

VIEWPOINT

Diastolic Dysfunction

Can it Be Diagnosed by Doppler Echocardiography?

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Heart failure with a normal ejection fraction (HFNEF) predominately afflicts older, female individuals and is considered to be a consequence of diastolic dysfunction. Doppler echocardiography has become the standard method for identifying and characterizing diastolic function. However, the important distinction between Doppler measures of *filling dynamics* and true indexes of *intrinsic ventricular diastolic chamber properties* is not widely appreciated. Herein, we delineate physiologic measures of intrinsic ventricular diastolic function, as determined by pressure volume analysis, and compare and contrast these measures with those derived from Doppler echocardiography. Doppler-derived indexes of ventricular filling do not provide specific information on intrinsic passive diastolic properties, and thus, abnormal filling dynamics do not necessarily equate with intrinsic myocardial diastolic dysfunction. This raises a fundamental question as to whether delayed relaxation and/or stiffened passive properties are the unifying pathophysiologic mechanisms in all patients who present with HFNEF. (J Am Coll Cardiol 2004;44:1543–9) © 2004 by the American College of Cardiology Foundation

A significant percentage of patients with symptomatic heart failure have a normal left ventricular (LV) ejection fraction (1). Most investigators postulate that the fundamental abnormality in these patients is a disorder of diastolic rather than systolic function. Accordingly, these patients are frequently referred to as having “diastolic heart failure” (DHF) (2,3). Although a small number of these patients have certain forms of idiopathic hypertrophic or restrictive cardiomyopathy—known forms of diastolic heart failure—a majority are elderly women with one or more co-morbid cardiovascular conditions (hypertension, diabetes, coronary artery disease, obesity) (1,4,5). According to the European Cardiology Society, establishment of the diagnosis of DHF requires: 1) the presence of a clinical syndrome of heart failure (dyspnea or fatigue at rest or with exertion, fluid overload, pulmonary vascular congestion on examination or X-ray); 2) demonstration of an ejection fraction $\geq 50\%$; and 3) demonstration of diastolic dysfunction (6). Doppler echocardiography has become the primary tool for identifying and grading the severity of diastolic dysfunction in these patients.

We (7) and others (8,9) have used the term “heart failure with a normal ejection fraction” (HFNEF) instead of “diastolic heart failure” because the latter presumes that we understand the mechanisms leading to this disorder and, therefore, can justify the substitution of a mechanistic term for a descriptive phrase. We have taken this position because

a thorough examination of data available in the literature (8,10,11) and our own preliminary studies (12,13) have led us to fundamentally question whether diastolic dysfunction is the underlying pathologic mechanism of the heart failure syndrome in all hypertensive patients with HFNEF. This may seem totally incomprehensible, as it is well known that patients with HFNEF almost uniformly have elevated ventricular filling pressures and abnormal filling patterns detected on Doppler echocardiography (14). Although we fully concur with these empiric findings, we challenge their common pathophysiologic interpretations. Although widely thought of as indexes of diastolic function, the important distinction between these measures of *filling dynamics* and true indexes of *intrinsic ventricular diastolic chamber properties* is not widely appreciated. Consequently, some common beliefs about DHF have emerged from ambiguous definitions of diastolic dysfunction and reliance on nonspecific measures of diastolic function. We now seek to clarify the ambiguities and focus attention on specific measures of diastolic function in order to reconcile clinical impressions with fundamental physiologic principals.

Basic concepts. What is diastolic dysfunction? Diastole encompasses the isovolumic relaxation and filling phases of the cardiac cycle and has active and passive components (15,16). Removal of calcium from the myofilaments and uncoupling of actin-myosin cross-bridge bonds constitute the molecular events governing the rate of myocardial relaxation and thus the rate of ventricular pressure decline. This active component of diastole is typically characterized by the time constant of relaxation (τ), determined by fitting a monoexponential curve to the isovolumic period of the ventricular pressure curve (17). Once maximal cross-

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Abbreviations and Acronyms

- EDPVR = end-diastolic pressure-volume relationship
- DHF = diastolic heart failure
- HFNEF = heart failure with a normal ejection fraction
- LA = left atrial/atrium
- LV = left ventricle/ventricular

bridge uncoupling has occurred, the mechanical properties of the chamber are determined by passive factors, such as the degree of myocellular hypertrophy (myocardial mass), cytoskeletal (18), and extracellular matrix (19) properties and chamber geometry. Collectively, these factors determine the end-diastolic pressure-volume relationship (EDPVR), which characterizes passive chamber properties. The EDPVR is inherently nonlinear (Fig. 1) (20,21). Ventricular chamber stiffness (i.e., slope of EDPVR at a given volume [dP/dV]) and compliance (the mathematical reciprocal of stiffness) are two terms commonly used to characterize diastolic ventricular properties. However, these indexes are load dependent and, therefore, cannot uniquely characterize diastolic properties. Specifically, chamber stiffness increases in proportion to filling pressure. This is analogous to the stiffness of a toy balloon in which the amount of pressure required to cause a given increase in volume increases as the volume of the balloon is increased.

Based on these basic descriptions, diastolic dysfunction may in general be considered present when abnormalities exist in either active or passive ventricular properties. Increased tau (i.e., slowing of relaxation) delays the onset of filling, thus decreasing the rate of ventricular filling at a fixed heart rate and may, therefore, change the shape of the instantaneous diastolic pressure-volume relationship during early diastole. Thus, with an increased tau, a higher mean left atrial pressure may be required to achieve normal filling volumes, especially at high heart rates. However, as discussed further subsequently, tau increases with all forms of

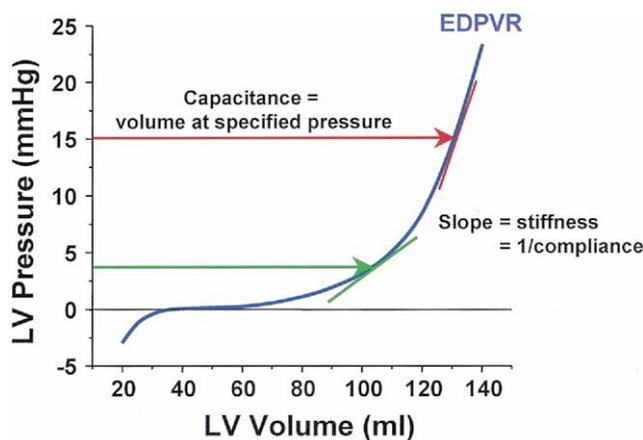


Figure 1. Nonlinearity of end-diastolic pressure-volume relationship (EDPVR). Terms used are depicted, including ventricular stiffness (slope of EDPVR at a given volume [dP/dV]), compliance (mathematical reciprocal of stiffness), and chamber capacitance (volume at a specific filling pressure). LV = left ventricle.

hypertrophy and during the normal aging process, is influenced by loading conditions (22), and is not ubiquitously associated with elevated mean left atrial pressure and heart failure.

Changes in the passive component of diastole (i.e., shift of EDPVR) have been considered to primarily account for the hemodynamic and symptomatic abnormalities of heart failure in HFNEF (2,23,24). Shifts in the EDPVR can be described by changes in chamber capacitance—the volume at a specific filling pressure (Fig. 1). A leftward/upward-shifted EDPVR is indicative of decreased chamber capacitance (Fig. 2A). Such a shift is considered pathologic because there is a need for increased filling pressure to achieve filling volumes necessary for the heart to generate a normal stroke volume and blood pressure. Conversely, a rightward/downward-shifted EDPVR (increased ventricular capacitance) occurs in all forms of dilated cardiomyopathy. This change is also pathologic and represents a different form of diastolic dysfunction; it is more commonly referred to as “ventricular remodeling.” There are multiple nonlinear equations used to represent the EDPVR, but there is no single accepted equation; therefore, there are a host of different parameters (in addition to capacitance) used to index passive chamber and myocardial stiffness (20,21).

The bottom portion of the instantaneous pressure-volume loop (Fig. 2B, arrows) is sometimes used to quantify passive ventricular properties (8,24), but it is important to note that this is distinctly different from the true EDPVR. In particular, at high filling pressures such as may exist in the heart failure state, there can be a large discrepancy between these two curves, even when the rate of relaxation is normal.

Because they are governed by different mechanisms, defects in active and passive diastolic properties may occur separately or in combination. For example, similarly increased values of tau occur with all forms of myocardial hypertrophy, including that associated with: 1) normal aging in which the EDPVR is normal; 2) idiopathic hypertrophic or restrictive cardiomyopathy in which the EDPVR is shifted upward and leftward; and 3) dilated cardiomyopathy in which the EDPVR is shifted downward and rightward. Furthermore, an increase in tau observed in all of these has never been proven by itself to be of sufficient magnitude (25) to explain pathologic limitations of filling or induction of heart failure (26). On the contrary, one study of patients with hypertrophy and HFNEF specifically showed that relatively large increases in tau encountered during exertion did not impair filling or result in incomplete relaxation (8).

Therefore, the term “diastolic dysfunction” by itself is ambiguous in that it does not distinguish between abnormalities in active properties and passive properties. Such a distinction has not always been clear in the previous literature but is critical for clarifying pathophysiologic mechanisms and may have therapeutic implications.

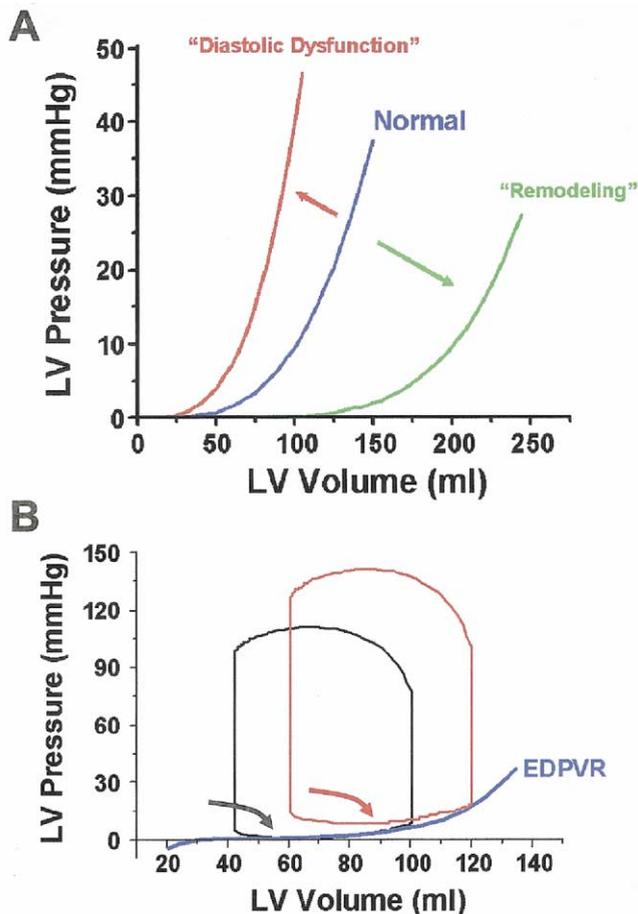


Figure 2. (A) Changes in the passive component of diastole (i.e., shift of end-diastolic pressure-volume relationship [EDPVR]). A leftward/upward-shifted EDPVR (decreased ventricular capacitance) results in a need for increased filling pressure to achieve filling volumes necessary for the heart to generate a normal stroke volume and blood pressure. Conversely, a rightward/downward-shifted EDPVR (increased ventricular capacitance) occurs in all forms of dilated cardiomyopathy and is commonly referred to as “ventricular remodeling.” (B) The EDPVR provides the lower boundary for the instantaneous pressure-volume loop. At low filling pressures (black loop), the filling phase of the loop (arrow) may coincide with EDPVR. At high filling pressures (red), however, the filling phase (arrow) may be elevated significantly above the EDPVR, even when tau is normal. This is a response of any normal heart and does not necessarily indicate diastolic dysfunction. LV = left ventricle.

Doppler echocardiographic assessment of diastolic properties. Although tau and EDPVR fundamentally characterize intrinsic active and passive diastolic ventricular properties, respectively, there are difficulties in adopting these measures into clinical practice and clinical research, because their assessment requires highly specialized invasive techniques, including the need to temporarily alter preload volume. Therefore, these measures have been employed primarily within the context of small research studies (10,11,27,28). Consequently, the range of normal parameter values is not well established, and the correlation between abnormal parameter values and clinical signs and symptoms of heart failure is unfamiliar and largely unknown. Accordingly, clinicians have turned to readily applicable noninvasive techniques, especially Doppler echocardiography.

However, because this technique is so widely available and applicable, several Doppler parameters have come to be accepted as surrogate definitions of intrinsic diastolic dysfunction, rather than the reality, which is that these parameters are merely measures of events occurring during diastole that are affected by, among multiple other factors, intrinsic diastolic properties.

Nevertheless, Doppler echocardiography has become the technique of choice in the evaluation of patients with HFNEF, and an armamentarium of Doppler techniques have been developed to help describe LV filling dynamics in this setting. Using these techniques, a host of characteristic changes in diastolic Doppler findings are frequently found in patients with HFNEF. Because these patients have abnormal diastolic Doppler parameters (14,29), the concept has been promulgated that these findings are indicative of an intrinsically stiffer ventricular chamber and that this is synonymous with an upward/leftward-shifted EDPVR and smaller chamber volume.

However, we believe that the diastolic Doppler abnormalities seen in patients with HFNEF are mainly the result of elevated LV filling pressure; they do not necessarily by themselves specifically indicate any intrinsic myocardial abnormality, nor do they define the relative position of EDPVR in comparison to normal. A closer examination of each of the Doppler techniques used to characterize diastolic function will further emphasize these points.

Pulsed-wave Doppler tracings of mitral inflow are frequently used to study LV filling (30). During early diastole, the flow velocity of blood filling the LV reflects the pressure gradient between the LV and the left atrium (LA) just after opening of the mitral valve. Under normal loading conditions, the relatively low LA-LV pressure gradient causes low velocity mitral inflow, with peak velocities typically around 1 m/s. If active relaxation is slowed (i.e., if tau is increased), early inflow velocity is slower and lasts for a longer duration (Fig. 2). These changes are responsible for the echocardiographic finding of E/A reversal seen in patients with impairments in active relaxation that accompany normal aging and hypertrophy (Fig. 3, grade 1). Such patients have normal mean LA pressures, further evidence that increased tau, alone, is not sufficient to account for symptomatic heart failure and does not explain the elevated filling pressures seen in HFNEF patients at rest (31). When LA pressure is increased, there is a higher LA-LV gradient, so that there is increased velocity of early inflow. Because ventricular and atrial pressures equilibrate quickly, early ventricular filling is terminated abruptly, causing a shortening of the time period during which early filling occurs and deceleration time is decreased (31). When volume overload is modest, the combination of prolonged relaxation and elevated LA pressure may be balanced, creating filling velocities and deceleration times similar to those seen with normal load and normal relaxation (Fig. 3, grade 2). This pattern on the echocardiogram is generally referred to as pseudo-normalization. When volume overload is severe, early filling

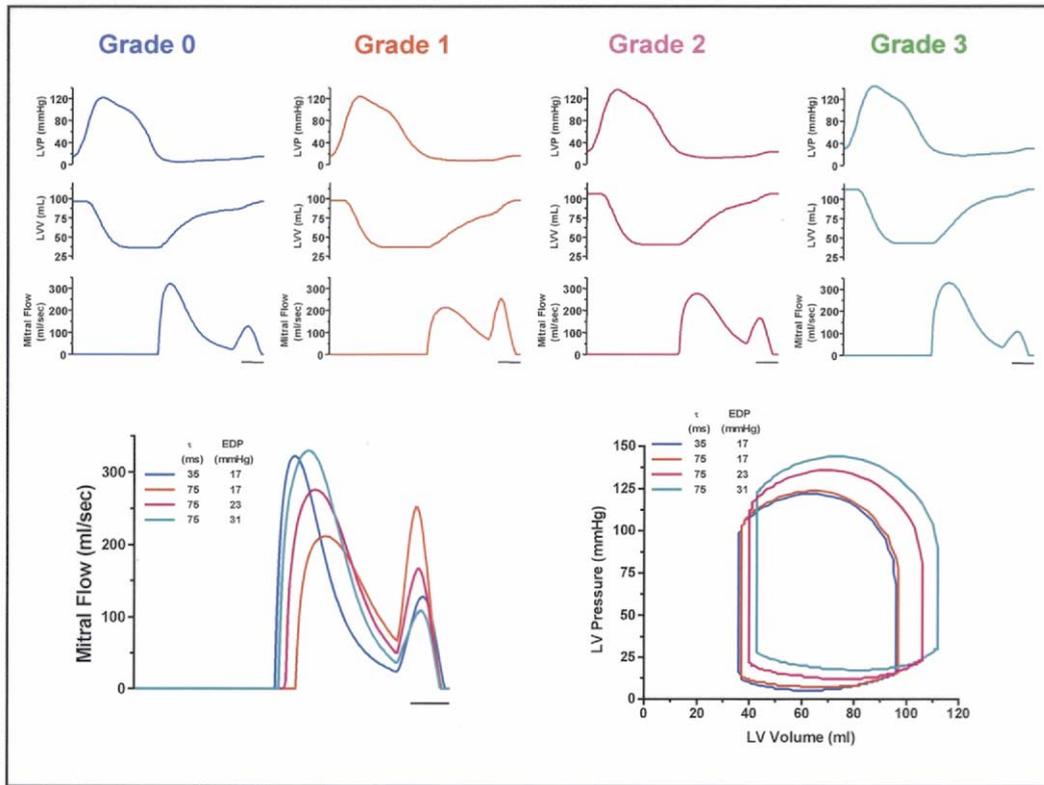


Figure 3. Echocardiographic Doppler grades of diastolic function based on mitral inflow patterns (30). Impaired relaxation (grade 1) results from impairments in active relaxation (prolonged tau) but is not associated with a change in mean left atrial pressure. Further grades of diastolic dysfunction by echocardiographic Doppler (grades 2 [pseudonormal] and 3 [restrictive]) are associated with an increased mean left atrial pressure. However, as depicted by the representative pressure-volume loops (**bottom right**), there is no shift in the end-diastolic pressure (EDP)-volume relationship, indicating that changes in Doppler filling patterns can be independent of alterations in the intrinsic passive diastolic properties of the left ventricle (LV). These curves are readily obtainable from a time-varying elastance-based simulation of the cardiovascular system. LVP = left ventricular pressure; LVV = left ventricular volume.

is rapid and the deceleration time is short (Fig. 3, grade 3). This echocardiographic pattern is called “restrictive” (31). Therefore, it is obvious that Doppler mitral inflow patterns are determined primarily by loading conditions (32) and do

not unambiguously signify an intrinsic abnormality of the LV musculature. This is underscored by the fact that the transmitral flow pattern may be changed by Valsalva’s maneuver, which decreases venous return, or by medications

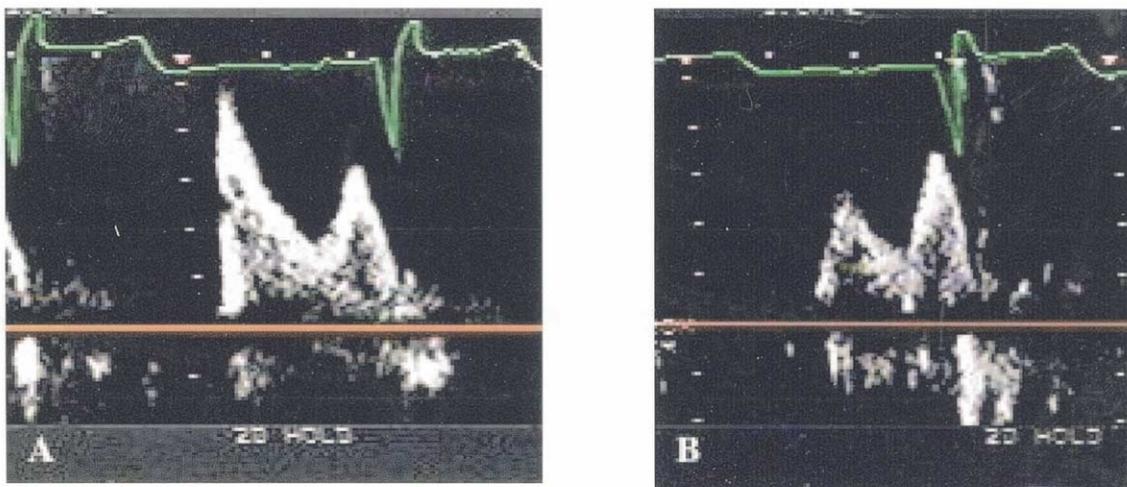


Figure 4. Transmittal flow velocity patterns in a patient with elevated left ventricular filling pressure. (A) Baseline. (B) During Valsalva maneuver. Decreases in venous return result in marked changes in the filling pattern, reflecting the fact that these parameters are determined primarily by loading conditions and not intrinsic passive diastolic properties of the left ventricle (33).

that change preload, such as nitroglycerin (Fig. 4) (33). Furthermore, the Doppler filling profile does not provide any insights into the relative position of EDPVR. For example, a restrictive pattern has been observed in subjects with leftward/upward-shifted EDPVRs characteristic of idiopathic hypertrophic/restrictive cardiomyopathies, but is also well described in patients with severe systolic heart failure characterized by a dilated LV with rightward/downward-shifted EDPVRs (34).

Tissue Doppler is a newer, sophisticated technique used to evaluate LV filling dynamics. This technique is used to directly measure the velocity of myocardial displacement as the LV expands in diastole, and this is an attempt to separate intrinsic LV contributions from those of preload. Diastolic tissue velocities measured at the mitral valve annulus generally show low-velocity deflections (~10 cm/s) during early filling and later in diastole with atrial contraction. Diastolic tissue velocities during mid-diastole are too low to be measured with conventional echocardiography. The tissue velocity measured during early filling (E') can be considered a surrogate marker for tau, as it is primarily determined by the expansion of the LV during relaxation (35,36). For this reason, the ratio of peak early transmitral flow velocity (E) to the peak early myocardial tissue velocity (E/E') is frequently cited as convincing evidence of myocardial diastolic dysfunction. This is because this fraction reflects the ratio of LA pressure elevation, compared with the degree of tau prolongation (36,37). However, neither of these parameters necessarily reflects a problem with myocardial expansion during mid-diastole, and neither describes the position of EDPVR. Thus, these parameters, though providing indirect indexes that correlate well with filling

pressure (38), provide no direct pathophysiologic insight into the mechanism responsible for causing volume overload in patients with heart failure.

There have also been attempts to evaluate LV end-diastolic pressure by measurement of the duration of transmitral flow and retrograde pulmonary flow during atrial contraction. These measurements are elaborate, difficult to obtain in many patients, and not routinely performed. Even if such measures were routinely available, it should be emphasized that estimation of this pressure with such techniques should also not be thought of as a surrogate index of diastolic function, nor does an elevation of diastolic pressure in the presence of a normal ejection fraction mandate that diastolic dysfunction exists. Factors extrinsic to the heart (e.g., overall volume status and venoconstrictive states) could importantly contribute to increases in diastolic pressure (39).

It is not our position that Doppler echocardiography be dismissed as a useless tool in the evaluation of patients with HFNEF. On the contrary, noninvasive Doppler findings indicative of increased filling pressures in a patient with a normal ejection fraction and symptoms compatible with congestive heart failure are confirmatory of the suspected diagnosis (14), can estimate LV filling pressures, and can help guide therapy toward alleviating the volume overload state and provide prognostic information. It is our position, however, that the finding of abnormal diastolic Doppler echocardiographic patterns should not lead to the conclusion that an intrinsic disorder of myocardial diastolic properties exists and is responsible for the heart failure state. Although such changes are associated with slowed relaxation (prolongation of tau), they provide no insight into changes of EDPVR and are heavily influenced by atrial and ventricular diastolic pressures. Abnormalities in Doppler filling parameters are therefore largely the result of increased filling pressures; they do not, a priori, equate with any intrinsic myocardial or ventricular abnormality that causes filling pressures to become elevated.

Heart failure with a normal ejection fraction. Is diastolic dysfunction the underlying mechanism of HFNEF in the majority of patients with this condition who are predominantly older women with hypertension? If so, is the heart failure related to an abnormality in the active or passive component of diastole? Typically, both are implicated. In light of recent data noted earlier, it is still uncertain whether abnormalities observed in tau are quantitatively sufficient to induce heart failure, and this question deserves specific investigation. Most (if not all) review articles attribute HFNEF primarily to increased myocardial stiffness due to hypertrophy, which purportedly induces a leftward/upward shift of EDPVR (2,15). It is noteworthy that after many decades of basic research, the first publication to actually provide data demonstrating decreased diastolic compliance in HFNEF patients has been published this year (24). Despite certain limitations (40,41), that study of relatively young, predominantly male, hypertensive and nonhyperten-

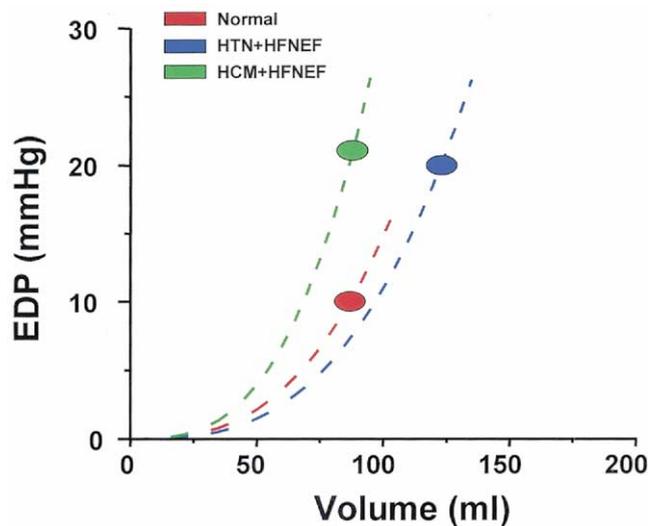


Figure 5. Hypothetical end-diastolic pressure-volume relationships for normal subjects (red) and two groups with heart failure and normal ejection fraction (HFNEF): subjects with idiopathic hypertrophic cardiomyopathy (HCM+HFNEF, green) and subjects with hypertensive hypertrophy (HTN+HFNEF, blue). The concept is based on results of preliminary studies (12,13). Curves were constructed using a standard equation ($EDP = \beta EDV^\alpha$) (21).

sive patients is important in advancing our understanding. We have noted that other data available in the literature and our own preliminary data suggest, however, this may not be the case in all patients with HFNEF (7,8). Our own preliminary studies in predominantly older women, all with hypertension and hypertrophy, have suggested that ventricular size in HFNEF is increased compared with normal (12,13). Compared with age, gender, and body size matched controls, increased ventricular filling pressures in our patients with HFNEF were associated with *increased* ventricular end-diastolic and systolic volumes, which is incompatible with an upward/leftward shift of EDPVR, as would be seen in a cohort of patients with true diastolic dysfunction, such as those with idiopathic hypertrophic cardiomyopathy (Fig. 5).

Therefore, we advocate generation and investigation of new concepts to delineate other possible mechanisms leading to HFNEF, with the goal of guiding development of badly needed treatments. For the case of heart failure due to systolic ventricular dysfunction, significant progress was achieved when focus shifted away from studies of ventricular dysfunction to studies of the associated abnormalities in neurohormonal activation and regulation of vascular tone, which led to the development of effective treatments of heart failure, including angiotensin-converting enzyme inhibitors and beta-blockers. We suggest, similarly, that progress may be achieved when it is recognized that factors other than those intrinsic to the heart could be primary factors in creating chronically elevated pulmonary venous pressures characteristic of this condition (39). It is well recognized that a majority of patients with HFNEF are elderly, with concomitant co-morbidities, including renal dysfunction, obesity, anemia, hypertension, and diabetes (4). These extra-cardiac conditions can result in a general increase in circulating blood volume and/or a central shift of circulating blood volume, which could result in the observed phenotype. Furthermore, as HFNEF occurs in a variety of settings, we need to be open to the possibility that different mechanisms, *including extracardiac factors*, may dominate in different groups of patients.

Conclusions. Although the diastolic dysfunction concept of HFNEF is widely accepted and embraced by clinical cardiologists (15), a critical examination reveals that there has been ambiguity in definitions of diastolic dysfunction and acceptance of nonspecific, Doppler-derived measures of filling dynamics as surrogates for EDPVR. We suggest that the following points may help to reconcile discrepancies between common clinical beliefs and fundamental physiologic principles:

1. As a stand-alone term, diastolic dysfunction is ambiguous. A clear distinction between abnormalities of *active* and *passive* diastolic properties needs to be established. The cellular and molecular mechanisms governing these two aspects of diastole are distinct and not directly linked.

2. The time constant of relaxation (τ) fundamentally characterizes active diastolic ventricular properties, and the EDPVR fundamentally characterizes intrinsic passive diastolic ventricular properties.
3. Correlations and mechanistic links between slowing of relaxation (i.e., increases in τ) and development of heart failure are not well established but need to be investigated.
4. Doppler-derived indexes of ventricular filling do not provide specific information on intrinsic passive diastolic properties (i.e., about EDPVR).
5. Accordingly, abnormal filling dynamics do not necessarily equate with intrinsic myocardial diastolic dysfunction.

It may be argued that some of these points are simply a matter of definition of what constitutes diastolic dysfunction. However, the emerging debate about the pathophysiology of HFNEF should not deteriorate into a debate over definitions. The fundamental question is whether delayed relaxation and/or stiffened passive properties (elevations of EDPVR) are the unifying pathophysiologic mechanisms of heart failure when it occurs in patients with a normal ejection fraction (42). It is our contention that the data available in the literature do not provide a definitive answer for all cases of HFNEF, a population composed primarily of elderly women with hypertension. Yet, the answer is pivotal, as elucidation of the mechanism will facilitate discovery of the most efficacious therapies.

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