Clinical Investigations

Left Heart Failure With a Normal Ejection Fraction: Identification of Different Pathophysiologic Mechanisms

MATHEW S. MAURER, MD, DONALD L. KING, MD, LYNA EL-KHOURY RUMBARGER, BS, RCDS, MILTON PACKER, MD, AND DANIEL BURKHOFF, MD, PhD

New York, New York

ABSTRACT

Background: Although heart failure with a normal ejection fraction (HFNEF) is a clinically heterogeneous syndrome, a single pathophysiologic mechanism, diastolic dysfunction, is often ascribed to explain this condition. In view of the clinical heterogeneity of these patients, we hypothesized that subgroups of HFNEF patients may have different underlying pathophysiologic mechanisms.

Methods and Results: Freehand 3-dimensional echocardiography was used to measure left ventricular end-systolic and end-diastolic volumes in 99 asymptomatic normal controls and 2 groups with chronic heart failure: 35 patients with normal ejection fraction with longstanding hypertension (hypertensive HFNEF) and 11 patients with hypertrophic cardiomyopathy without a history of hypertension (nonhypertensive HFNEF). These data, combined with cuff sphygmomanometry and Doppler estimates of LV end-diastolic pressure (EDP) yielded estimated pressure-volume loops and slope ($E_{es,sb}$) of the end-systolic pressure-volume relationship, a load independent index of chamber contractility. Nonhypertensive HFNEF patients required high EDPs (21 ± 2 versus 15 ± 3 mm Hg in normals, $P < .0001$) to achieve normal EDVs (98 ± 25 versus 95 ± 21 mL in normals, P = NS). Although systolic function ($E_{es,sb}$) did not differ from normal, systolic blood pressure was lower than normal in these patients (114 ± 10 versus 124 ± 14 mm Hg in normals, $P < .05$). Hypertensive HFNEF patients also had increased EDP (20 ± 2 mm Hg), but this was observed at *higher than normal* EDVs (118 ± 29 mL, $P < .05$). Among patients with hypertensive HFNEF, 2 subgroups emerged, 1 with a high $E_{es,sb}$ (4.23 ± 0.54 versus 2.1 ± 0.7 mm Hg/mL) and 1 with normal $E_{es,sb}$ (2.31 ± 0.51 mm Hg/mL). The former group was composed of elderly women with small body size (body surface area 1.7 ± 0.2 versus 1.9 ± 0.2 m^2, $P = .02$) who had concentrically remodeled ventricles and low stroke volumes. The latter group was more diverse in age, body size, and included patients of both genders with increases in ventricular volumes, stroke volume, and mass consistent with a volume overload state.

Conclusion: Although HFNEF is commonly thought of as being the result of a single hemodynamic mechanism, these data indicate that subgroups exist with distinctly different underlying pathophysiologies.

Key Words: Heart failure, diastole, hemodynamics, echocardiography.

Heart failure frequently occurs in patients with a normal ejection fraction (HFNEF).[1] Although some have argued that systolic function may be impaired despite the apparent preservation of ejection fraction,[2–4] the cause of heart failure in these patients has generally been attributed to an abnormality of diastolic function.[5] These patients typically have been given the diagnosis of "diastolic heart failure." Despite the diversity of underlying clinical pathologies and comorbid conditions present in these patients,[6] a common pathophysiologic explanation is generally applied to explain their clinical symptoms—concentric hypertrophy leading to a small chamber size with decreased diastolic capacitance (decreased volume at a specific filling pressure), which manifests as an upward/leftward shift of the end-diastolic pressure-volume relationship and impaired active relaxation.[7] It is postulated that a high resting left ventricular (LV) filling pressure is required for such hearts to maintain

From the Columbia University, College of Physicians & Surgeons, New York, New York.

Manuscript received June 9, 2004; revised manuscript received October 18, 2004; revised manuscript accepted October 18, 2004.

Reprint requests: Mathew Maurer, MD, Division of Circulatory Physiology, Columbia University, 177 Fort Washington Avenue, MHB 5-435, New York, NY 10032.

M.S.M. supported by a Career Development Award (K23) from the National Institute on Aging (AG-00966).

1071-9164/$ - see front matter

© *2005 Elsevier Inc. All rights reserved.*

doi:10.1016/j.cardfail.2004.10.006

normal cardiac output under such conditions. The high resting filling pressure contributes to dyspnea, effort intolerance, and, in extreme cases, pulmonary edema.[8,9]

Although this explanation is plausible, widely accepted,[8] and supporting data have recently been provided,[7] data available in the literature from other investigators[10,11] raise questions as to the general applicability of this paradigm to *all* patients presenting with HFNEF.[12] Specifically, in these studies the end-diastolic pressure-volume relationships measured from patients with the diagnosis of *diastolic heart failure* were not uniformly shifted toward lower volumes, but may be similar to normal or even may be shifted rightward toward larger volumes. There appears to be similar disparity within the literature regarding systolic contractile strength as measured by end-systolic pressure-volume relationships or other measures of contractility, with some indications of normal,[13] increased,[10] or decreased[2,14] contractile strength.

From a physiologic perspective, there are at least 3 possible combinations of end-systolic and end-diastolic pressure-volume relationships (ESPVR and EDPVR, respectively) that can result in heart failure (ie, increased end-diastolic pressure) with a normal ejection fraction and that could potentially account for the apparently varied findings in the literature (Fig. 1). First (Fig. 1A) is the classical paradigm of diastolic heart failure with normal ESPVR with upward shifted EDPVR (ie, decreased diastolic capacitance). With this scenario, systolic blood pressure is normal or reduced compared with normal. Second (Fig. 1B) is the case in which both the ESPVR and the EDPVR are upward shifted (decreased diastolic capacitance along with enhanced systolic properties). Finally (Fig. 1C), is the case in which the ESPVR is normal (or near normal) and the EDPVR is near normal or even shifted toward larger volumes. In the latter 2 cases, blood pressure is elevated, as is the case in patients with HFNEF who have longstanding hypertension.

In concert with the view that the complexity of heart failure and potential for heterogeneity in this condition requires a broader physiologic view,[15] the purpose of the present study was to characterize ventricular size and function and determine which of the mechanisms presented previously exists in HFNEF patients referred to our clinic. Previously validated freehand 3-dimensional (3D) echocardiography[16,17] was used to measure LV volumes and mass. When combined with noninvasive estimates of ventricular diastolic pressures and sphygmomanometric measurements of arterial pressure, this technique permits noninvasive estimation of indices of ventricular properties typically derived from invasive pressure-volume analysis.[18] We hypothesize that HFNEF is not the consequence of a single underlying pathophysiologic mechanism.

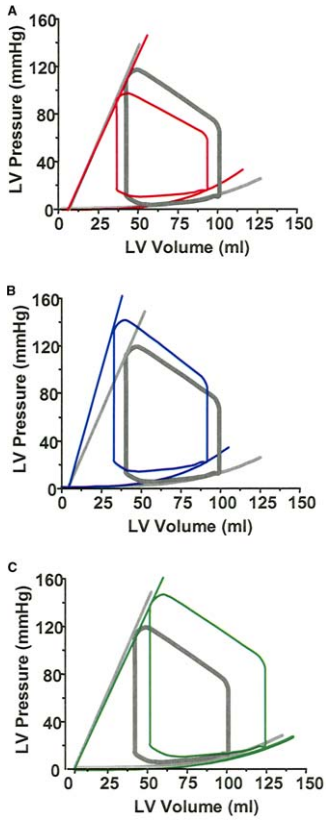

Fig. 1. Ventricular systolic and diastolic properties associated with heart failure (ie, increased end-diastolic pressure) with a normal ejection fraction (HFNEF). Normal conditions shown in black; various combinations of end-systolic pressure-volume relationship (ESPVR) and end-diastolic pressure-volume relationship (EDPVR) associated with heart failure shown in colors as detailed here. (A) Classic paradigm of diastolic heart failure with normal ESPVR and decreased diastolic capacitance (upward/leftward shifted EDPVR) accompanied by normal or low blood pressure (red). (B) Elevated ESPVR and upward/leftward shifted EDPVR (blue). (C) Normal (or near normal) ESPVR and normal or even rightward shifted EDPVR (green). In the latter 2 cases, note that blood pressure is elevated, as is the case in patients with heart failure with a normal ejection fraction (HFNEF) who have longstanding hypertension.

Methods

Study Patients

All patients provided informed consent forms and were evaluated as outpatients while medically stable and clinically euvolemic (no rales, lower extremity edema, or ascites), according to a protocol approved by the Institutional Review Board of Columbia University. The main group of patients (n = 56) comprised subjects with heart failure and a normal ejection fraction (by 2-dimensional [2D] echocardiography) referred by their primary cardiologists with a diagnosis of *diastolic heart failure*. For comparison, data from this group were contrasted to those obtained from normal controls (n = 99) who were recruited to derive normal values for the freehand 3D echocardiographic technique.

All normal control subjects were clinically healthy and ambulatory at the time of study. There was no history or evidence of cardiovascular disease on physical examination or on resting electrocardiogram and none of the patients were taking antihypertensive or other cardiac medications.

Subjects with heart failure and a normal ejection fraction fulfilled criteria for "diastolic heart failure" as defined by the European Society of Cardiology,[19] which requires (1) signs and symptoms

of heart failure, (2) a normal or at most mildly reduced LV ejection fraction, and (3) invasive or noninvasive evidence of abnormal diastolic function. All patients had heart failure based on the criteria developed by Rich et al,[20] which requires a history of acute pulmonary edema or the occurrence of ≥2 of the following that improves with diuretic therapy without another identifiable cause: dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, bilateral lower extremity edema, or exertional fatigue. Patients with valvular heart disease, chronic pulmonary disease, serum creatinine >2.0 mg/dl, significant anemia (hemoglobin <10 mg/dL) were excluded. All of these patients had a LV ejection fraction of ≥50% by visual assessment with 2D echocardiography and evidence of abnormal mitral filling patterns by Doppler flow echocardiography. The subjects with HFNEF were initially subdivided into those with longstanding hypertension (n = 45), defined by a blood pressure >140/90 mm Hg or the use of medications to treat hypertension, and those without any history of hypertension (n = 11) because, based on Fig. 1, the presence of hypertension may be a factor that distinguishes between different pathophysiologic states. These groups shall be designated hypertensive HFNEF and nonhypertensive HFNEF, respectively. Subjects falling into the latter category included patients with idiopathic hypertrophic cardiomyopathy (n = 6), cardiac amyloid (n = 2), and idiopathic restrictive cardiomyopathy (n = 3). For subjects with hypertensive HFNEF, the initial evaluation of the quantitative 3D echocardiogram revealed ejection fractions between 40% and 50% in 10 of the subjects; because these subjects do not clearly fall in either of the groups of major interest in the present study, they were excluded from further analysis.

2D and 3D Echocardiography

Standard 2D echocardiography was performed on each subject in accordance with recommendations of the American Society of Echocardiography.[21] The thickness of the posterior wall of the left ventricle and its internal dimensions were measured 1 cm below the mitral valve leaflet tips. Transmitral flow velocity was measured using pulse wave Doppler imaging with the sample volume positioned between the tips of the mitral valve leaflets during diastole or in the pulmonary vein. Standard indices of filling dynamics were derived from these recordings, and LV filling pressures were estimated by Doppler echocardiography using the difference between duration of blood flow during atrial contraction in the mitral and pulmonary venous Doppler profile (eg, delta duration) according to the formula LVEDP = 16.8 + 0.117*delta duration.[22–24]

Freehand 3D echocardiography was performed in each subject using equipment and methods that have been described previously.[17,25–28] A conventional real-time echocardiogram and a 3D acoustic spatial locater were interfaced with a personal computer having custom software to digitize and store eleven short axis images (approximately 1 cm apart, spanning from the inferior aortic valve surface to epicardial apex) along with the corresponding spatial coordinates of the probe. The endocardial and epicardial boundaries of end-diastolic and end-systolic images were traced for 3D reconstruction of endocardial and epicardial end-diastolic and end-systolic surfaces from which chamber and myocardial volumes were determined to yield end-diastolic and end-systolic volumes and ejection fraction. Myocardial volume was multiplied by myocardial density (1.05 g/mL) to obtain myocardial mass. The centerline length was calculated as the length of the line joining the centers of each of the eleven traced boundaries from base to apex. A sphericity index, defined as the ratio between ventricular centerline length and 2D width was also calculated. A single experienced cardiac sonographer (L.E.K.R.), who was blinded as to the factors being investigated in this study and to patient classification, performed every echocardiographic examination and analyzed each ventricular reconstruction.

Ventricular volume is known to vary with age, gender, and body size.[29] Therefore, volumes were compared between groups using absolute values and age, gender, and body size normalized volumes. This normalization was achieved by dividing measured end-diastolic and end-systolic volumes by volume predicted (EDV_p and ESV_p) for each individual and multiplying by 100. EDV_p and ESV_p were determined by the following equations:

$$EDV_p = 30.6 + 11.7\ \text{gender} + 38.2\ \text{BSA} - 0.24\ \text{age} \quad \text{(Eq. 1)}$$

$$ESV_p = 18 + 6.4\ \text{gender} + 12.8\ \text{BSA} - 0.09\ \text{age} \quad \text{(Eq. 2)}$$

where gender = 0 for females and 1 for males; BSA is body surface area (m^2); age is in years. These equations were determined by applying multiple linear regression analysis to our dataset of 99 normal subjects. These normalized volumes were expressed as percent of predicted values.

Echocardiographic Estimates of Ventricular Chamber Properties

The slope, end-systolic elastance (E_{es}), and a volume axis intercept (V_o) of the end-systolic pressure-volume relationship (ESPVR, examples shown in Fig. 1) were estimated noninvasively by the single-beat method ($E_{es(sb)}$) described by Chen et al.[30] This method relies on the measurement of stroke volume, noninvasive systolic and diastolic arterial blood pressures (SBP and DBP, respectively, measured just before the echocardiograms) and the durations of isovolumic contraction and ejection, each determined from synchronized echo-Doppler and echocardiogram recordings:

$$E_{es(sb)} = [DBP - E_{Nd(est)} \times SBP \times 0.9]/[SV \times E_{Nd(est)}] \quad \text{(Eq. 3)}$$

$$V_{o(sb)} = ESV - SBP \times 0.9/E_{es(sb)} \quad \text{(Eq. 4)}$$

where $E_{Nd(est)}$ is derived empirically from isovolumic contraction and ejection. After $E_{es(sb)}$ and $V_{o(sb)}$ are specified, the ESPVR can be drawn on the pressure-volume diagram in relationship to the pressure-volume loop. Because $E_{es(sb)}$ and $V_{o(sb)}$ are each dependent on ventricular size, both these values were also normalized to account for age, gender, and body size as described previously.

Effective arterial elastance (E_a), a lumped index of vascular hemodynamic load primarily related to total peripheral resistance and heart rate, was estimated by $E_a \approx SV/P_{es}$,[31] where P_{es} is the LV end-systolic pressure estimated by 0.9 × SBP.[32,33] This parameter, which has the same units as E_{es} (ie, mm Hg/mL) has been shown to be useful for estimating the degree of mismatching between ventricular and vascular properties in health and disease through the use of the ventricular-vascular coupling ratio: E_a/E_{es}.

Measurement of Plasma Volume

Plasma volume was measured by the following technique. A total of 25 μCi of I^{131} serum albumin (Megatope, Iso-Tex Diagnostics, Inc, Friendswood, Texas) were injected in a peripheral vein from a prefilled syringe. Twelve minutes after injection, 5 mL venous blood was collected at 6-minute intervals for 36 minutes. Plasma radioactivity was measured in an automated counter (BVA-100 Blood Volume Analyzer, Daxor Corp). Plasma volume was

determined as the volume of distribution of albumin and compared with normal values for sex, height, and weight.[34] Plasma volumes are expressed in absolute numbers and as percent deviation from predicted values.

Statistical Analysis

Summary data are expressed as mean ± SD. Clinical and demographic differences between the patients with heart failure and normal controls were compared. Dichotomous variables were compared by a chi-square analysis with Fisher's exact tests. Differences in continuous variables between the patients with heart failure and normal controls were compared using analysis of variance with a Bonferroni correction for multiple comparisons. Because LV chamber systolic function is described by both the slope, E_{es}, and V_o of the end-systolic pressure-volume relationship, we employed multiple repeated measures analysis of covariance (which simultaneously accounts for E_{es} and V_o) to compare estimated end-systolic pressure-volume relationships between groups. Similarly, to compare the end-diastolic pressure volume point among subgroups (normal controls versus hypertensive HFNEF versus nonhypertensive HFNEF and normal controls versus hypertensive HFNEF with high and normal elastance) and simultaneously control for the EDP and EDV, we used a multivariate analysis of variance (MANOVA). A P value $<.05$ was considered to be statistically significant. SAS (Windows 8.0, Cary, NC) was used for all analyses.

Results

Clinical Characteristics

Consistent with previous reports,[6,35,36] patients with hypertensive HFNEF were primarily elderly women, whereas patients with nonhypertensive HFNEF did not differ significantly from controls with regard to age or gender distribution (Table 1). All groups were reasonably similar with regard to body surface area. Diabetes mellitus was prevalent in all heart failure groups. Coronary artery disease defined by presence of electrocardiographic evidence of a prior myocardial infarction or documented by cardiac catheterization was present in a small minority of the hypertensive HFNEF group, but it was absent from the nonhypertensive HFNEF group. However, none of the subjects had evidence of active cardiac ischemia during the study.

Doppler assessments revealed abnormalities of diastolic mitral flow patterns in all hypertensive HFNEF and nonhypertensive HFNEF patients (Table 2). In the group with hypertensive HFNEF, 15 patients had impaired relaxation, 18 patients had a pseudonormal-filling pattern, and 2 patients had a restrictive pattern. In the nonhypertensive HFNEF group, 7 patients had a pseudonormal-filling pattern and 4 had a restrictive pattern. Based on these measurements, noninvasively estimated LV end-diastolic pressure was 15 ± 3 in normal controls, 20 ± 2 mm Hg in hypertensive HFNEF, and 21 ± 2 in nonhypertensive HFNEF.

Echocardiographic Measurements

When compared with normal subjects, the hearts of patients with nonhypertensive HFNEF had increased heart mass, but their volumes and dimensions were not enlarged (Table 3). Consequently, the hypertrophy seen in these patients was primarily related to an increase in wall thickness and myocardial volume rather than an increase in chamber size; therefore, volume-to-mass ratio was decreased (concentric hypertrophy). Fractional shortening and ejection fraction were preserved in this group.

The 2D echocardiographic dimensions and fractional shortening in the hypertensive HFNEF group were also similar to those of the control group, except for posterior wall thickness and relative wall thickness, which were indicative of hypertrophy. However, ventricular length was increased in this group compared with controls so that mean volumes (end-systolic and end-diastolic) were significantly larger than normal in addition to the marked increase in LV mass. The volume-to-mass ratio was lower than normal and the LV sphericity was statistically different from normal.

When volumes were normalized to account for the fact that hypertensive HFNEF patients were older with a greater proportion of females, the differences in end-diastolic and end-systolic volume from the normal controls were even more pronounced.

Pressure-Volume Analyses and Ventricular-Vascular Coupling

Idealized, group-averaged pressure-volume loops were constructed using the mean values for absolute end-systolic and end-diastolic volumes, estimated end-diastolic and end-systolic pressures, and $V_{o(sb)}$ determined for each group (Tables 3 and 4) as shown in Fig. 2. Patients with nonhypertensive HFNEF (Fig. 2A) had ventricular volumes similar to normal controls, but estimated end-systolic pressure was reduced, whereas estimated end-diastolic pressure was increased. These characteristics are consistent with the classic paradigm of *diastolic heart failure* summarized in Fig. 1A.

In hypertensive HFNEF (Fig. 2B), end-systolic and end-diastolic volumes were *increased* compared with normal volumes. Consequently, the group averaged pressure-volume loop was shifted toward higher volumes than normals. These characteristics were distinctly different from those seen with nonhypertensive HFNEF and were more consistent with the HFNEF paradigm outlined in Fig. 1C. The group-averaged, end-diastolic pressure-volume points are presented in Fig. 2C. These data emphasize that the end-diastolic pressure-volume point in nonhypertensive HFNEF is shifted upward compared with normal ($P < .001$ by MANOVA), whereas this point is shifted upward and rightward in hypertensive HFNEF ($P = .047$ by MANOVA for comparison of end-diastolic pressure-volume point between hypertensive and nonhypertensive HFNEF). These findings are further exaggerated when volume is normalized to account for age, gender, and body size (note in Table 3 that normalized EDV is more than 30% larger than normal).

The group averaged ESPVR predicted from the methods of Chen et al[30] are depicted by the colored lines in Figs. 2A, 2B, and 2C. In both nonhypertensive HFNEF and hypertensive HFNEF, the ESPVRs are shifted slightly rightward.

Table 1. Baseline Characteristics

Parameter	Normals	Non-hypertensive HFNEF	Hypertensive HFNEF
Number	99	11	35
Age (y)	46 ± 20	57 ± 20	72 ± 11*
Gender (M/F)	49/50	5/6	10/25*
Height (cm)	169 ± 10	169 ± 11	164 ± 12*
Weight (kg)	72 ± 15	86 ± 15*	81 ± 17*
BSA (m^2)	1.8 ± 0.2	2.0 ± 0.2	1.9 ± 0.2
Diabetes mellitus, %	0	18	43*
Coronary artery disease, %	0	0	17*
SBP (mm Hg)	124 ± 14	114 ± 10*	143 ± 19*†
DBP (mm Hg)	75 ± 9	67 ± 10	72 ± 11
MBP (mm Hg)	90 ± 16	83 ± 9*	96 ± 10†
HR (beats/min)	68 ± 11	69 ± 16	67 ± 10
Concomitant medications, %			
ACE/ARB	0	0	94*†
Ca channel blockers	0	36*	53*
β-blockers	0	73*	59*
Diuretics	0	100*	100*
Nitrates	0	0	9

HFNEF, heart failure with a normal ejection fraction; BSA, body surface area; SBP, systolic blood pressure; DBF, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
*$P < .05$ vs. control, †$P < .05$ versus nonhypertensive HFNEF.

In nonhypertensive HFNEF, this shift is also associated with a small decrease in $E_{es(sb)}$, whereas in hypertensive HFNEF there is a small increase in the $E_{es(sb)}$. A quantitative summary of the changes in $E_{es(sb)}$ and $V_{o(sb)}$, including absolute and normalized values, are presented in Table 4 with the results of statistical comparison between groups using repeated measures analysis of covariance, which simultaneously controls for differences in $E_{es(sb)}$ and $V_{o(sb)}$.

Subgroup Analysis of Hypertensive HFNEF

The analyses presented previously lumped all patients with hypertensive HFNEF into a single group. However, because this group is heterogeneous with regard to comorbid conditions, age, gender, and body size[6] and potentially other important factors not examined, it is possible that subgroups exist that have different underlying pathophysiologic mechanisms. In particular, recent literature has focused on the role of large conduit arterial properties and increases in ventricular and vascular elastance in this group.[10,37] Therefore, we examined the distribution of LV function as indexed by $E_{es(sb)}$ within the hypertensive HFNEF group compared with normal (Fig. 3A).

In the control subjects, there was a somewhat skewed distribution of $E_{es(sb)}$. Although there was considerable overlap in the distribution of this parameter between normals and hypertensive HFNEF, the distribution of the later was shifted toward higher values ($P = .0003$). In particular, 6 of the 35 hypertensive HFNEF patients (17%) exhibited $E_{es(sb)}$ values that were equal to or greater than the highest values encountered in the control group. To explore ventricular characteristics of these extreme cases, we compared data from these 6 patients with those of the rest of the hypertensive HFNEF group. When segregated in this manner, these 2 patient subgroups did not differ significantly with regard to the type or overall number of comorbid conditions or with regard to prescribed medications. Comparison of key clinical characteristics between high versus low $E_{es(sb)}$ groups (Table 5) did reveal, however, that the high $E_{es(sb)}$ group was composed exclusively of smaller (decreased body height, weight, and BSA), older women with higher systolic and mean arterial pressures. The ventricles were substantially smaller in all dimensions and volumes and were less hypertrophic with regard to both posterior wall thickness and LV mass. According to the selection criteria, $E_{es(sb)}$ values were higher, but this was also accompanied by increased $V_{o(sb)}$ values and E_a values with a lower $Ea/E_{es(sb)}$ ratio, indicating preserved ventricular-vascular coupling.

Although the absolute volumes of the hearts were substantially smaller in the high $E_{es(sb)}$ group than the normal $E_{es(sb)}$ group, the significant imbalance between groups in body size, age, and gender requires that normalized values also

Table 2. Doppler Echocardiographic Parameters

Parameter	Controls	Nonhypertensive HFNEF	Hypertensive HFNEF
Doppler mitral inflow			
Isovolumetric relaxation time (ms)	87 ± 10	92 ± 23	94 ± 17
E wave velocity (cm/s)	77 ± 21	80 ± 19	93 ± 23*
A wave velocity (cm/s)	73 ± 20	41 ± 28*	71 ± 33†
A wave duration (ms)	147 ± 19	132 ± 26	138 ± 29
E:A ratio	1.2 ± 0.5	2.6 ± 1.3*	1.9 ± 1.4
Doppler pulmonary veins			
Systolic flow velocity (cm/s)	62 ± 13	35 ± 14*	47 ± 17*
Diastolic flow velocity (cm/s)	60 ± 13	55 ± 16	58 ± 21
A wave velocity (cm/s)	28 ± 4	34 ± 9	36 ± 8*
A wave duration (ms)	128 ± 12	173 ± 43*	166 ± 23*
Systolic/diastolic flow ratio	1.1 ± 0.3	0.7 ± 0.2	0.9 ± 0.5
Estimated EDP (mm Hg)	15 ± 3	21 ± 2*	20 ± 2*

HFNEF, heart failure with a normal ejection fraction; EDP, end-diastolic pressure.
*$P < .05$ vs. controls.
†$P < .05$ vs. nonhypertensive HFNEF.

Table 3. Echocardiographic Parameters

Parameter	Controls	Nonhypertensive HFNEF	Hypertensive HFNEF
2D measures			
LVIDd (cm)	4.7 ± 0.5	4.0 ± 0.8*	4.6 ± 0.5†
LVIDs (cm)	3.1 ± 0.5	2.8 ± 0.8	3.1 ± 0.6
PWT (cm)	1.0 ± 0.1	1.7 ± 0.6*	1.3 ± 0.3*†
RWT (cm)	0.43 ± 0.07	0.93 ± 0.52*	0.58 ± 0.19*†
Fractional shortening (%)	34 ± 13	30 ± 9	32 ± 10
3D measures			
End-diastolic length (cm)	10.6 ± 1.1	11.2 ± 1.1	11.4 ± 1.2*
EDV (mL)	95 ± 21	98 ± 25	118 ± 29*†
Normalized EDV (%)	100 ± 18	100 ± 21	134 ± 25*†
ESV (mL)	40 ± 10	49 ± 14	54 ± 14*
Normalized ESV (%)	100 ± 22	118 ± 29	145 ± 31*†
Ejection fraction (%)	58 ± 4	50 ± 4*	54 ± 4*†
LV mass (g)	129 ± 28	202 ± 543*	174 ± 43*
EDV/LV mass (mL/g)	0.74 ± 0.10	0.52 ± 0.19*	0.69 ± 0.14†
Sphericity index	2.3 ± 0.3	2.9 ± 0.7*	2.5 ± 0.3*†

HFNEF, heart failure with a normal ejection fraction; 2D, 2-dimensional; LVIDd, left ventricular internal dimension in diastole; LVIDs, left ventricular internal dimension in systole; PWT, posterior wall thickness; RWT, relative wall thickness; 3D, 3-dimensional; EDV, end-diastolic volume; ESV, end-systolic volume; LV, left ventricular.

*$P < 0.05$ vs Controls, †$P < 0.05$ versus non-hypertensive HFNEF.

be compared. In the low and high $E_{es(sb)}$ subgroups, normalized end-diastolic volumes averaged 138 ± 26% and 115 ± 13% of predicted, respectively. Thus, although the high $E_{es(sb)}$ hearts where substantially smaller than the normal $E_{es(sb)}$ hearts, they were still larger than normal for their age, gender, and BSA. Comparison of the averaged estimated pressure-volume loops for these 2 groups (Fig. 3B) emphasizes the importance of normalizing volumes to come to the proper conclusion about the potential contribution of diastolic dysfunction to the heart failure state. Before normalization, the end-diastolic point of the loop for the high $E_{es(sb)}$ group is shifted upward/leftward (suggestive of diastolic dysfunction). After normalization, the end-diastolic pressure-volume point is shifted rightward compared to normal, suggesting that diastolic dysfunction is not a contributing factor.

Plasma Volume Measurements

To explore one possible mechanism by which ventricular volumes and end-diastolic pressures were increased in hypertensive HFNEF subjects, plasma volume measures were performed in a subset of these subjects (n = 18). Despite taking daily diuretics in a mean dose of furosemide of 95 ± 119 mg/day (median dose 80 mg/day), plasma volume was increased (3399 ± 865 mL) as compared with normal values (2910 ± 354 mL, $P < .01$). Thus average plasma volume was expanded by 489 ± 593 mL or 16 ± 19% greater than normal.

Table 4. Echocardiographically Determined Parameters of Ventricular Performance and Ventricular Vascular Coupling

Parameter	Controls	Nonhypertensive HFNEF	Hypertensive HFNEF
$E_{es(sb)}$ (mm Hg/mL)	2.1 ± 0.7	2.2 ± 0.7†	2.6 ± 0.9†
Normalized $E_{es(sb)}$ (mm Hg)	2.2 ± 0.8	2.1 ± 0.5	2.3 ± 0.7
$V_{o(sb)}$ (mL)	−19 ± 10	−2 ± 13†	1 ± 10†
E_a (mm Hg/mL)	2.2 ± 0.7	2.2 ± 0.7	2.1 ± 0.6
$E_a/E_{es(sb)}$	1.1 ± 0.1	1.0 ± 0.2	0.8 ± 0.1*‡

HFNEF, heart failure with a normal ejection fraction, $E_{es(sb)}$, end-systolic elastance measured by single-beat method; $V_{o(sb)}$, volume axis intercept measured by single-beat method; E_a, effective arterial elastance; MANOVA, multivariate analysis of variance; ANOVA, analysis of variance.

†$P < .05$ compared with normal by MANOVA.

*$P < .05$ compared with normal by ANOVA, ‡$P < .05$ compared with nonhypertensive HFNEF by ANOVA.

Discussion

Theory predicts (Fig. 1) and our measurements of ventricular size and function support (Fig. 2) the hypothesis that the mechanisms leading to heart failure in the setting of a normal ejection fraction differ among patient subgroups. Using a simple clinical variable, the presence or absence of elevated blood pressure or clinical history of hypertension, and echocardiographic measures of ventricular size and function, we identified 2 distinct subgroups of subjects with HFNEF: (1) nonhypertensive HFNEF and (2) hypertensive HFNEF. Within the second group, we also identified of relatively broad range of ventricular and vascular properties that further suggests that this may not be a pathophysiologically homogenous group of patients.

In patients with HFNEF in the absence of a history of hypertension, the LV chambers were normal or smaller than normal in volume and markedly hypertrophied. This group itself was clinically heterogeneous, including patients with idiopathic hypertrophic cardiomyopathy and infiltrative diseases. However, the pathophysiologic characteristics of all these patients were similar, justifying pooling of data. Indexes of systolic strength (including predicted end-systolic pressure-volume relations) were similar to normal controls. The abnormal position of the group-averaged end-diastolic pressure-volume point in these patients (ie, increased filling pressure at normal end-diastolic volume, Fig. 2C) is compatible with an upward/leftward shift of the end-diastolic

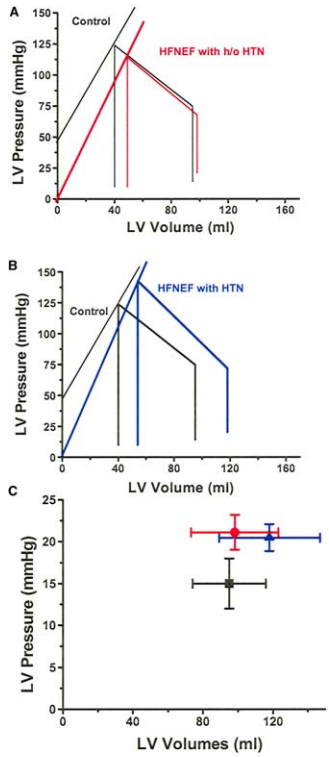

Fig. 2. Group averaged end-systolic pressure-volume relations (ESPVR) predicted from the methods of Chen et al[30] for nonhypertensive heart failure with a normal ejection fraction (HFNEF) (A) and hypertensive HFNEF (B) in comparison with normals. (C) The group-averaged, end-diastolic pressure-volume point with the mean and standard deviation for each group shown: controls (black), hypertensive HFNEF (blue), and nonhypertensive HFNEF (red). See text for details.

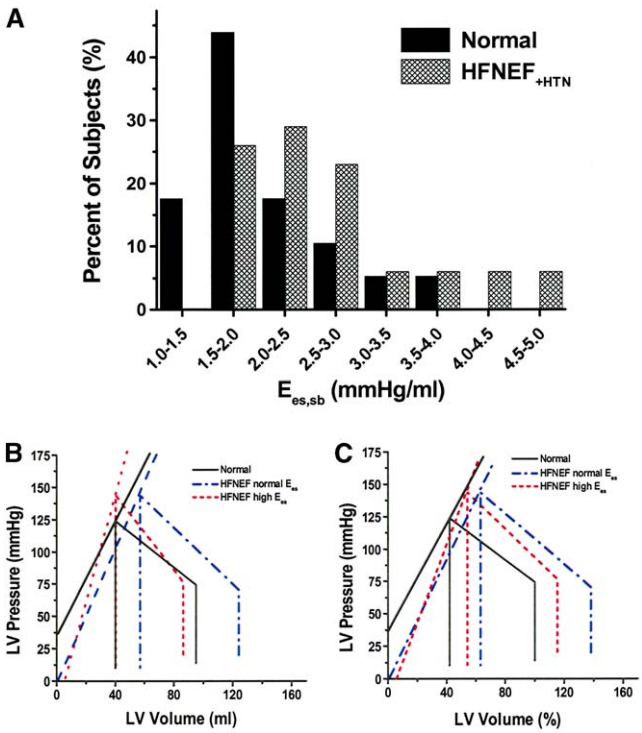

Fig. 3. Distribution of left ventricular function as indexed by $E_{es(sb)}$ within the hypertensive heart failure with a normal ejection fraction (HFNEF) compared with distribution of $E_{es(sb)}$ among normals (A) and group-averaged pressure-volume relations in the hypertensive HFNEF with high and low elastance (B) with absolute and normalized volumes. The end-diastolic pressure volume point was significantly different among normal controls and hypertensive HFNEF with high elastance ($P = .0033$) and normal controls and hypertensive HFNEF with normal elastance ($P < .0001$).

pressure-volume curve, indicative of passive diastolic dysfunction and the classic paradigm of diastolic heart failure depicted in Fig. 1A. This abnormality in diastolic properties limits ventricular systolic pressure and stroke volume generation and explains our observation (also reported in earlier studies[38]) that patients with nonhypertensive HFNEF generally have lower than normal blood pressures and reduced cardiac output.[9]

In patients with HFNEF having a history of hypertension, indexes of systolic function were also similar to normal controls. However, we observed that accompanying the marked increase in LV mass in these patients was an *increase* in end-diastolic volume. This conforms to the pattern depicted in Fig. 1C and explains the coexistence of elevated filling pressure, normal ejection fraction, *and* hypertension. Although LV end-diastolic volume was, on average, increased in patients with hypertensive HFNEF, the wide range of end-diastolic volumes suggests that a spectrum of abnormalities in the position of the EDPVR can occur in subjects with hypertensive HFNEF. As we have noted previously,[12] studies in which pressure-volume relations have been measured invasively over a range of loading conditions to delineate the end-diastolic pressure-volume relationships in HFNEF patients[10,11,38] have revealed EDPVRs of patients with HFNEF that were similar to normal, rightward shifted, or leftward shifted; implying that a consistent abnormality is not present in all patients with hypertensive HFNEF.

All patients with HFNEF had abnormal filling patterns as assessed by Doppler echocardiography of the mitral inflow velocities. Such changes are also seen in patients with dilated cardiomyopathies[39] and thus do not provide any insights into the relative position of EDPVR. Rather they are primarily indicative of elevated filling pressures and do not, a priori, equate with any intrinsic myocardial or ventricular abnormality that causes filling pressures to become elevated. Mild (Grade 1) changes are typically linked with prolonged time constant of relaxation (τ).[40] More significant changes (Grade 2 and 3) as observed in the present study are the consequence of elevated filling pressures from any cause.[41] Therefore, the presence of such abnormal filling patterns cannot differentiate elevated filling pressure associated with a leftward shift of the EDPVR from an elevated filling pressure caused by a fluid overload state.

Although the classic paradigm of diastolic heart failure is advocated by some investigators to apply to all patients

Table 5. Comparison of Characteristics of Hypertensive HFNEF Patients with High or Low $E_{es,sb}$

Parameter	Low $E_{es(sb)}$ (n = 29)	High $E_{es(sb)}$ (n = 6)	*P*
Demographics			
Gender (% female)	66%	100%	
Age (y)	70.46 ± 10.61	78.14 ± 10.08	.134
Height (meters)	1.66 ± 0.11	1.54 ± 0.07	.010
Weight (kg)	83.10 ± 16.70	68.30 ± 12.80	.038
BSA (m^2)	1.90 ± 0.23	1.66 ± 0.17	.016
SBP (mm Hg)	139.83 ± 17.99	159.50 ± 13.59	.014
DBP (mm Hg)	71.14 ± 11.47	76.67 ± 7.89	.183
MAP (mm Hg)	93.81 ± 9.95	104.00 ± 6.09	.007
Echocardiographic parameters			
LV EDD (cm)	4.7 ± 0.5	4.3 ± 0.3	.018
LV length (cm)	11.6 ± 1.2	10.3 ± 0.7	.004
PWT (cm)	1.3 ± 0.3	1.1 ± 0.1	.010
RWT	0.6 ± 0.2	0.5 ± 0.1	.278
EDV (mL)	124 ± 27	86 ± 4	<.001
Normalized EDV (%)	138 ± 26	115 ± 13	.007
ESV (mL)	57 ± 14	40 ± 3	<.001
Normalized ESV (%)	149 ± 32	125 ± 16	.04
SV (mL)	68 ± 15	46 ± 3	<.001
EF (%)	55 ± 4	54 ± 2	.504
LV mass (g)	180 ± 44	145 ± 11	.001
EDV/LV mass (mL/g)	0.71 ± 0.15	0.60 ± 0.05	.004
Pressure-volume analysis			
$E_{es(sb)}$ (mm Hg/mL)	2.31 ± 0.51	4.23 ± 0.54	<.001
Normalized $E_{es(sb)}$ (mm Hg)	2.1 ± 0.5	3.2 ± 0.6	.006
$V_{o(sb)}$ (mL)	−0.12 ± 10.67	5.67 ± 1.83	.010
Ea (mm Hg/mL)	1.93 ± 0.40	3.11 ± 0.41	.000
$Ea/E_{es(sb)}$	0.85 ± 0.15	0.74 ± 0.08	.025
EDP (mm Hg)	20.43 ± 1.33	20.71 ± 2.85	.821

MAP, mean arterial pressure; EDD, end diastolic dimension; SV, stroke volume.

All other abbreviations, see previous tables.

with HFNEF,[5,8,9,42] several studies have sought alternate explanations for why heart failure exists in these patients. Several groups have focused on abnormalities in afterload and ventricular-vascular mismatching.[10,37,43,44] For example, in a series of papers from Kass and colleagues,[10,11,38,45] HFNEF was observed to be associated with increased values of E_a and concomitant increases in E_{es}. Although these studies examine a relatively small number of patients, they are significant in that they are the only studies in which pressure-volume relations have been measured invasively over a range of loading conditions to delineate the end-systolic and end-diastolic pressure-volume relationships in HFNEF patients.[10,11,38] There are several similarities in findings of the present study to those reported in these prior studies. First, data presented in the figures of these articles[12] did not reveal a leftward and upward shift in the EDPVR compared with normal in all subjects. Second, as corollary, end-diastolic volumes in several of the examples shown in these articles are large (eg, 120 mL to 140 mL), which is consistent with our measurements. Finally, as discussed previously, we identified a subgroup of patients with hypertensive HFNEF having significantly higher than normal values of E_{es} and E_a.

Two important, distinguishing features of the present study are the use of a validated tomographic method of measuring LV volume and mass and inclusion of an analysis to account for age, gender, and body size in the evaluation of heart size and function. The 3D echocardiographic technique employed is comparable to cardiac magnetic resonance imaging for evaluation of LV volume, mass and function, and uses a similar reconstruction methodology.[25,26] Indeed, EDVs predicted using the regression equation derived from our normal population (Eq. 1) and reported values for mean age and body size measured in the Framingham heart study[29] compare favorably with those measured using cardiac magnetic resonance imaging in both males (105 mL versus 115 mL) and females (80 mL versus 85 mL).

These factors proved particularly important when we performed a subgroup analysis on the hypertensive HFNEF group. As noted, investigators recently identified a group of patients that had very high values of end-systolic elastance indicating the existence a group of patients that conforms to the paradigm depicted in Fig. 1B.[10] From among our cohort, the patients exhibiting this pattern were nearly a decade older, were all female, and were almost 15% smaller (in terms of BSA) than the other hypertensive HFNEF patients. Deviations of the values of each of these demographic characteristics from the mean values of the normal cohort were even more pronounced (compare Tables 1 and 4). Accordingly, the pathophysiologic mechanisms suggested by pressure-volume analysis were significantly different if nonnormalized or normalized data were employed (Fig. 3B); we believe it is more appropriate to derive conclusions from the normalized data.

As noted, earlier studies of HFNEF have relied on short axis[35,46] 2D echocardiographic measures[36] and nonoptimally matched control groups.[46] Yet, the available data are not dissimilar to the corresponding data in our study. For example, in a recent report of more than 600 patients hospitalized with heart failure and a normal ejection fraction,[6] the mean LV end-diastolic dimension was 4.7 ± 0.8 cm, which was even larger than the dimension reported in our study (Table 2). Similar values for end-diastolic dimension in HFNEF have been reported in other large studies.[35,46] Data from the Cardiovascular Health Study provide further supporting evidence for our findings. End-diastolic LV dimension measured in that study of 170 patients with HFNEF (a majority with hypertension) was 4.93 ± 0.1 cm (mean ± SEE), which compared with 4.65 ± 0.1 cm in a group of gender matched controls ($P < .001$).[47] This approximate 3 mm increase in chamber dimension indicates that heart size is larger than normals. The similarity of our data to those reported in these prior studies[35,46] further serve to assure that our patients are representative of the general HFNEF population and are not a special, possibly rare subset.

Taken together with these data in the literature, our findings suggest that a leftward shift in the EDPVR may not be a predominant factor contributing to heart failure in *all* patients with hypertensive HFNEF. Why, then, is LV end-diastolic pressure increased in these patients? We speculate that the

extracardiac factors, which could contribute to or cause a volume overload state including renal dysfunction, obesity, and anemia among others, may play important roles. The hemodynamic profile we identified in these patients (compatible with Fig. 1C) resembles that reported for volume overload states[48,49] and we suggest that our plasma volume data support the notion that a volume overload state may be an important factor to consider, but the present study has not identified the explanation.

Limitations

The findings of the current study rely on noninvasive methods to quantify volumes, estimate pressures, and predict end-systolic pressure-volume relationships, which have traditionally been evaluated using invasive techniques. We recognize that invasive measurements of ventricular pressure-volume loops over a range of volumes to delineate the entire EDVPR are still the most accurate means of quantifying both systolic and diastolic ventricular properties, and without such measures the exact nature of the shift in the EDPVR in patients with HFNEF cannot be determined definitely. However, invasive techniques can only be applied to very small number of patients and may not be either appropriate or possible in normal control subjects. As a result, accurate noninvasive methods remain the primary approach to performing the measurements and defining the issues addressed in this report in a meaningful number of patients. The noninvasive approaches that we used have been shown to correlate well with similar measurements performed invasively or using other accurate methods as detailed above. However, a number of assumptions employed in our noninvasive estimates of LV end-systolic and end-diastolic pressures, which rely on cuff sphygmomanometry and Doppler echocardiography, respectively, could be sources of error. In addition, blood pressure in elderly individuals with isolated systolic hypertension may be dynamic, varying significantly from one reading to the next. Vascular stiffening often encountered in these patients may alter the normal relation between brachial systolic pressure and LV end-systolic pressure because of concomitant wave reflection,[50] thus potentially influencing the accuracy of noninvasive end-systolic pressures estimation. Additionally, although multiple Doppler techniques have been employed to estimate LV end-diastolic pressure,[23,51,52] there is potential for error in the estimates of pressure using these methods. Nevertheless, our main conclusions are primarily based on measurements of ventricular volumes and would not be materially altered even if our estimates of pressure had a meaningful error. Importantly, the approach we used was sufficiently sensitive to identify the presence of passive *diastolic dysfunction* indexed by an elevated filling pressure at normal volume (Fig. 2A) in the group of patients with nonhypertensive HFNEF. Although the proportion of patients from within our cohort conforming to the paradigm of Fig. 1B was relatively small, no conclusion about the prevalence of this or any of the profiles in Fig. 1 should be made. Our cohort is composed of patients referred for care of HFNEF to a tertiary referral center and may not reflect prevalence in the general population. Finally, all measurements were made with patients at rest. HFNEF patients can frequently be minimally symptomatic at rest and it is only in the presence of a stressor (eg, increased heart rate, hypertension) in which symptoms are overt. It is possible therefore that characterization of ventricular properties identified in the present study may not apply to conditions when stress is present. One prior study has demonstrated, however, with regard to ventricular size and function no difference in these patients between times when they are in pulmonary edema and after appropriate treatment.[43]

In conclusion, our data show that on average, ventricular properties are different in HFNEF patients with a history of hypertension compared to those without a history of hypertension. Systolic contractile properties were well preserved (as indexed by the ESPVR) and end-diastolic pressures were elevated in both conditions. Nonhypertensive HFNEF was associated with marked concentric hypertrophy, low systolic pressures, and normal sized chamber. Conversely, hypertensive HFNEF was associated with increased ventricular mass and increased end-diastolic volume. The differences in chamber structure and function in these 2 groups leads to the hypothesis that, in general, HFNEF should not be considered a single disease entity, but more likely is a consequence of different pathophysiologic mechanisms and different ventricular systolic and diastolic properties (Fig. 1). Even within the hypertensive HFNEF group, a wide range of end-diastolic volumes and $E_{es(sb)}$ values were encountered, suggesting that even this designation may not identify a pathophysiologically homogeneous group of patients. Future research focused on definitive characterization of cardiac and noncardiac factors that lead to heart failure symptoms in these patients could therefore prove useful in clarifying different mechanisms by which heart failure develops, thus leading to development of more effective treatments.

References

1. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA 1996;275: 1557–62.
2. Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction. Circulation 2002;105:1195–201.
3. Petrie MC, Caruana L, Berry C, McMurray JJ. "Diastolic heart failure" or heart failure caused by subtle left ventricular systolic dysfunction? Heart 2002;87:29–31.
4. Yip G, Wang M, Zhang Y, Fung JW, Ho PY, Sanderson JE. Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition? Heart 2002;87:121–5.
5. Angeja BG, Grossman W. Evaluation and management of diastolic heart failure. Circulation 2003;107:659–63.
6. Klapholz M, Maurer M, Lowe AM, Messineo F, Meisner JS, Mitchell J, et al. New York Heart Failure Consortium. Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction:

results of the New York Heart Failure Registry. J Am Coll Cardiol 2004;43:1432–8.
7. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004;350:1953–9.
8. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: part II: causal mechanisms and treatment. Circulation 2002;105:1503–8.
9. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: part I: diagnosis, prognosis, and measurements of diastolic function. Circulation 2002;105:1387–93.
10. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation 2003;107:714–20.
11. Liu CP, Ting CT, Lawrence W, Maughan WL, Chang MS, Kass DA. Diminished contractile response to increased heart rate in intact human left ventricular hypertrophy. Systolic versus diastolic determinants. Circulation 1993;88:1893–906.
12. Burkhoff D, Maurer MS, Packer M. Heart failure with a normal ejection fraction: is it really a disorder of diastolic function? Circulation 2003; 107:656–8.
13. Ruzumna P, Gheorghiade M, Bonow RO. Mechanisms and management of heart failure due to diastolic dysfunction. Curr Opin Cardiol 1996; 11:269–75.
14. Aurigemma GP, Silver KH, Priest MA, Gaasch WH. Geometric changes allow normal ejection fraction despite depressed myocardial shortening in hypertensive left ventricular hypertrophy. J Am Coll Cardiol 1995; 26:195–202.
15. Redfield MM. Understanding "diastolic" heart failure. N Engl J Med 2004;350:1930–1.
16. Gopal AS, Schnellbaecher MJ, Shen Z, Akinboboye OO, Sapin PM, King DL. Freehand three-dimensional echocardiography for measurement of left ventricular mass: in vivo anatomic validation using explanted human hearts. J Am Coll Cardiol 1997;30:802–10.
17. Gopal AS, Shen Z, Sapin PM, Akinboboye OO, Sapin PM, King DL. Assessment of cardiac function by three-dimensional echocardiography compared with conventional noninvasive methods. Circulation 1995; 92:842–53.
18. Kass DA, Maughan WL. From "Emax" to pressure-volume relations: a broader view. Circulation 1988;77:1203–12.
19. How to diagnose diastolic heart failure. European Study Group on Diastolic Heart Failure. Eur Heart J 1998;19:990–1003.
20. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. N Engl J Med 1995;333:1190–5.
21. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2: 358–67.
22. Poelzl G, Gattermeier M, Kratzer H, Zeindlhofer E, Kuehn P. Feasibility and accuracy of transthoracic Doppler echocardiographic estimation of pulmonary capillary wedge pressure applying different methods. Eur J Heart Fail 2001;3:553–60.
23. Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. J Am Coll Cardiol 1993;22:1972–82.
24. Rossvoll O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. J Am Coll Cardiol 1993;21:1687–96.
25. Gopal AS, Schnellbaecher MJ, Shen Z, Boxt LM, Katz J, King DL. Freehand three-dimensional echocardiography for determination of left ventricular volume and mass in patients with abnormal ventricles: comparison with magnetic resonance imaging. J Am Soc Echocardiogr 1997;10:853–61.
26. Gopal AS, Keller AM, Rigling R, King DL Jr, King DL. Left ventricular volume and endocardial surface area by three- dimensional echocardiography: comparison with two-dimensional echocardiography and nuclear magnetic resonance imaging in normal subjects. J Am Coll Cardiol 1993;22:258–70.
27. Gopal AS, King DL, Katz J, Boxt LM, King DL Jr, Shao MY. Three-dimensional echocardiographic volume computation by polyhedral surface reconstruction: in vitro validation and comparison to magnetic resonance imaging. J Am Soc Echocardiogr 1992;5:115–24.
28. Sapin PM, Schroder KM, Gopal AS, Smith MD, DeMaria AN, King DL. Comparison of two- and three-dimensional echocardiography with cineventriculography for measurement of left ventricular volume in patients. J Am Coll Cardiol 1994;24:1054–63.
29. Salton CJ, Chuang ML, O'Donnell CJ, Kupka MJ, Larson MG, Kissinger KV, et al. Gender differences and normal left ventricular anatomy in an adult population free of hypertension. A cardiovascular magnetic resonance study of the Framingham Heart Study Offspring cohort. J Am Coll Cardiol 2002;39:1055–60.
30. Chen CH, Fetics B, Nevo E, Rochitte CE, Chiou KR, Ding PA, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol 2001;38:2028–34.
31. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol 1983;245:H773–80.
32. Kelly R, Fitchett D. Noninvasive determination of aortic input impedance and external left ventricular power output: a validation and repeatability study of a new technique. J Am Coll Cardiol 1992;20:952–63.
33. Kelly RP, Ting CT, Yang TM, Liu CP, Maughan WL, Chang MS, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation 1992;86:513–21.
34. Feldschuh J, Enson Y. Prediction of the normal blood volume. Relation of blood volume to body habitus. Circulation 1977;56:605–12.
35. Kitzman DW, Gardin JM, Gottdiener JS, Arnold A, Boineau R, Aurigemma G, et al. Cardiovascular Health Study Research Group. Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. Am J Cardiol 2001;87:413–9.
36. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002;288:2144–50.
37. Hundley WG, Kitzman DW, Morgan TM, et al. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. J Am Coll Cardiol 2001;38:796–802.
38. Pak PH, Maughan L, Baughman KL, Hamilton CA, Darty SN, Stewart KP, et al. Marked discordance between dynamic and passive diastolic pressure-volume relations in idiopathic hypertrophic cardiomyopathy. Circulation 1996;94:52–60.
39. Pinamonti B, Di Lenarda A, Sinagra G, Camerini F. Restrictive left ventricular filling pattern in dilated cardiomyopathy assessed by Doppler echocardiography: clinical, echocardiographic and hemodynamic correlations and prognostic implications. Heart Muscle Disease Study Group. J Am Coll Cardiol 1993;22:808–15.
40. Rivas-Gotz C, Khoury DS, Manolios M, Rao L, Kopelen HA, Nagueh SF. Time interval between onset of mitral inflow and onset of early diastolic velocity by tissue Doppler: a novel index of left ventricular relaxation: experimental studies and clinical application. J Am Coll Cardiol 2003;42:1463–70.
41. Yu CM, Sanderson JE, Shum IO, Chan S, Yeung LY, Hung YT, et al. Diastolic dysfunction and natriuretic peptides in systolic heart failure. Higher ANP and BNP levels are associated with the restrictive filling pattern. Eur Heart J 1996;17:1694–702.
42. Zile MR. Heart failure with preserved ejection fraction: is this diastolic heart failure? J Am Coll Cardiol 2003;41:1519–22.

43. Gandhi SK, Powers JC, Nomeir AM, Fowle K, Kitzman DW, Rankin KM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 2001;344:17–22.
44. Little WC. Hypertensive pulmonary oedema is due to diastolic dysfunction. Eur Heart J 2001;22:1961–4.
45. Kass DA. Assessment of diastolic dysfunction. Invasive modalities. Cardiol Clin 2000;18:571–86.
46. Devereux RB, Roman MJ, Liu JE, Welty TK, Lee ET, Rodeheffer R, et al. Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study. Am J Cardiol 2000;86:1090–6.
47. Gottdiener J, Kitzman D, Aurigemma GP, Arnold AM, Egher CS, Fowle KN, Hill JC. Left atrial volume is more strongly associated with prevalent congestive heart failure and predictive of incident congestive heart failure in the elderly than Doppler mitral inflow velocities or deceleration time. J Am Coll Cardiol 2003;41.
48. Vardi P, Markiewicz W, Levy J, Adler O, Riss E, Benderley A. The heart in acute glomerulonephritis: an echocardiographic study. Pediatrics 1979;63:782–7.
49. Iwashima Y, Horio T, Takami Y, Inenaga T, Nishikimi T, Takishita S, et al. Effects of the creation of arteriovenous fistula for hemodialysis on cardiac function and natriuretic peptide levels in CRF. Am J Kidney Dis 2002;40:974–82.
50. O'Rourke MF, Mancia G. Arterial stiffness. J Hypertens 1999;17:1–4.
51. Nagueh SF, Sun H, Kopelen HA, Middleton KJ, Khoury DS. Hemodynamic determinants of the mitral annulus diastolic velocities by tissue Doppler. J Am Coll Cardiol 2001;37:278–85.
52. Yamamoto K, Nishimura RA, Chaliki HP, Appleton CP, Holmes DR Jr, Redfield MM. Determination of left ventricular filling pressure by Doppler echocardiography in patients with coronary artery disease: critical role of left ventricular systolic function. J Am Coll Cardiol 1997;30:1819–26.