop being displaced rightward, ejection fraction is decreased, and the end-systolic pressure-volume line is displaced downward and to the right. In DHF, concentric remodeling results in no significant changes in volumes, ejection fraction remains normal, chamber stiffness is increased, and the diastolic pressure-volume relation is displaced upward and to the left.

Patients with DHF have an increased incidence of LV hypertrophy (LVH) (defined as an LV mass $\geq$125 g/m^2). However, LVH is neither required to make the diagnosis of DHF nor a prerequisite for the development of DHF. Often, even when LV mass is within the reference range, it is inappropriately large for the volume of the left ventricle. As such, the volume vs mass ratio and/or the chamber dimension vs wall thickness ratio will be decreased, indicating the presence of concentric remodeling. Like LVH, however, although patients with DHF have an increased incidence of concentric remodeling, it is neither required to make the diagnosis of DHF nor a prerequisite for the development of DHF. For example, the remodeling changes seen in one well-defined group of DHF patients ranged from concentric remodeling with an increase in LV mass to neither concentric remodeling nor an increase in LV mass.[11-13] Forty percent of the patients with DHF had an LV wall thickness greater than 1.2 cm, 60% had a relative wall thickness greater than 0.45, and 40% had an LV mass greater than 125 g/m^2. Thirty-four percent of the patients with DHF had neither an increased relative wall thickness nor an increase in LV mass, 45% had both.[13] These data are supported by other published studies such as that by Kitzman et al.[19]

Functional Remodeling in DHF: LV Systolic and Diastolic Properties

Diastolic Properties

Patients with DHF have been shown to have abnormal active diastolic relaxation as evidenced by slow and incomplete isovolumic pressure decline, slow and decreased early diastolic filling rate and volume, and compensatory increased late diastolic filling caused by atrial contraction. These abnormalities have been detected using both invasive micromanometer catheter–based methods and noninvasive methods of echocardiography, Doppler echocardiography, radionuclide angiography, and magnetic resonance imaging. Although the sensitivity and specificity of each measurement may vary, recent studies have shown that all symptomatic patients with DHF have clear abnormalities in active relaxation and diastolic passive stiffness.[11,12] Patients with DHF have a significant increase in LV end-diastolic pressure, an increase in the LV end-diastolic pressure vs LV end-diastolic volume ratio (an index of instantaneous operative end-diastolic stiffness), and an increase in the LV chamber stiffness constant (the exponent of the relationship between LV diastolic pressure and volume). Recent studies were the first to provide definitive evidence that patients with DHF have abnormalities in the diastolic properties of the left ventricle that are sufficient to explain the hemodynamic abnormalities and the occurrence of heart failure in these patients.[11,12]

Systolic Properties

It has been postulated that patients with DHF have detectable abnormalities in LV systolic performance, function, and/or contractility despite the presence of a normal ejection fraction.[6,7,29-33] Furthermore, it has been hypothesized that abnormalities in LV systolic properties constitute an important pathophysiological mechanism for the occurrence of heart failure in these patients.[30,33] This notion is based on studies that examined the extent and velocity of LV long-axis shortening, mitral annular systolic velocity, and myocardial strain and strain rate.[29-32] However, it is likely that these measurements, like all indices of LV systolic function, are affected by coexistent changes in LV loading conditions and geometry—as well as changes in contractility.[34,35] In addition, it is possible, if not likely, that some of these indices of LV systolic function reflect changes in ventricular remodeling independent of changes in contractility.[36-38] Therefore, to accurately determine whether and to what extent patients with DHF have abnormalities in LV systolic properties, "load- and remodeling-independent" indices must be examined. Many such indices have been proposed, but there is no single universally agreed-upon index of LV systolic properties that is independent of load and remodeling.[34] We hypothesized that if multiple indices are measured in a given patient population and if the results are in general agreement and viewed in aggregate, it should be possible to determine whether patients with DHF have significant abnormalities in LV systolic performance, function, and contractility.

Using this approach in a recent study, we showed that measurements of LV systolic performance (stroke work), function (ejection fraction, preload-recruitable stroke work), and contractility ([+]d*P*/d*t*, stress vs shortening, end-systolic elastance) were not significantly different in patients with DHF compared with normal control subjects with no evidence of cardiovascular disease. To our knowledge, this was the first time such a comprehensive evaluation of LV systolic properties has been made in patients with DHF. Because all these LV systolic parameters were normal in patients with DHF, it seems reasonable to conclude that the underlying pathophysiology causing the symptoms and signs of heart failure is not based on abnormalities in these LV systolic properties. By contrast, the underlying pathophysiology is more likely based on abnormalities in diastolic function, including abnormal active relaxation and increased passive stiffness. In addition, factors such as abnormal arterial elastance, chronic renal insufficiency, and anemia may contribute to the precipitation of heart failure in these patients. However, the predominant and necessary factor for the occurrence of heart failure in these patients is abnormal diastolic function.

Alternate Terminology

A number of suggestions have been made for the terminology used to describe the 2 groups of patients with CHF. In addition to SHF and DHF, these include the following: (1) CHF with decreased or normal (or preserved) ejection fraction (or systolic function), (2) CHF with increased or normal LV volume, (3) CHF with systolic or diastolic dysfunction, (4) CHF with normal or abnormal arterial-ventricular coupling, and (5) CHF with eccentric or concentric remodeling. In our opinion, SHF and DHF remain the most appropriate and useful terminology; there is insufficient rationale to justify changing this traditional nomenclature, this terminology has become an integral part of our daily practice and is likely to continue to be used by clinicians, hospitals, and third-party payers. However, it is essential that the use of these terms be equated with the constellation of descriptive features characterizing the 2 major groups of heart failure (ie, DHF is characterized by concentric remodeling, normal LV volumes, and a predominant abnormality in diastolic properties whereas SHF is characterized by eccentric remodeling, progressive LV dilation, and a predominant abnormality in systolic properties).

Because of their increasing use, the appropriateness of the terms *heart failure with a normal ejection fraction* (HFNEF) and *heart failure with preserved systolic function* (HFPSF) requires a more detailed discussion. Table 3 presents a partial list of all conditions that can cause HFNEF/HFPSF. First, it should be recognized that not all patients with some symptoms or some signs compatible with CHF in fact actually have CHF. For example, peripheral edema can be caused by venous insufficiency, medications (such as thiazolidinediones, calcium-channel blockers, and nonsteroidal anti-inflammatory drugs), or renal insufficiency even without CHF. Dyspnea can be caused by obesity, deconditioning, or pulmonary disease in the absence of CHF. Therefore, some patients who are said to have HFNEF/HFPSF in fact do not have CHF at all. In addition, although most patients who have HFNEF/HFPSF have DHF, some may have CHF caused by valvular heart disease, pericardial disease, or circulatory congestive states. Therefore, the term *HFNEF/HFPSF* (like the other alternate suggestions) is a descriptive, nonspecific term that includes patients who do not have DHF. This issue of the *Progress in Cardiovascular*

Table 3. Causes of Heart Failure With a Normal Ejection Fraction or Preserved Systolic Function

DHF
Pressure-overload hypertrophy
Ischemic heart disease
Hypertrophic cardiomyopathy
Diabetes/metabolic syndrome
Valvular heart disease
Acute aortic
Mitral regurgitation
Mitral stenosis
Aortic stenosis
Pericardial disease
Constriction
Tamponade
Circulatory congestive states
Rapid fluid administration
Arteriovenous fistula
Severe anemia
Thyrotoxicosis

Diseases focuses on 50% of all CHF patients who have DHF.

Thus, we will continue to advocate using the term DHF in this issue of the *Progress in Cardiovascular Diseases*. However, as guest editor for this issue, I did not proscribe the use of the term DHF, nor did I prevent the use of alternate terms. Each author remained free to choose and use their own preferred terminology.

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