

Ventricular Pump Function in Heart Failure with Normal Ejection Fraction: Insights from Pressure-Volume Measurements

Mathew S. Maurer, Itzhak Kronzon, and Daniel Burkhoff

The syndrome of heart failure in the setting of normal ejection fraction (HFNEF) is manifest in a clinically heterogeneous group of patients with multiple and varied comorbid conditions. In this report, we review available data derived from pressure-volume (PV) analyses in patients with and in animal models of HFNEF. Pressure-volume analysis of ventricular function is challenging in the clinical setting but provides unique insights into the systolic, diastolic, and overall pumping characteristics of the heart. Results of such analyses have thus far been limited to small cohorts of patients but suggest that different cohorts of patients with HFNEF having PV relations that imply different pathophysiologic mechanisms exist. This emphasizes the need to take a view of this syndrome, which extends beyond diastolic dysfunction, particularly when it comes to proposing and investigating therapeutic targets. We therefore propose that progress can be made in advancing therapeutics for HFNEF if it is appreciated that different underlying pathophysiologic mechanisms may be important in different cohorts and if attention expands beyond diastolic dysfunction as the sole target. Similar to the success that was achieved in advancing therapeutics for systolic heart failure when attention shifted away from the heart to the neurohormonal and renal axes, our

interpretation of data in human beings and in animal models suggests that addressing similar targets (perhaps not in exactly the same manner) may prove to be fruitful, at least for some patients with HFNEF as well.

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The incidence and prevalence of heart failure are increasing exponentially.^{1,2} Epidemiologic studies have demonstrated that more than half of patients with heart failure have a normal ejection fraction.¹⁻⁴ Although these patients have traditionally been classified as having diastolic heart failure, we and others prefer the term *heart failure with normal ejection fraction* (HFNEF) because it is descriptive. Use of the term *diastolic heart failure* implies precise understanding of the mechanism that would apply to all patients with HFNEF. However, the pathophysiology of HFNEF is not completely understood and it is not clear that all patients with HFNEF have the same disease. Indeed, there are many theories about the pathophysiology of HFNEF that have emerged from studies on different patient populations with and animal models of HFNEF.⁵⁻⁸

Nevertheless, one factor that undoubtedly contributes to the current state of confusion and disagreement among investigators is the desire by some to explain this clinical syndrome by a single pathophysiologic mechanism—namely, diastolic dysfunction. Classically, the term *syndrome* is used in medicine for grouping together multiple symptoms with a single pathophysiologic etiology. However, a syndrome can also refer to a symptom (or a complex of symptoms) resulting from multiple diseases and contributing risk factors.⁹ Although there are

From the Division of Geriatric Medicine and Aging, Department of Medicine, Columbia University Medical Center, Columbia University College of Physicians and Surgeons, New York, NY, New York University Medical School, Division of Cardiology, New York, NY, and Jack H. Skirball Center for Cardiovascular Research, Cardiovascular Research Foundation, Orangeburg, NY.

Address reprint requests to Daniel Burkhoff, MD, PhD, Jack H. Skirball Center for Cardiovascular Research, Cardiovascular Research Foundation, 8 Corporate Drive, Orangeburg, NY 10962. E-mail: dburkhoff@crf.org

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many clinical signs and symptoms expressed in HFNEF, 3 features are particularly common in all patient subgroups: (1) high resting left ventricular (LV) end-diastolic pressure (EDP),¹⁰ (2) reduced exercise capacity,¹¹ and (3) propensity for acute pulmonary edema.¹² The frequency and intensity with which these features manifest are highly variable in patients. A fundamental unresolved question is whether this constellation of variably expressed signs and symptoms is always caused by a single underlying pathology.

The prototypical patient with HFNEF is an older individual with multiple comorbid conditions, which can include hypertension, diabetes, coronary artery disease, obesity, renal dysfunction, and anemia. Many of these factors lead to ventricular hypertrophy and/or interstitial fibrosis, both common in HFNEF, which in turn have been associated with diastolic dysfunction. However, many of these factors can impact myocardial, ventricular, vascular, and extracardiovascular properties in other ways that can individually and collectively contribute to the signs and symptoms of HFNEF via mechanisms that are not all related to diastolic dysfunction. In addition, some patients do not fit these typical demographics. For example, a young patient with an inherited form of hypertrophic cardiomyopathy and an individual with amyloidosis differ from the prototypical patient with regard to demographics, clinical presentation, and responses to therapy. We believe that an essential element of furthering the understanding of HFNEF is recognition that HFNEF is not one disease with one single mechanism. In fact, as summarized in Table 1, there are numerous well-known disorders always considered in the differential diagnosis of HFNEF that can cause or contribute to the clinical syndrome. In many of these cases, HFNEF need not be a result of an intrinsic abnormality of myocardial diastolic function; neither does diastolic dysfunction need to be present for signs and symptoms to be manifest.

In this report, we review available data derived from pressure-volume (PV) analyses in patients with and in animal models of HFNEF. We focus on PV analysis because we believe that pressure-volume-time relations are the most thorough means of characterizing global, ventricular systolic, and ventricular diastolic properties of the

Table 1. Heart Failure With Normal Ejection Fraction: Differential Diagnosis of Underlying Mechanisms and Contributing Factors*

DHF
Restrictive cardiomyopathy
Infiltrative cardiomyopathy
Amyloid
Hemochromatosis
Hypertrophic cardiomyopathy
Hypertensive heart disease
Hypertensive heart disease not caused by diastolic dysfunction
Volume overload state with the following causal or contributing factors:
Chronic renal dysfunction
Diabetes
Salt/Water handling abnormality
Anemia
Obesity
Ventricular vascular coupling abnormality
Excessive venoconstriction
Right heart failure
Primary (precapillary pulmonary hypertension)
Right ventricular infarct
Arrhythmogenic right ventricular dysplasia
Atrial septal defect
Pericardial disease
Cardiac tamponade
Constrictive pericarditis
Intracardiac mass
Atrial myxoma
Pulmonary vein stenosis
Valvular heart disease
Significant valvular stenosis
Significant valvular regurgitation

*Modified from *J Am Coll Cardiol* 2006;47:500-506.

heart as a hemodynamic pump.^{13,14} Our goal was to address the question of whether data derived from these measurements indicate if the underlying pathophysiology of HFNEF relates to abnormalities of systolic properties, diastolic properties, both, or neither. We show that data from patients with and animal models of HFNEF provide examples of each of these possibilities. This emphasizes the need to take a view of this syndrome, which extends beyond diastolic dysfunction, particularly when it comes to proposing and investigating therapeutic targets.

Pressure-Volume Relations

For decades, the PV paradigm has been used to characterize ventricular systolic and diastolic pump properties.¹⁵⁻¹⁹ A complete review of the PV paradigm is beyond the scope of this report but has been provided recently.^{20,21} The

essential elements are summarized Fig 1. In brief, in a given state, the ventricular PV loop is constrained within the boundaries provided by the end-systolic PV relation (ESPVR) and end-diastolic PV relation (EDPVR) (Fig 1A). The preload (eg, EDP) and afterload (eg, arterial impedance) determine the position and shape of the loop. The ESPVR reflects the stiffness of the chamber at the point of maximum myofilament activation. Changes in the ESPVR indicate changes in systolic pump performance (Fig 1B). For example, when positive inotropic agents are administered, the ESPVR shifts upward (greater end-systolic pressure at any given end-systolic volume), which can be manifest as an increase in the end-systolic elastance (E_{es} ; (slope of the ESPVR) and/or a reduction of V_0 (volume axis intercept of ESPVR). Conversely, pharmacologic agents that depress muscle strength create downward shifts of the ESPVR, with reduced E_{es} and/or increased V_0 . Because the ESPVR is sensitive to inotropy and relatively insensitive to loading conditions, it is considered to be an index of ventricular chamber contractility.

At the other extreme of the cardiac cycle, the EDPVR reflects the passive mechanical properties of the ventricle at the point of complete myofilament inactivation. Shifts in the EDPVR signify changes in ventricular capacitance (the volume that a ventricle holds at a given filling pressure) and compliance. Compliance is the slope of the EDPVR (ie, the change in filling pressure required to create a given change in filling volume); because the EDPVR is nonlinear, compliance varies with filling pressure. When the EDPVR shifts upward/leftward, passive diastolic dysfunction is said to be present because the heart has less capacitance and is less compliant. When the EDPVR shifts downward/rightward, the heart is said to have undergone ventricular remodeling, as what typically occurs in systolic heart failure. Although this terminology is imperfect, we retain it here for the sake of simplicity.

The parameters of diastolic properties obtained from the EDPVR (ie, compliance and capacitance) are to be distinguished from changes in the rates of filling during different phases of diastole that may be measured by Doppler echocardiography. In general, there is no close relationship between the EDPVR and parameters derived from Doppler echocardiog-

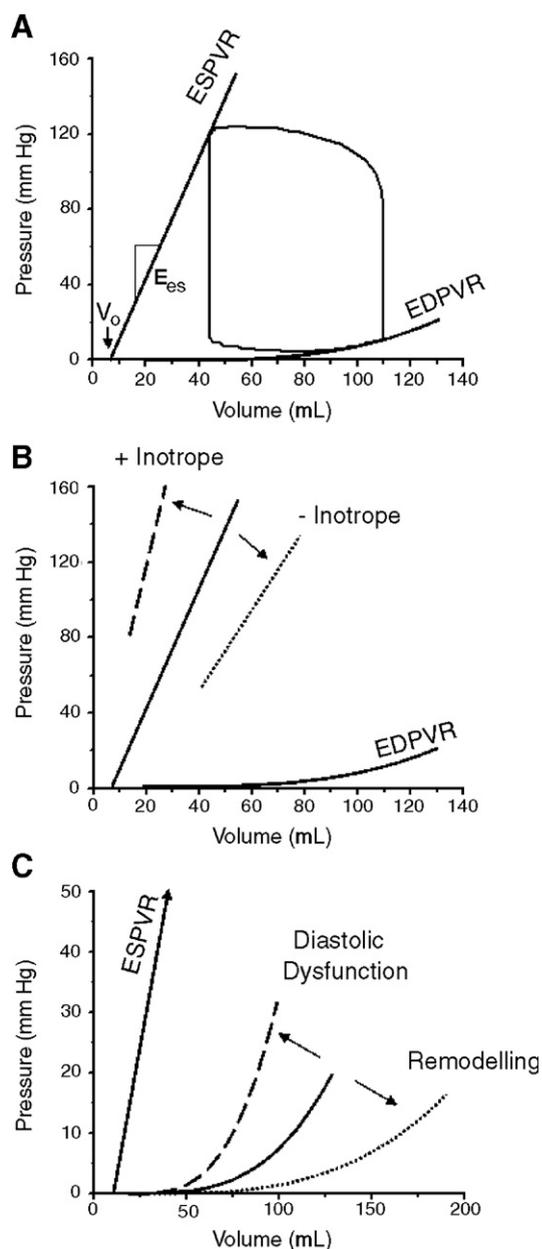


Fig 1. Pressure-volume analyses demonstrating the normal PV loop and the determinants of ventricular function, including the ESPVR (characterized by the slope [E_{es}] and the volume axis intercept [V_0]) and the EDPVR (Panel A). Shifts in the ESPVR are often equated with changes in inotropic state (Panel B), while shifts in the EDPVR toward smaller volumes or reduced capacitance (diastolic dysfunction) or toward larger volumes or increased capacitance (remodelling) shown in panel C.

raphy. Doppler echocardiography is considered by most clinicians to be the Rosetta Stone of LV diastolic function (and dysfunction).²² The Doppler echocardiography armamentarium used clinically includes transmitral and pulmonary venous flow velocity patterns measured by pulsed Doppler echocardiography, color flow propagation in the left ventricle, and tissue Doppler echocardiography patterns of mitral ring motion. These technologies are capable of demonstrating early diastolic relaxation abnormalities (which are extremely common and frequently asymptomatic) and measuring the early diastolic transmitral pressure gradient.

The combination of an elevated pressure gradient between early diastolic left atrial and LV pressures (high-velocity E wave) and abnormal early relaxation (best depicted by low-velocity tissue Doppler e' wave) usually indicates high LV diastolic filling pressure. An E/e' ratio of 15 or greater indicates elevated pulmonary capillary wedge pressure. Most clinicians use and report the combination of normal ejection fraction and abnormal Doppler echocardiography finding as evidence for diastolic dysfunction, regardless of LV volume or PV relationship.²³

The EDPVR and ESPVR reflect global LV chamber pump properties, which are determined only partly by intrinsic diastolic and systolic myocardial properties, respectively. Each relationship is also heavily influenced by factors such as muscle mass, chamber architecture (ie, the manner in which muscle fibers are assembled in the wall), chamber geometry, and, for the ESPVR, myocardial activation sequence. Thus, changes in the EDPVR or EDPVR can reflect intrinsic changes in myocardial properties or simple changes in ventricular structure with no change in intrinsic properties. Conversely, abnormal myocardial properties may be identified, yet chamber pump properties can still be normal if appropriately compensated by changes in ventricular structure. This is particularly important in discussions of HFNEF because most patients with HFNEF have significant hypertrophy. It is well known that hypertrophied cardiac muscle exhibits a host of abnormalities in systole and diastole. The fundamental question that must be addressed is whether those abnormalities are causative of the signs and symptoms of heart failure when they occur

in patients with normal ejection fraction or whether they are epiphenomena. We believe that, to date, this question has largely been addressed only by inference and not by objective experimental proof.

Beyond ESPVR and EDPVR: A Means of Assessing Integrated Pump Performance From PV Relations

Zile et al²⁴ noted limitations of using the ESPVR alone to quantify pump function in the presence of abnormalities of EDPVRs. This is particularly important in the interpretation of pump function in HFNEF. As will become clear, shifts of EDPVRs and ESPVRs that are present in different stages of LV hypertrophy make it difficult to

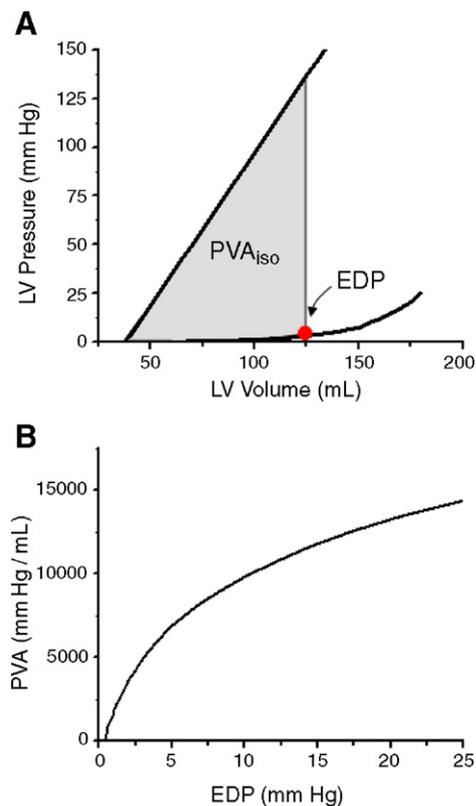


Fig 2. Demonstration of how PVA_{150} is calculated from the PV diagram. One value for PVA_{150} can be obtained for each end-diastolic PV point. The end-diastolic PV point for this example is shown by the solid red circle. The relationship between PVA_{150} and EDP is constructed from the EDPVRs and ESPVRs in panel A and is shown graphically in panel B.

understand the degree to which pump function is actually altered in various settings. It has been proposed that the area between the EDPVR and the ESPVR measured as a function of EDP be used to index overall pump function to overcome this limitation (Fig 2).²⁵ This specific area, called the isovolumic PV area (PVA_{iso}), is independent of afterload and can be calculated analytically as a function of LVEDP once curve fitting has been used to define the EDPVR and the ESPVR. For example, if the ESPVR is assumed to be linear and of the form $P_{es}=E_{es}(V-V_0)$ and if the EDPVR is assumed to be nonlinear and of the form $P_{ed}=\beta^*e^{\alpha V}$, then

$$\begin{aligned} PVA_{iso}(V) &= \int [P_{es}(V) - P_{ed}(V)] dV \\ &= 0.5E_{es}(V - V_0)^2 - (\beta/\alpha) e^{\alpha*V}. \end{aligned}$$

At increasing values of end-diastolic volume (EDV), EDP increases according to the EDPVR and PVA_{iso} increases according to the relative positions of the EDPVR and ESPVR. The PVA_{iso} is a measure of the total possible mechanical energy that the ventricle can generate at the specified preload pressure and thus provides an afterload-independent measure of the pumping capability of the heart. Specific examples of the use of the PVA_{iso} -EDP curve provided below will illustrate its utility.

Pressure-Volume Data in Animal Models of HFNEF

Significant insights into PV relations have been gleaned lately from animal models of HFNEF.²⁶⁻³³ The most commonly used animal model of HFNEF is the Dahl rat, which has dietary salt-dependent hypertension, salt and water retention, and renal dysfunction.²⁸⁻³⁴ However, it was only recently that a detailed characterization of how PV relations change over time in this model has been shown (Figs 3 and 4).²⁸ These rats develop severe hypertension quickly after the initiation of a high salt diet (HS) in comparison with Dahl rats maintained on a low salt diet (LS). The hypertension leads to development of hypertrophy and, eventually, signs of heart failure. Fig 3 shows representative steady-state PV loops at different time points after the initiation of HS as compared with continued LS; also shown in the insert of each

panel is the group-averaged EDP. At 8 weeks (panel A), volumes were similar in both groups and EDP was slightly elevated in HS-fed rats. However, end-systolic pressure was markedly elevated in HS-fed as compared with LS-fed rats, a reflection of hypertension. At 12 weeks, the marked hypertension persisted but the PV loop showed a marked reduction in LVEDV (Fig 3B), suggestive of the development of passive diastolic dysfunction. Despite this, however, there was no significant change in EDP as compared with that measured at week 8. At weeks 16 and 20, the PV loops of the HS groups shifted rightward such that EDVs again became similar to those of the LS group. It is at these time points that EDP exhibits significant increases.

Group-averaged results of the ESPVR and EDPVR analyses are summarized in Fig 4 (group-averaged values of EDP at each time point reported in Fig 3 are shown again in this figure). The slopes of the ESPVR did not vary significantly between groups or between time points. However, the curves in the HS group shifted significantly upward at weeks 8 and 12, indicative of increased systolic function. By week 20, the ESPVRs converged in both groups.

With regard to the EDPVRs, there was no detectable difference in the EDPVRs between the 2 groups at 8 weeks. At 12 weeks, however, the EDPVR of LS-fed rats shifted toward larger volumes (a consequence of normal growth) whereas that of the HS group shifted toward smaller volumes, indicative of passive diastolic dysfunction. Importantly, despite development of rather prominent diastolic dysfunction at this time point, there was no further rise in EDP beyond what was observed at 8 weeks. At 16 weeks, the EDPVR shifted toward larger volumes in both groups, with the HS group again becoming indistinguishable from the LS group. At 20 weeks, there was no further enlargement noted in the LS group whereas the HS group showed a trend toward additional enlargement.

Comparisons of integrated overall pump function indexed by the PVA_{iso} -EDP relationship between the HS and LS groups are summarized at each time point in the panels on the right side of Fig 4. At 8 weeks, the PVA_{iso} -EDP relationship was slightly increased in HS-fed rats, indicating superior overall pump function. At 12 weeks, the net impact of the leftward/upward shifts

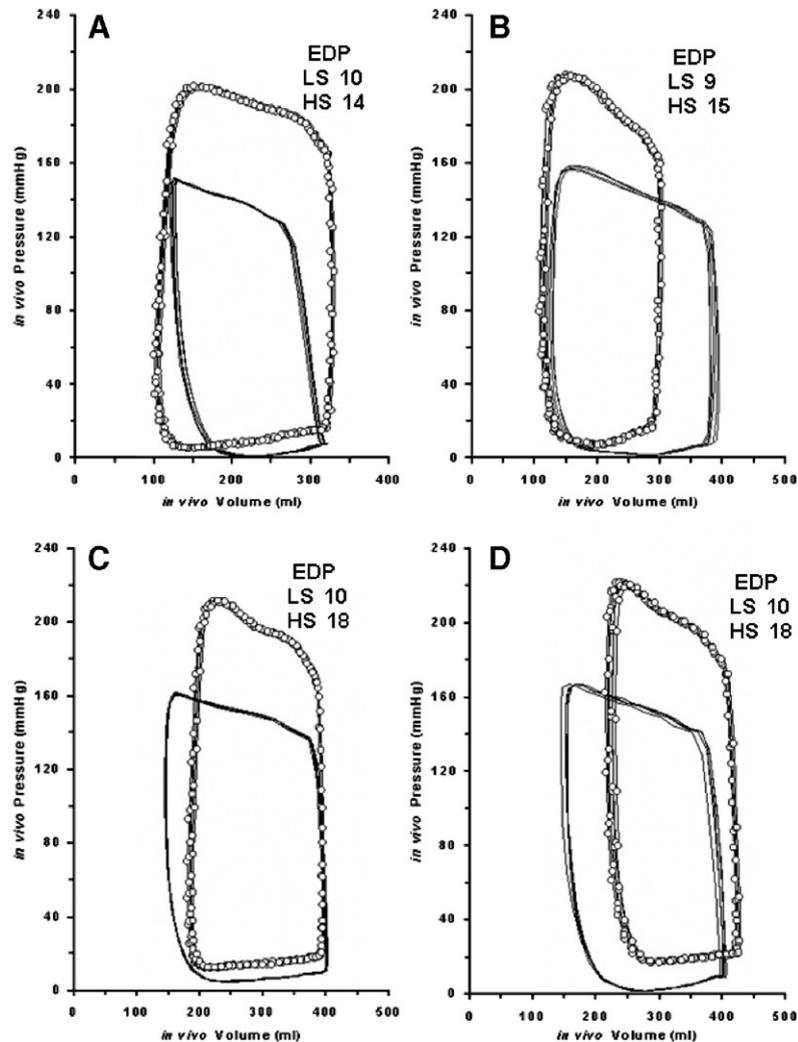


Fig 3. Representative PV loops from individual Dahl rats fed with HS and those fed with LS for 8 (A), 12 (B), 16 (C), and 20 (D) weeks. Group-averaged EDPs are shown in the inset of each panel. The shape of the PV loops in LS-fed rats showed no dramatic change over 20 weeks except for an age-dependent small shift to larger EDVs. In contrast, the loops from the HS-fed rats showed a shift toward smaller volumes at week 12. Subsequently, the loop shifted rightward and upward by week 20. Reprinted from *Hypertension* 2006;47(5):901-911 with permission from authors.

of EDPVR and ESPVR was a PVA_{iso} -EDP relationship shifted significantly upward, indicating enhanced overall pump function at that time point; specifically, this means that, at any given filling pressure, the heart is capable of generating more pressure and more work. At later times, as the EDPVRs and ESPVRs of the 2 groups converged, so too did the PVA_{iso} -EDP relationships. Importantly, the overall pump function curve and ESPVR of the HS group never fell below those of the LS group. Despite normal or enhanced overall pump function in

the HS group even at these later times, EDP (and wet lung weight) increased, indicative of development of heart failure. These observations suggest that a volume overload state plays an important pathophysiologic role in the development of the rise in EDP despite preserved overall ventricular pump function in this model of chronic hypertension. Indeed, data suggest the presence of renal dysfunction (indexed by increased serum creatinine) in HS-fed Dahl rats that appeared concomitantly with the development of the HFNEF phenotype.²⁸

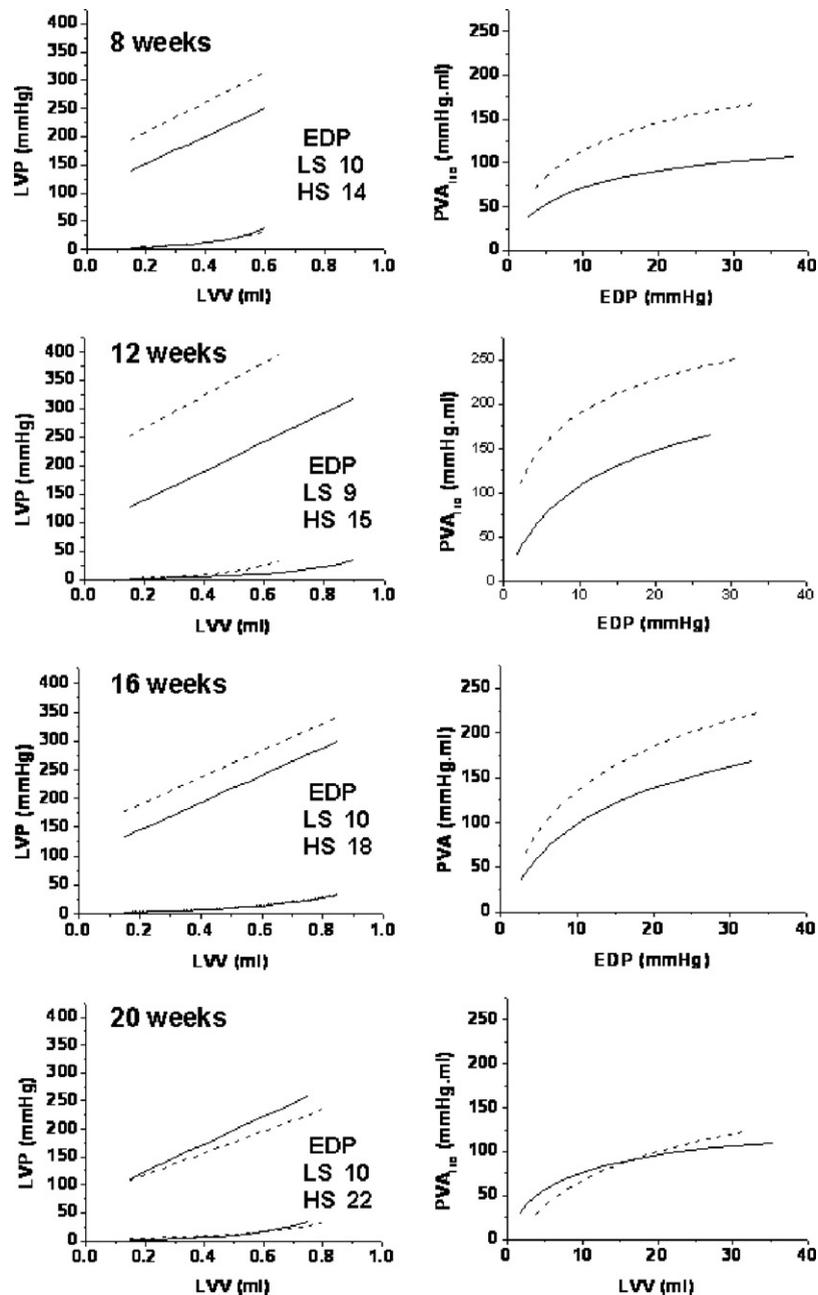


Fig 4. Group-averaged ESPVR and EDPVR (left) and resultant overall pump function curve indexed by the relationship between PVA_{10} and EDP are shown for each time point. Rats fed with LS are represented by the solid lines, and the corresponding data from rats fed with HS are represented by the dashed lines. Group-averaged EDPs are shown in the inset of each panel. Note that prominent leftward/upward shifted EDPVR is present in HS-fed rats at 12 weeks. The ESPVR is also shifted leftward/upward, even more so than the EDPVR. Consequently, the PVA_{10} -EDP relationship is also shifted upward, indicating enhanced overall pump function at that time point. Therefore, at this time point in particular, the upward shifted EDPVR by itself is not enough to conclude the presence of pump dysfunction. At later times, the EDPVRs and ESPVRs of the 2 groups converged, as did the PVA_{10} -EDP and PVA_{10} -EDV relationships; the overall pump function curve and ESPVR of the HS group never fell below those of the LS group. Abbreviations: LVP, LV pressure; LVV, LV volume. Reproduced from Hypertension 2006;47(5):901-911 with permission from authors.

Two canine models of HFNEF in which PV relations were measured have also been developed. The first model is based on a small amount of myocardial injury induced by daily coronary microembolizations (using plastic beads $\sim 100 \mu\text{m}$ in diameter). Whereas approximately half of the dogs undergoing this procedure developed heart failure and significant reductions in LV contractile performance, the other half developed overt signs and symptoms of heart failure within 16 ± 6 days (LVEDP, 12 ± 2 vs 21 ± 2 mm Hg; $P < .001$) with no significant change in indices of ventricular performance, including dP/dt_{max} (2999 ± 97 vs 2846 ± 189 mm Hg/s) and ejection fraction ($57\% \pm 5\%$ vs $53\% \pm 4\%$). Thus, these animals developed HFNEF. The PV relations (Fig 5) showed that whereas E_{es} did not change significantly (3.1 ± 0.9 vs 2.9 ± 0.8 mm Hg/mL), there was an approximately 10-mL increase in V_0 (14 ± 12 vs 25 ± 16 mL; $P < .01$) indicative of a relatively subtle degree of systolic dysfunction. The EDPVR and time constant of relaxation (τ , 25 ± 3 vs 28 ± 3 milliseconds) in these animals did not change significantly, demonstrating that HFNEF did not a priori equate with either passive or active diastolic dysfunction.

With regard to the mechanism of development of increased EDP in this model, it was hypothesized that the subtle reduction in systolic function invoked neurohormonal activation, which in turn resulted in salt and water retention. Indeed, these animals demonstrated neurohormonal activation (elevations of norepinephrine, angiotensin II, B-type natriuretic peptide) that was accompanied by intravascular volume expansion of approximately 16% ($P < .05$).

Evaluation of myocardial histology and passive myocardial material properties provided additional interesting insights. Histologic examination of the myocardium revealed replacement fibrosis that was expected to cause increased myocardial stiffness and contribute to diastolic dysfunction. However, there was no change in calculated myocardial stiffness and an increase in chamber stiffness that was present at approximately 2 weeks of embolization returned to normal levels at later time points. Most importantly, there was no significant relationship

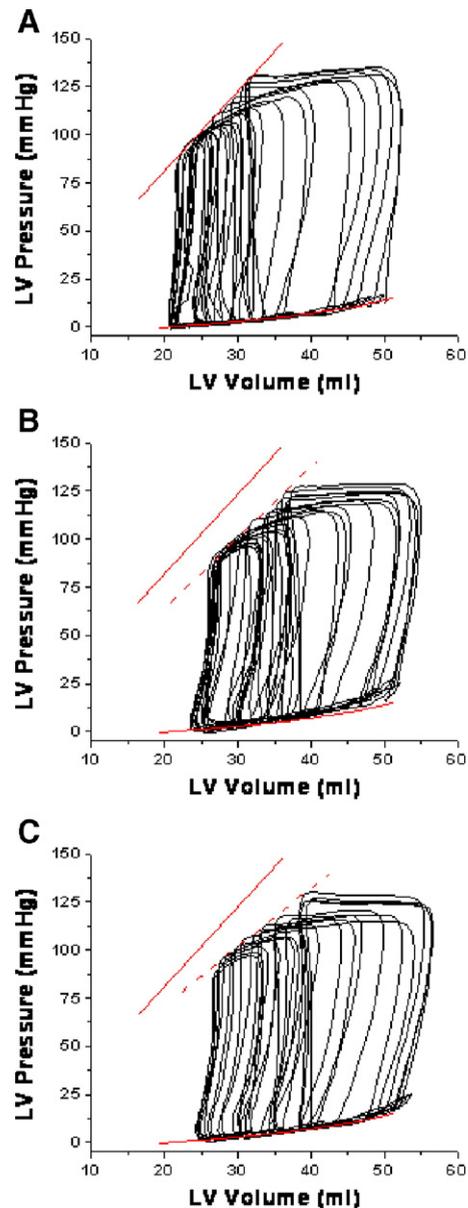


Fig 5. Pressure-volume relationships obtained at baseline (A), approximately 2 weeks after the establishment of heart failure state (B), and approximately 3 weeks after the establishment of heart failure state (C) in a representative animal with following repeated coronary microembolization. There is a small but significant rightward shift of the ESPVR after the establishment of heart failure that is sustained during the follow-up period (C). There is also a small upward shift of the EDPVR that is not sustained during the follow-up period. Reprinted from *Cardiovasc Res* 2004;64(1):72-83 with permission from authors.

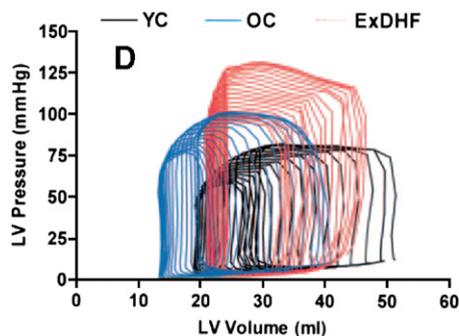


Fig 6. Representative ESPVRs in young control (black), old control (blue), and experimental dogs with HFNEF (red) induced by renal artery wrapping. Notice the absence of any significant shift in the diastolic PV relation in the animals with heart failure. Reprinted from *Circulation* 2005;111(9):1128-1135 with permission from authors.

between the value of chamber stiffness constant and EDP in this model.

A second large animal model of HFNEF, proposed by Munagala et al,²⁶ is based on renal artery banding in older dogs.^{26,35} In this model, hypertension develops and results in increases in LV mass and interstitial fibrosis without concomitant changes in circulating neurohormonal levels (plasma angiotensin II or endothelin 1 levels). It is not clear from the publication what criteria were used to prove that the animals were actually in heart failure. Nevertheless, overall chamber performances indexed by E_{es} , E_{es}/LV mass, and preload recruitable stroke work were all increased in dogs with heart failure. However, there was no information presented regarding V_0 . Representative PV loops from young control dogs, old control dogs, and old dogs in which hypertension had been induced are reproduced in Fig 6. In these examples, we can see that, in comparison with the old control dog, the PV loops of the old dog with renal banding are shifted to larger volumes and the EDPVR is essentially unchanged. This is similar to the findings noted in rats and microembolization animals. Also concordant with other animal^{27,28} and human⁶ data, the investigators did not find increases in the coefficient of passive LV diastolic stiffness (β) despite the presence of LV hypertrophy and fibrosis in this experimental model.

Pressure-Volume Data in Patients with HFNEF

Available data regarding invasively measured PV relations in human beings with HFNEF have been limited to small series of patients studied in specialized research centers.^{7,36} The initial series, which used the conductance catheter technique to measure the EDPVR from multiple beats, was published by Kawaguchi et al⁷ Data from their investigation⁷ and another small series³⁶ did not suggest that patients with HFNEF have a specific or characteristic abnormality of the EDPVR. Instead, data from these studies suggested that EDPVRs of patients with HFNEF may be shifted toward lower volumes as compared with control subjects, may be similar to those of control subjects, or may be shifted toward larger volumes (Fig 7). These findings led us to question whether diastolic dysfunction is the universal underlying mechanism of HFNEF.³⁷ The data collected seemed to undermine the premise that increased diastolic stiffness impairs the ability of the heart to increase preload volume during exercise. Indeed, the absence of a distinct and consistent abnormality in the EDPVR in patients with HFNEF, coupled with the finding using direct invasive measurements that during exercise patients with HFNEF were able to increase preload volume with very little if any effect on the EDPVR despite a

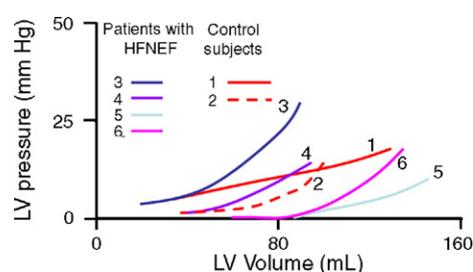


Fig 7. End-diastolic PV relations replotted from the work of Kawaguchi et al⁷ (curves 1 and 3 from Fig 1 as well as curves 4 and 5 from Fig 4) and from that of Liu et al³⁶ (curves 2 and 6 from Fig 3). End-diastolic PV relations of the patients with HFNEF may be shifted to the left (curve 3), shifted to the right (curves 5 and 6), or may not be significantly different (curve 4) from those of control subjects (curves 1 and 2). Knowledge of patient age, sex, and body size would enhance the ability to interpret the meaning of these differences. Reproduced from *Circulation* 2003;107(5):656-658 with permission from authors.

substantial prolongation of the time constant of relaxation,⁷ argued against the diastolic dysfunction paradigm.³⁷

Accordingly, in concert with the view that the complexity of heart failure and the potential for heterogeneity in this condition require a broader view of the pathophysiology,⁸ we hypothesized that HFNEF is not a consequence of a single underlying pathophysiologic mechanism. Using validated freehand 3-dimensional echocardiography³⁸⁻⁴⁰ to measure LV volumes and mass combined with noninvasive estimates of ventricular diastolic pressures and sphygmomanometric measurements of arterial pressure, we evaluated indices of ventricular properties typically derived from invasive PV analysis (Fig 8).⁴¹

From a physiologic perspective, we proposed that there were at least 3 possible combinations

of EDPVRs and ESPVRs possibly resulting in HFNEF that could potentially account for the varied findings in the literature: (1) the classic paradigm of diastolic heart failure (DHF) with normal ESPVR with upward shifted EDPVR (ie, decreased diastolic capacitance); (2) the case in which the ESPVR and the EDPVR are upward shifted (decreased diastolic capacitance along with enhanced systolic properties); and (3) the case in which the ESPVR is normal (or near normal) and the EDPVR is near normal or even shifted toward larger volumes. Importantly, one fundamental distinguishing feature between these combinations is that blood pressure is predicted to be elevated (as would typically be observed in patients with HFNEF having long-standing hypertension) in the latter 2 cases whereas it is reduced (as typically observed in

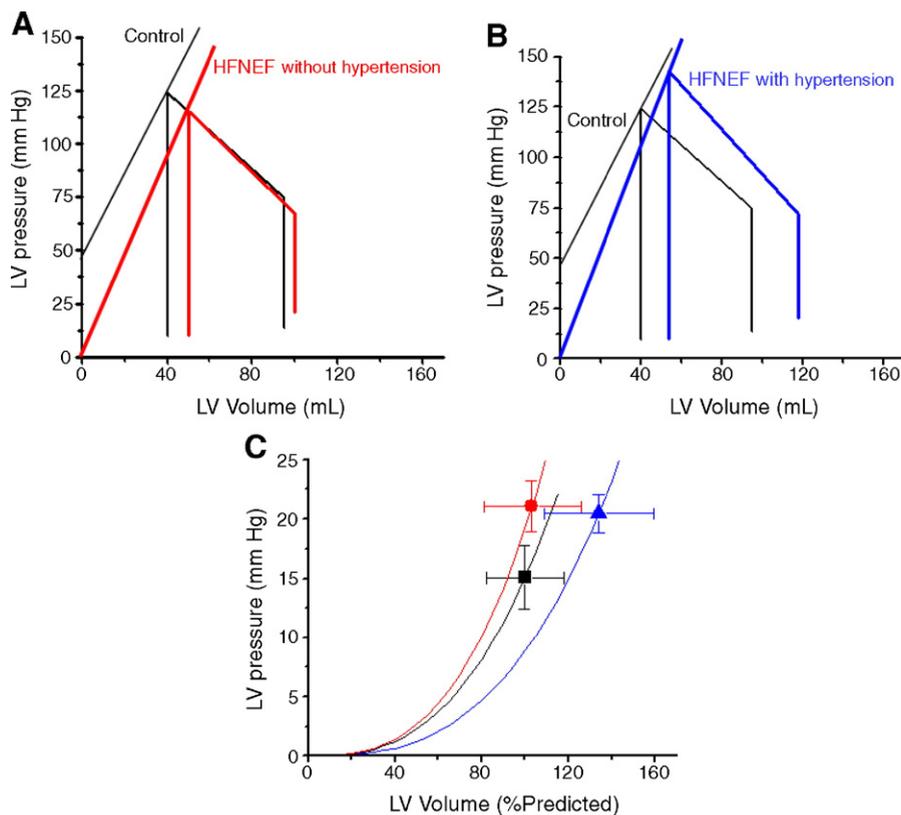


Fig 8. Group-averaged ESPVRs predicted from the methods of Chen et al⁴² for nonhypertensive HFNEF (A) and hypertensive HFNEF (B) in comparison with control (C). The group-averaged end-diastolic PV point as well as the mean and standard deviation for each group are shown along with the estimated EDPVR by the method of Klotz et al⁴³: control (black), hypertensive HFNEF (blue), and nonhypertensive HFNEF (red). Reproduced from *J. Cardiac Failure* 2005;11(3):177-187 with permission from authors.

cases of patients with hypertrophic cardiomyopathy, amyloid heart disease, and a restrictive cardiomyopathy) in the first case.

In this investigation,⁶ patients with HFNEF without a history of hypertension (Fig 8A) had ventricular volumes similar to those of control subjects; however, estimated end-systolic pressure was reduced whereas estimated EDP was increased, indicative of an upward shifted EDPVR as compared with control subjects (Fig 8C). The estimated PV relations of this patient group therefore exhibited a pattern that was compatible with the classic paradigm of DHF. In contrast, in HFNEF with a history of hypertension (Fig 8B), end-systolic volumes and EDVs were increased as compared with volumes of control subjects; as a result, the group-averaged PV loop was shifted toward volumes higher than those in control subjects. The estimated EDPVR for this group was shifted rightward toward slightly larger volumes. These characteristics were different from those seen with nonhypertensive HFNEF and were inconsistent with the DHF paradigm. In contrast, this behavior was more consistent with a mild volume overload state. Indeed, total plasma volume measures performed in a subset of these subjects demonstrated a $489\% \pm 593\%$ ($16\% \pm 19\%$) increase greater than that in control subjects despite the fact that these patients were taking daily diuretics with a mean furosemide dose of 95 ± 119 mg/d (median dose, 80 mg/d).

Because subjects with hypertensive HFNEF constitute a heterogeneous group with regard to comorbid conditions, age, sex, and body size, as well as potentially other important factors, we further evaluated the possibility that subgroups that have different underlying pathophysiologic mechanisms exist. In particular, because several investigators have focused on the role of large conduit arterial properties and increases in ventricular and vascular elastance in this group,^{7,44} we examined the distribution of LV function as indexed by E_{es} and the distribution of arterial elastance (E_a). Arterial elastance is a lumped index of vascular impedance that is mainly determined by total peripheral resistance and heart rate. Although there was considerable overlap in the distribution of these parameters between control subjects and hypertensive patients with HFNEF, the distributions of E_{es}

and E_a were shifted toward higher values. In particular, 17% of the hypertensive patients with HFNEF exhibited E_{es} values that were equal to or greater than the highest values encountered in the control group, and this subgroup was composed exclusively of smaller (decreased body height, weight, and body surface area) older women with higher systolic and mean arterial pressures. Other investigations have confirmed these findings of enhanced ventricular contractile performance in at least a subgroup of patients with HFNEF. These patients with HFNEF and increased arterial and ventricular elastances are typically characterized as being nonobese elderly women with a short stature and long-standing hypertension.^{6,45}

The ventricles of the subgroup with hypertensive HFNEF and combined ventricular and vascular stiffening (ie, increased E_a and E_{es}) were substantially smaller in all dimensions and volumes and were less hypertrophic with regard to posterior wall thickness and LV mass. On the surface, these characteristics appeared to be consistent with the DHF paradigm. However, although the absolute volumes of the hearts were substantially smaller in the high E_{es} group than in the control E_{es} group, the significant imbalance between groups in body size, age, and sex required that appropriately normalized values of these parameters be compared. Both subgroups of hypertensive patients with HFNEF, including those with low and high E_{es} values, had enlarged hearts when EDVs were indexed for age, sex, and body surface area. Thus, after accounting for differences in demographics and body morphometrics, comparison of normalized LV volumes led to the conclusion that, even in these patients, heart size is increased as compared with control subjects. This meant that the estimated EDPVR of this subgroup of hypertensive patients with HFNEF with seemingly small hearts was basically normal and not consistent with the DHF paradigm.

Other investigators have used combinations of invasively measured pressure and noninvasive determinations of volumes to characterize ventricular systolic and diastolic properties in patients with HFNEF.^{5,46} In contrast to the findings reviewed, the results of those studies demonstrated significant upward and leftward shifts of the EDPVRs along with increased values

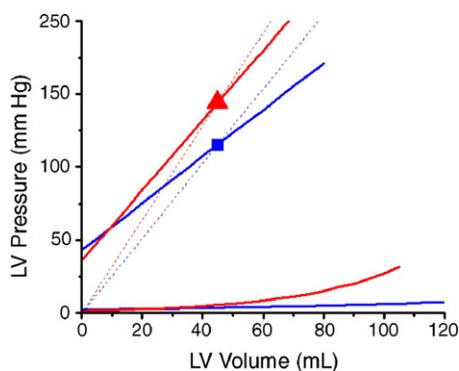


Fig 9. The EDPVR⁵ and ESPVR^{5,46} from the data by Zile et al.⁵ The ESPVRs (solid lines) were determined from reported values of E_{es} and specified group-averaged values of end-systolic pressures and volumes (solid figures) for control subjects (blue) and subjects with DHF (red). Dotted lines show the P_{es}/V_{es} ratio also reported in the original articles. Note that the upward and leftward shift of the EDPVR is accompanied by a similar shift in the ESPVR.

of τ (time constant of relaxation) that were interpreted as being causal agents of the heart failure state.⁵ When combined, data from these 2 reports provide estimates of group-averaged ESPVRs and EDPVRs (Fig 9). Several features of these data are noteworthy. First, data from subjects with hypertensive and those with non-hypertensive HFNEF were pooled in these analyses under the assumption that ventricular characteristics are the same in all patients with HFNEF. Second, ventricular volume was estimated by standard 2-dimensional echocardiography.^{47,48} This technique may underestimate volumes in hypertensive patients with HFNEF because the predominant increase in heart size is caused by an increase along the long axis, not the short axis.⁴⁹ Third (as shown in Fig 9), the parameters for the EDPVR of the control subjects yield a curve that is unusually flat, with an estimated EDV of more than 120 mL for a filling pressure of less than 10 mm Hg. Finally, the demographics of this patient population is quite different from that of patients studied in our prior study—namely, a younger and predominantly male population as compared with an older predominantly female population.

The implications surrounding the enhanced ventricular chamber contractility (high E_{es}) in subjects with HFNEF have been a subject of

debate. Some investigators have taken this to indicate that the increased large conduit arterial stiffness and the compensatory ventricular elastance play a predominant role in the syndrome of HFNEF^{7,26,45} and that therapies targeted at these abnormalities⁵⁰⁻⁵² may be useful. However, others submit that the enhanced chamber contractility is simply a reflection of a high myocardial mass, not of an enhanced myocardial contractility.²⁵

Comparisons of overall pump function curves (indexed by the PVA_{iso} -EDP relationships) between control and HFNEF groups that can be estimated from these various clinical reports are naturally as varied as the differences between EDPVRs and ESPVRs. For example, PVA_{iso} -EDP relations based on the average relations shown in Fig 8 (panel A) would show slightly reduced pump function in patients with HFNEF without a history of hypertension as compared with control subjects. However, the relations estimated from the patients with HFNEF with a history of hypertension (panel B) would be very similar to those from the control group. In contrast, the EDPVRs and ESPVRs shown in Fig 9 would result in a PVA_{iso} -EDP relationship that would be markedly depressed in the heart failure group as compared with the control group.

Summary and Conclusions

The syndrome of HFNEF is manifest in a clinically heterogeneous group of patients with multiple and varied comorbid conditions. Pressure-volume analysis of ventricular function is challenging in the clinical setting but provides unique insights into the systolic, diastolic, and overall pumping characteristics of the heart. Results of such analyses have thus far been limited to small cohorts of patients; hence, generalization of results to large patient cohorts should be made with caution. At the present time, we believe that it can safely be concluded that different cohorts of patients with HFNEF having PV relations that imply different pathophysiologic mechanisms exist. At one extreme are patients who have heart failure on the basis of diastolic dysfunction (eg, hypertrophic cardiomyopathy and amyloid); at another extreme are patients with a history of hypertension whose hearts appear to be very mildly dilated,

with little or no detectable abnormality of systolic or diastolic PV relations. In these patients, total body fluid overload may be contributory. These concepts are recapitulated in animal models of HFNEF. An additional concept, not yet correlated in a clinical setting, is that subtle systolic dysfunction (eg, in response to coronary artery disease with or without small infarcts) is not evident by measurement of ejection fraction but is sufficient to induce a neurohormonal response that can lead to salt and water retention. We therefore propose that progress can be made in advancing therapeutics for HFNEF if it is appreciated that different underlying pathophysiologic mechanisms may be important in different cohorts and if attention expands beyond diastolic dysfunction as the sole target. Success was made in advancing therapeutics for systolic heart failure when attention shifted away from the heart to the neurohormonal and renal axes. Our interpretation of data in human beings and in animal models suggests that addressing similar targets (perhaps not in exactly the same manner) may prove to be fruitful, at least for some patients with HFNEF as well.

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