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Heart Failure With a Normal Ejection Fraction Is It Really a Disorder of Diastolic Function?

Daniel Burkhoff, MD, PhD; Mathew S. Maurer, MD; Milton Packer, MD

A large proportion of patients who present with symptoms of heart failure have a left ventricular ejection fraction within the normal range.¹ Although some have postulated that ventricular systolic function is impaired,² most investigators have concluded that the fundamental abnormality in these patients is a disorder of diastolic (rather than systolic) function,^{3–5} and in fact, these patients are frequently referred to as having diastolic heart failure. The use of such a term is troublesome, however, because it presumes that we understand the mechanisms leading to this disorder and therefore can justify the substitution of a mechanistic term for a descriptive phrase. A less presumptuous approach is to refer to these patients as having heart failure with a normal ejection fraction (HFNEF), a descriptive approach that makes no assumptions about our knowledge about the pathophysiology of this disorder.

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Do most patients with heart failure and a normal ejection fraction have diastolic dysfunction? Patients with HFNEF are generally elderly women who have associated hypertension, diabetes, and/or coronary artery disease.⁶ These comorbid conditions have been linked to myocardial hypertrophy, ischemia, and/or interstitial fibrosis, each of which can prolong relaxation and increase passive myocardial stiffness.⁷ However, the coexistence of disorders known to affect these aspects of diastole is not sufficient to establish that diastolic dysfunction is the cause of heart failure when it occurs in patients with a normal ejection fraction. To determine that an abnormality of diastolic function is the cause of the patient's symptoms, we need to demonstrate the existence of such a derangement and determine that it is sufficient to limit exercise tolerance.

What kind of diastolic abnormalities can cause symptoms of heart failure? The sequestration of calcium and cross-bridge uncoupling after the end of systole are responsible for the active process of ventricular relaxation, but it is unclear whether retardation of this active process as encountered clinically is sufficient to lead to clinically meaningful limitations of ventricular filling, except at high heart rates⁸

(discussed further below). In contrast, changes in the passive component of diastole (the component determined by the dispensability of the myocardium) are fundamentally considered to account for the hemodynamic and symptomatic abnormalities of heart failure.^{4,5} Unfortunately, most measures used to assess diastolic function do not assess this key passive component of diastole. The use of invasive measurements to calculate the rate of decline in ventricular pressures in early diastole (τ) evaluates only the active process of diastole.⁹ Furthermore, the use of echocardiographic or radionuclide techniques to quantify the rate of blood flow or volume changes in the ventricles during diastole generates parameters that are influenced by loading conditions in the heart¹⁰ and therefore cannot be viewed as specific indexes of the passive component of diastole.

The only way to truly demonstrate that patients with HFNEF have an abnormality of passive diastolic properties is to show that their ventricular end-diastolic pressure-volume relation (EDPVR)¹¹ is shifted upwards compared with normal (Figure 1A). By characterizing the EDPVR, it is possible to show not only that left ventricular diastolic pressure is elevated, but that such elevation is seen in ventricles that have decreased capacitance (ie, a decreased filling volume at any specified filling pressure; Figure 1B). Precisely such an abnormality has long been assumed to represent the fundamental abnormality of patients with HFNEF.^{4,5} Characterization of an upward shift of the EDPVR is critical, because in the absence of such a demonstration, left ventricular end-diastolic pressures may be increased simply because of an increase in preload volume without any meaningful change in diastolic properties.

Unfortunately, characterization of the EDPVR is a challenging task that requires simultaneous assessment of both pressure and volume across a wide range of values. Given the difficulties in this determination, most investigators have used limited approximations of the EDPVR in evaluating the diastolic properties of the heart. For example, earlier studies of ventricular hypertrophy relied on assessment of diastolic myocardial stiffness rather than EDPVR.¹² Stiffness is defined as the change in ventricular pressure for a given change in volume ($\Delta P/\Delta V$) and therefore is related to the slope of the EDPVR at a given filling pressure. Because the EDPVR is not linear, however, the slope of the EDPVR (ie, stiffness) increases as filling pressure increases (Figure 1C and Figure 2). This non-linearity means that any condition that results in an increase in ventricular filling pressures will lead to an increase in calculated stiffness, even if it does not modify the EDPVR. As a result, studies showing an increase in diastolic myocardial stiffness in patients with hypertrophy are not sufficient to show that passive diastolic properties are abnormal.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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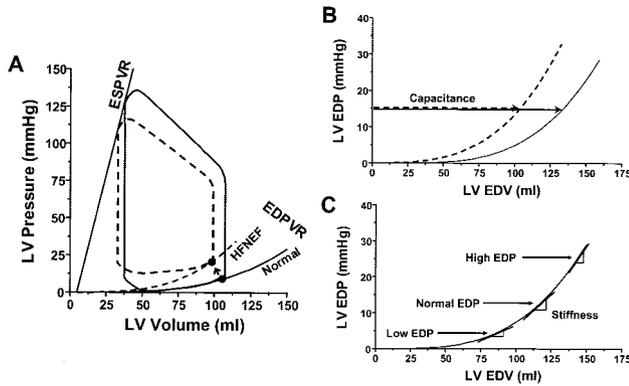


Figure 1. A, Pressure-volume representation of prevailing paradigm of HFNEF, showing elevated EDPVR with no significant effect on end-systolic pressure-volume relationship (ESPVR). Respective end-diastolic pressure-volume point shown by filled circle. B, When the entire EDPVR cannot be measured, an alternate means of indexing diastolic properties for purposes of comparing heart sizes is via capacitance, the volume at a specified filling pressure. C, EDPVR is nonlinear, so that stiffness (the slope of the relationship, $\Delta P/\Delta V$) depends on filling pressure, as indicated by the tangent line at each level of end-diastolic pressure (EDP). EDV indicates end-diastolic volume.

mal in these patients, because the major factor that determines these properties is the relative position of the EDPVR compared with normal, not the stiffness at any given point.

What disorders have been shown to be characterized by an upward shift of the EDPVR? Acute, pathological upward shifts of the EDPVR have been reported in patients with coronary artery disease in whom acute ischemia was provoked by rapid atrial pacing.¹³ Upward shifts in EDPVR have also been demonstrated in disorders of the pericardium or right ventricles, which can cause pericardial constraint and ventricular interactions.¹⁴ Abnormalities of the EDPVR are also apparent in patients with specific forms of restrictive and hypertrophic cardiomyopathies that are characterized by a notable reduction in left ventricular chamber size.¹⁵ However, none of these pathophysiological conditions are present in most patients with heart failure associated with a normal ejection fraction. What does the EDPVR look like in these patients? The article by Kawaguchi et al¹⁶ in the current issue of *Circulation* (taken together with earlier work by the same group¹⁷) provides important insights into this question, because to our knowledge, these authors are the first to describe the EDPVR in patients with heart failure and a normal ejection fraction. Examination of their data (reproduced in Figure 3), however, does not suggest that patients with HFNEF have a specific or characteristic abnormality of the EDPVR. Instead, their data show that EDPVRs of patients with HFNEF may be shifted toward lower volumes compared with normal, may be similar to normal, or may be shifted toward larger volumes. Furthermore, the authors demonstrate that values for τ , the index reflecting the active component of diastole, were within the normal range, a finding that contrasts with that of Zile et al.¹⁸ Finally, the findings of Kawaguchi et al seem to undermine the premise that increased diastolic stiffness impairs the ability of the heart to increase preload volume during exercise. Such an impairment would be expected if the EDPVR were abnormal in patients

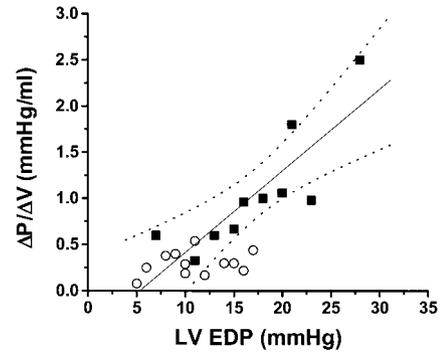


Figure 2. Data re-plotted from Table 1 of Grossman et al¹¹ showing, as suggested in Figure 1C, that diastolic stiffness ($\Delta P/\Delta V$) varies directly with filling pressure. Data from 10 hypertrophic hearts (solid squares) span high filling pressures and stiffness values. Data from 1 patient of the original publication with aberrant data (EDP of 52 mm Hg and stiffness of 0.9 mm Hg/mL) was excluded. Line of linear regression ($\pm 95\%$ confidence intervals) was determined for data from these hypertrophic hearts. Data from 12 non-hypertrophic patients (open circles) have lower filling pressures and lower values of stiffness; a majority of these data fall within the 95% confidence intervals of the regression line determined from the patients with hypertrophy.

with HFNEF. Instead, using direct invasive measurements, Kawaguchi et al¹⁶ show that, during exercise, patients with HFNEF were able to increase preload volume with very little if any effect on the EDPVR, despite a substantial prolongation of τ , the time constant of relaxation.¹⁶

In our view, these findings are sufficient to raise the provocative hypothesis that there exists no consistent abnormality of intrinsic diastolic properties that can explain the occurrence of heart failure with a normal ejection fraction. Left ventricular filling pressures may be increased in these patients not because left ventricular volumes are small, but because left ventricular volumes are increased — with patients remaining on an EDPVR that is unchanged or even shifted rightward (Figure 3). Even in cases of upward shift of the EDPVR, it is not clear whether the degree of upward shift would be sufficient to explain the magnitude of the increase in left ventricular filling pressure. That is not to say that ventricular filling patterns are normal in these patients. The

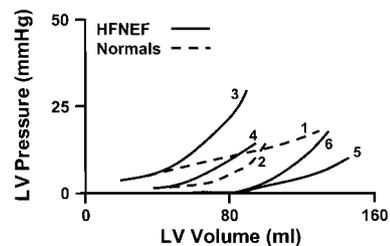


Figure 3. End-diastolic pressure-volume relations re-plotted from Kawaguchi et al¹⁵ (curves 1 and 3 from Figure 1; curves 4 and 5 from Figure 4) and from Figure 3 of Liu et al¹⁶ (curves 2 and 6). EDPVRs of the HFNEF patients may be shifted to the left (curve 3), shifted to the right (curves 5 and 6), or may not be significantly different (curve 4) than those of normal patients (curves 1 and 2). Knowledge of patient age, sex, and body size would enhance ability to interpret the meaning of these differences.

rapidity of ventricular flow and indices of ventricular relaxation may be slowed in these patients and myocardial stiffness may be increased,^{5,7,18} but these may be the result, rather than the cause, of the elevation of ventricular filling pressures. If this is correct, then we must seek a different cause of the increased ventricular end-diastolic pressure in patients with HFNEF (eg, combined ventricular and vascular stiffening as suggested by Kawaguchi et al).¹⁶

These observations need to be interpreted cautiously, however. Invasive assessment of left ventricular volume using the conductance method has important limitations. Calibration of the signal into absolute volumes relies on cross-calibration with other methods (eg, ventriculography or thermodilution cardiac output) or an independent calibration scheme (based on injection into the pulmonary artery of hyper- or hypotonic solution) that is limited by statistical uncertainty.¹⁹ Furthermore, the invasive nature of the conductance method limits its ability to be applied to large numbers of patients, to normal control subjects, or to longitudinal studies in individual patients. Indeed, Kawaguchi et al¹⁶ present data from 58 patients; only 10 of these patients had heart failure and a normal ejection fraction and only 33 were studied using the invasive conductance catheter methods. These limited data were obtained over a 14-year period by a group that has some of the most collective experience in the world with this technique in the clinical setting. Therefore, we can only speculate as to how applicable the findings of the current study may be to most patients with HFNEF. To complicate matters further, comparison of EDPVRs is necessarily dependent on interpretation of ventricular chamber size; however, normal values for ventricular volume are determined by age, body size, and sex.²⁰ Yet, comparisons of EDPVRs generally do not account for the demographic characteristics of the patients or the control subjects.

Despite these limitations and the conclusions reached in prior studies, we are faced with the uneasy realization that there is still no evidence to support the hypothesis that pathologically shifted EDPVRs are present in most patients with heart failure and a normal ejection fraction. The increase in left ventricular filling pressures seen in these patients may be the cause (and not the result) of the abnormalities of diastolic filling that have been observed in this disorder. Such a conclusion would present a direct challenge to the diastolic dysfunction hypothesis, and we expect such a proposal to generate considerable controversy. The diastolic dysfunction hypothesis is so widely accepted and is so ingrained in our thinking that it has formed the sole basis of both basic research and clinical trials of new treatments for HFNEF for the past 30 years.^{21,22} Yet, despite detailed studies of the biochemistry and molecular biology of ventricular relaxation, this research has yet to lead to a single effective treatment for HFNEF. Have we failed because diastolic dysfunction is too

difficult to understand or manage, or is it because HFNEF has nothing to do with diastolic dysfunction at all?

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