Cardiac Structure and Ventricular–Vascular Function in Persons With Heart Failure and Preserved Ejection Fraction From Olmsted County, Minnesota

Carolyn S.P. Lam, MBBS, MRCP; Véronique L. Roger, MD, MPH; Richard J. Rodeheffer, MD; Francesca Bursi, MD, MSc; Barry A. Borlaug, MD; Steve R. Ommen, MD; David A. Kass, MD; Margaret M. Redfield, MD

Background—Mechanisms purported to contribute to the pathophysiology of heart failure with normal ejection fraction (HFnlEF) include diastolic dysfunction, vascular and left ventricular systolic stiffening, and volume expansion. We characterized left ventricular volume, effective arterial elastance, left ventricular end-systolic elastance, and left ventricular diastolic elastance and relaxation noninvasively in consecutive HFnlEF patients and appropriate controls in the community.

Methods and Results—Olmsted County (Minn) residents without cardiovascular disease (n=617), with hypertension but no heart failure (n=719), or with HFnlEF (n=244) were prospectively enrolled. End-diastolic volume index was determined by echo Doppler. End-systolic elastance was determined using blood pressure, stroke volume, ejection fraction, timing intervals, and estimated normalized ventricular elastance at end diastole. Tissue Doppler e′ velocity was used to estimate the time constant of relaxation. End-diastolic volume (EDV) and Doppler-derived end-diastolic pressure (EDP) were used to derive the diastolic curve fitting (α) and stiffness (β) constants ($EDP=\alpha EDV^{\beta}$). Comparisons were adjusted for age, sex, and body size. HFnlEF patients had more severe renal dysfunction, yet smaller end-diastolic volume index and cardiac output and increased EDP compared with both hypertensive and healthy controls. Arterial elastance and ventricular end-systolic elastance were similarly increased in hypertensive controls and HFnlEF patients compared with healthy controls. In contrast, HFnlEF patients had more impaired relaxation and increased diastolic stiffness compared with either control group.

Conclusions—From these cross-sectional observations, we speculate that the progression of diastolic dysfunction plays a key role in the development of heart failure symptoms in persons with hypertensive heart disease. **(*Circulation*. 2007; 115:1982-1990.)**

Key Words: diastole ■ heart failure ■ hypertension ■ mechanics

Heart failure (HF) with normal ejection fraction (EF) (HFnlEF) is a major public health problem of increasing prevalence.[1] In contrast to the improvements in survival observed in patients with HF and reduced EF, mortality for patients with HFnlEF has remained stable, emphasizing the lack of proven therapies.[1] An important barrier to advances in therapy is relative uncertainty about the fundamental pathophysiological mechanisms. Left ventricular (LV) diastolic dysfunction (impaired relaxation and increased passive diastolic stiffness), increased systolic ventricular–vascular stiffening, and cardiac volume overload have been implicated in previous seminal studies.[2–9] Although well designed, these important studies were small, with both control and HFnlEF cohorts subject to potential limitations in regard to selection and referral bias and, in some instances, with populations preselected for features of cardiac remodeling or dysfunction. The relative incidence of each putative mechanism remains to be defined in large, prospectively enrolled, control and HF populations recruited from the same community and studied in a comprehensive and uniform manner.

Clinical Perspective p 1990

In this study of residents of Olmsted County, Minn, we used previously validated noninvasive methods to assess LV volume,[10] end-systolic LV[11] and effective arterial stiffness (elastance),[12] LV relaxation,[13,14] and diastolic elastance[15] to compare cardiac structure and ventricular–vascular function in consecutive patients with HFnlEF with those observed in

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From the Division of Cardiovascular Diseases, Mayo Clinic and Foundation, Rochester, Minn (C.S.P.L., V.L.R., R.J.R., B.A.B., S.R.O., M.M.R.); Yong Loo Lin School of Medicine, National University of Singapore, Singapore (C.S.P.L.); Department of Cardiology, University Policlinico Hospital, Modena, Italy (F.B.); and Division of Cardiology, Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, Md (D.A.K.).

Correspondence to Margaret M. Redfield, MD, Mayo Clinic and Foundation, 200 First St SW, Rochester, MN 55905. E-mail redfield.margaret@mayo.edu

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randomly selected persons without cardiovascular disease or with hypertension but no HF. We hypothesized that more advanced diastolic dysfunction and systolic ventricular–vascular stiffening distinguish HFnlEF from disease-free and hypertensive control subjects without HF in this community.

Methods

Study Setting

The unique aspects of Olmsted County favoring population-based research have been previously described.[16] The study was approved by the Mayo Institutional Review Board.

Identification of Patients and Study Procedures

Subject groups were as follows: nonobese controls without cardiovascular disease (CON), subjects with hypertension but without HF (HTN), and patients with HFnlEF. To recruit the first 2 groups, a random sample of the population ≥45 years of age was prospectively identified and evaluated as previously described.[16] Data from this study have previously been published, but these subsets and many of the indexes presented here have not. Medical records were reviewed by trained nurse-abstractors using established criteria for hypertension and HF. Clinical diagnoses of coronary artery disease, diabetes mellitus, valvular heart disease, cardiomyopathy, atrial fibrillation, and transient ischemic attack or stroke were recorded. In each participant, cuff blood pressure, height, and weight were measured and body mass index and body surface area (BSA) were calculated. Echocardiographic assessment of EF was performed by M-mode, quantitative, and semiquantitative 2-dimensional methods. Subjects with EF <50% were excluded. Of 2042 participants, 617 had none of the above validated or suspected cardiovascular diagnoses, a systolic pressure <140 mm Hg at the time of echocardiography, and a body mass index <30 kg/m^2, thus constituting the CON group. Subjects with hypertension but no HF (n=719) constituted the HTN group. The HFnlEF group was prospectively identified in an Olmsted County HF surveillance study by real-time interrogation of electronic medical records using natural language processing techniques.[17] Briefly, all inpatient and outpatient electronic notes were searched (most within 24 hours of presentation) using a wide range of terms indicative of HF, enabling rapid identification of all potential cases of HF with a diagnostic sensitivity of 100%.[17] The final diagnosis of HF was validated by trained nurse-abstractors using the Framingham criteria. Of 811 HF patients identified between September 10, 2003, and August 24, 2005, 570 (70%) consented to participate, and 516 (91%) underwent echocardiography within a median (25th, 75th percentile) of 1 day (range, 1 to 5 days) of diagnosis. Of these, 276 patients had EF ≥50%. Hemodynamically significant valve disease was detected on Doppler echocardiography in 32 patients (11.6%), who were excluded. The remaining 244 patients made up the HFnlEF group. Reflecting the ethnic composition of the community, subjects were almost exclusively white.

Plasma brain natriuretic peptide was determined by immunoradiometric assay (nonextracted) using an antibody to human brain natriuretic peptide (Shionogi Co Ltd, Tokyo, Japan). Glomerular filtration rate was estimated using the simplified modification of diet in renal disease study equation. All echocardiograms were performed by registered diagnostic cardiac sonographers using standardized instruments and techniques[16] and were reviewed by a cardiologist (C.S.P.L., M.M.R.).

Assessment of Cardiac Volume

LV volume was determined in each subject by 3 methods. The Teichholz method[18] used short-axis LV dimension measured from 2-dimensional or M-mode images. This was available in 532 CON (86%), 551 HTN (77%), and 222 HFnlEF (91%) subjects. In 73 subjects, LV short-axis dimension was measured from both 2-dimensional and M-mode images and correlated well (r=0.73, P<0.001) with no systematic error (mean±SD difference, 0.79±4.2 mm, Bland-Altman analysis) and no relationship between mean difference and the average of the 2 methods (r=0.02, P=0.85). LV volume calculated by the area-length formula[10] used both long- and short-axis LV dimensions. This was available in 496 CON (80%), 492 HTN (68%), and 188 HFnlEF (77%) subjects. LV volume also was calculated independently of geometric assumptions by dividing stroke volume (SV; using left ventricular outflow tract dimension and pulsed-wave Doppler velocity profile) by EF. This was available in 611 CON (99%), 697 HTN (97%), and 223 HFnlEF (91%) subjects. Left atrial volume was calculated by the ellipse formula.[19] LV mass and relative wall thickness were calculated by standard methods.[10] Measurements were indexed to BSA when appropriate. LV hypertrophy (LVH) was defined as LV mass index >95 g/m^2 (women) or >115 g/m^2 (men), and LV geometry was classified as normal, concentric remodeling, concentric LVH, or eccentric LVH.[10]

Determination of Vascular Function

Effective arterial elastance (Ea) was estimated as end-systolic pressure divided by SV.[12] End-systolic pressure was estimated as systolic pressure times 0.9, as previously validated.[11,12] Total arterial compliance was estimated by the SV-to-pulse-pressure ratio[20] and systemic vascular resistance index by mean arterial pressure divided by cardiac index times 80.

Determination of LV End-Systolic Elastance

The modified single-beat method was used to estimate end-systolic elastance (Ees) from arm-cuff pressures, SV, and pre-ejection and total systolic periods determined on continuous-wave Doppler of aortic flow, EF, and an estimated normalized ventricular elastance at arterial end diastole, as previously validated[11,21] and used in recent studies.[4,22,23]

Determination of Early LV Relaxation Velocity and Filling Pressures

The medial mitral annular early diastolic velocity (e′) was determined by spectral tissue Doppler imaging using standard methods. The e′ velocity is relatively preload independent and inversely related to the time constant of isovolumic relaxation (τ), which was derived from this formula: [τ=(14.70−100e′)/0.15].[13,14] Early transmitral flow velocity (E) was measured by pulsed-wave Doppler. End-diastolic pressure (EDP) was estimated as follows: (EDP=11.96+0.596 · E/e′), as previously determined from Doppler and invasive EDP measurements at our institution.[13]

Determination of LV Diastolic Stiffness

The recently developed and validated single-beat approach proposed by Klotz et al[15] was used to characterize the EDP–end-diastolic volume (EDV) relationship (EDPVR, where EDP=αEDV$^{\beta}$; α is a curve-fitting constant and β is a diastolic stiffness constant). On the basis of the premise that volume-normalized EDPVRs share a common shape, this method allows estimation of α and β and hence the entire EDPVR from a single pressure–volume point. Measured EDP and EDV were used to derive α and β in each subject. A modified method was used when EDP was >28 mm Hg to address the recognized mathematical limitations of the original equations (see the Appendix). To account for covariance in α and β,[24] both of which are indicative of the shape and position of the EDPVR, derived α and β in each subject were used to predict the EDV at a common EDP of 20 mm Hg (EDV_{20}). Comparison of EDV_{20} indexed to BSA ($EDVI_{20}$) was then used as a comparison of overall diastolic stiffness between groups.

Statistical Analysis

Categorical variables were compared by use of Pearson's χ^2 test. Continuous variables were log transformed as necessary and compared between groups through the use of 1-way ANOVA with Bonferroni's correction for multiple unadjusted comparisons. Regression analysis was used to adjust for age, sex, and BSA or the presence of other diseases in group comparisons, where the depen-

TABLE 1. Subject Characteristics

	CON (n=617)	HTN (n=719)	HFnlEF (n=244)
Age, y (range)	57 (45–96)	66 (46–91)*	76 (22–99)*†
Males, %	45	44	45
Height, cm	169±10	167±10*	165±13*
Weight, kg	73±13	84±19*	86±25*
Body surface area, m^2	1.85±0.21	1.96±0.26*	1.97±0.31*
Body mass index, kg/m^2	25.4±2.7	29.8±5.9*	32.2±20.7*†
Hypertension, %	0	100*	96*
Coronary artery disease, %	0	16*	53*†
Diabetes mellitus, %	0	11*	37*†
Glomerular filtration rate, $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	74.4±14.1	74.7±37.0	64.3±28.1*†
BNP (Shionogi), pg/mL	20.0±40.3	30.5±45.2*	260.7±330.2*†
Log BNP (Shionogi), pg/mL	1.06±0.41	1.23±0.46*	2.15±0.55*†
Ejection fraction, %	63±5	65±6	62±6*†
Heart rate, bpm	65±10	67±12	71±15*†
Systolic blood pressure, mm Hg	118±12	143±21*	132±23*†
Diastolic blood pressure, mm Hg	70±8	76±11*	67±14†
Pulse pressure, mm Hg	48±11	67±18*	65±20*

BSA indicates body surface area; BNP, B-type natriuretic peptide. Data are mean±SD unless otherwise stated. Analysis is unadjusted.

*$P<0.05$ vs CON; †$P<0.05$ vs HTN.

dent variable was the normally distributed continuous (linear least-squares regression) or categorical (logistic regression) outcome variable of interest; factors entered into the model were age, sex, BSA, and group (dummy variable). Any interaction between these variables also was evaluated and accounted for as appropriate. All analyses were 2 sided, and significance was judged at $P<0.05$.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Subject Characteristics

HFnlEF patients were older, were more obese, had higher prevalence of coronary artery disease and diabetes mellitus, and had lower glomerular filtration rate than HTN or CON (Table 1).

LV Structure

After adjustment for age and sex, EDVI in HFnlEF was similar (area-length) or smaller (Teichholz and Doppler) compared with CON and smaller (by all 3 methods) compared with HTN (Table 2). After adjustment for age and sex, SV index in HFnlEF was smaller compared with CON or HTN, whereas cardiac index in HFnlEF was similar to that in CON but reduced compared with HTN. After adjustment for age and sex, LV mass index, relative wall thickness, and ratio of LV mass to volume were increased in HFnlEF and HTN compared with CON, but these parameters were similar in HFnlEF and HTN. The percent LVH was greater in HTN and HFnlEF than CON but similar in HFnlEF and HTN. LV geometry patterns varied considerably in both control populations and HFnlEF. Although HFnlEF patients had more concentric LVH and less normal geometry compared with CON, these patterns were not significantly different compared with HTN after adjustment for age.

Vascular Function

With adjustment for age, sex, and BSA when appropriate, Ea, systemic vascular resistance index, and pulse pressure were increased whereas arterial compliance was decreased in HFnlEF and HTN compared with CON, but all these parameters were similar in HFnlEF and HTN (Table 2). Unadjusted comparisons gave similar results.

LV Systolic Stiffness

After adjustment for age, sex, and BSA, Ees was increased in HFnlEF and HTN compared with CON but was similar in HFnlEF and HTN (Table 2). Similar results were observed in unadjusted comparisons and after normalizing Ees for LV mass (Ees times LV mass) and EDV (Ees times EDV) (and adjusting for age and sex), suggesting that the differences in Ees could not be attributed solely to differences in chamber size. Systolic vascular-ventricular coupling ratio (Ea/Ees) was preserved across groups. Predicted end-systolic pressure–volume relationship equations derived from group-averaged data are given in Figure 1.

Estimated LV Filling Pressures

EDP was higher in HFnlEF compared with both CON and HTN (Figure 2), with corroborating evidence of elevated filling pressures provided by plasma brain natriuretic peptide and left atrial volume index measurements.

LV Diastolic Function

In both unadjusted and adjusted (adjusting for age, sex, and BSA) comparisons, HFnlEF patients had more impaired relaxation (lower e′, longer τ) and higher β compared with CON and HTN (Table 2). After adjusting for age and sex and controlling for covariance in α and β, overall diastolic LV

TABLE 2. Measures of Cardiovascular Structure and Function

	CON (n=617)	HTN (n=719)	HFnlEF (n=244)
LV structure			
EDV, mL			
Teichholz	110.6±23.6	113.3±26.1	110.2±32.6
Area-length	123.2±30.3	125.9±32.9	119.4±39.3†
Doppler	134.4±31.4	141.1±35.5	132.8±37.7†
EDVI, mL/m^2			
Teichholz	60.6±10.9	59.7±12.2	56.4±14.4*†
Area-length	66.6±12.3	64.9±13.9	60.9±16.1†
Doppler	72.5±12.9	72.2±15.5	68.1±16.6*†
Stroke volume index, mL/m^2	45.8±7.5	46.3±9.5	42.3±10.0*†
Cardiac index, L · min^{-1} · m^{-2}	2.94±0.57	3.04±0.70	2.95±0.79†
LV mass, g	164.2±38.8	195.0±53.2*	200.4±67.1*
LV mass index, g/m^2	88.8±16.3	100.2±22.7*	102.1±29.0*
LV mass/EDV, mg/mL	1.50±0.28	1.75±0.39*	1.85±0.47*
Relative wall thickness	0.38±0.06	0.42±0.07*	0.45±0.10*
LV hypertrophy, %	18	40*	42*
Normal geometry, %	66	39*	31*
Concentric remodeling, %	16	21	27
Concentric hypertrophy, %	5	21*	26*
Eccentric hypertrophy, %	13	19	16
Vascular function			
Ea, mm Hg/mL	1.30±0.30	1.50±0.41*	1.53±0.43*
Systemic vascular resistance index, dyne · s · cm^{-5} · m^2	2424±521	2703±657*	2588±873*
Arterial compliance, mL/mm Hg	1.86±0.58	1.45±0.55*	1.41±0.93*
LV systolic function			
Ees, mm Hg/mL	1.99±0.59	2.30±0.80*	2.39±0.87*
Ees · LV mass	319.7±96.4	439.6±163.7*	461.8±209.7*
Ees · EDV	215.5±60.7	256.3±86.3*	254.0±105.3*
Ea/Ees	0.68±0.13	0.68±0.17	0.69±0.22
LV diastolic function			
E, m/s	0.660±0.131	0.671±0.169*	0.979±0.347*†
A, m/s	0.561±0.161	0.722±0.203*	0.848±0.267*†
E/A ratio	1.25±0.38	0.99±0.37*	1.21±0.69*†
Deceleration time, ms	222±33	239±43	208±54*†
e′, m/s	0.094±0.035	0.077±0.039*	0.060±0.021*†
τ, ms	35.2±23.4	46.8±26.0*	58.1±14.3*†
E/e′ ratio	7.55±2.29	9.43±3.32*	18.43±9.65*†
LV EDP, mm Hg	16.5±1.4	17.6±2.0*	22.9±5.7*†
β	5.96±0.06	6.05±0.41*	7.09±3.55*†
$EDVI_{20}$, mL/m^2	61.7±11.4	59.7±11.9*	55.7±14.5*†
EDP/EDV, mm Hg/mL	0.16±0.04	0.16±0.05	0.23±0.11*†

Data are mean±SD. Comparisons were adjusted for age, sex, and body surface area when appropriate.
*P<0.05 vs CON; †P<0.05 vs HTN.

stiffness was higher (lower $EDVI_{20}$) in HFnlEF than in CON or HTN (Table 2). Predicted EDPVR curves derived from group-averaged data are illustrated in Figure 3.

Further Analyses

In view of the large age range of subjects (Table 1) and recognizing that unaccounted confounders may be present at the extremes of ages, a subanalysis of subjects 60 to 95 years of age was performed and gave similar results (Table 3). Further recognizing the potential confounding effects of diabetes and renal function, we adjusted for these, in addition to age, sex, and body size (Table 4). Overall results were similar.

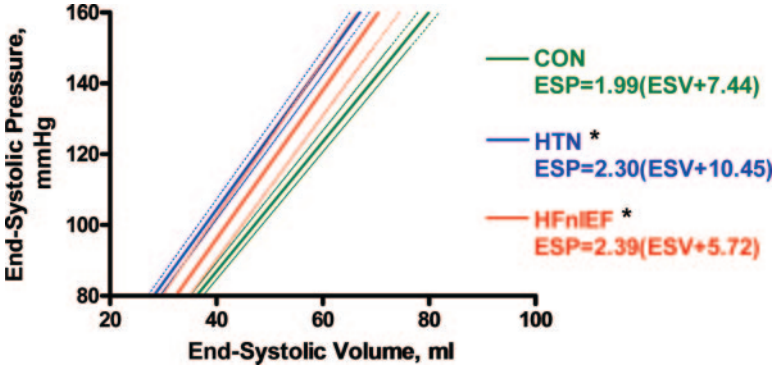

Figure 1. Schematic of group-averaged end-systolic pressure–volume relationship (ESPVR), where ESP=Ees(ESV−V_0) (V_0 is volume intercept). Solid lines represent the mean ESPVR; dotted lines, 95% CI for each group. For comparison of Ees (slope) between groups, *$P<0.05$ vs CON.

Discussion

This is the largest population-based study to date comparing vascular and ventricular structure and function in an HFnlEF cohort with those observed in healthy and hypertensive control populations without HF. The present study serves to confirm, clarify, and extend smaller, seminal studies describing a variety of structural and functional perturbations in more select cohorts with HFnlEF. Several findings are noteworthy. The HFnlEF cohort had worse renal function yet smaller LV volume and cardiac output compared with hypertensive controls. Although LV mass was, on average, increased in HFnlEF compared with healthy controls, HFnlEF patients did not have more severe LVH than hypertensive controls. Compared with healthy controls, the HFnlEF cohort had increases in both the resistive and pulsatile components of vascular load with proportional increases in LV systolic stiffness. However, these abnormalities were similar to those observed in hypertensive controls without HF. In contrast, diastolic dysfunction (both impairment in relaxation and increases in diastolic stiffness) was more severe in HFnlEF patients compared with healthy or hypertensive controls.

The present findings are consistent with previous studies that used invasive assessment of LV function in HFnlEF. Liu et al[25] used conductance catheters with preload reduction (multiple-beat method) in 10 patients with LVH and normal EF (7 with HFnlEF) and found impaired relaxation with increased diastolic stiffness in this group compared with 8 younger, healthy control subjects. All subjects were referred for cardiac catheterization at a tertiary center. In a landmark invasive study using a single-beat method, Zile et al[2] also found more impaired relaxation and higher diastolic stiffness in HFnlEF (n=47). These HFnlEF patients were predominantly male with echocardiographic evidence of LVH who were recruited at a Veterans Administration Hospital as part of a clinical trial and were compared with 10 healthy age-matched control subjects. In both studies, the control group had no cardiovascular disease, raising concern as to whether the observed differences were specifically attributable to HFnlEF or to hypertensive heart disease. Borbely et al[26] measured chamber and myocyte stiffness in 12 HFnlEF patients and 8 control subjects and found increased estimated LV diastolic stiffness in HFnlEF by invasive measurements. However, nearly half of the HFnlEF patients and 75% of the control subjects had previously undergone cardiac transplantation, thus confounding the effects of occult rejection or immunosuppression may have influenced the findings.

Other studies used noninvasive methods to characterize diastolic function.[27] Ahmed et al[6] identified 26 patients with LVH and HFnlEF undergoing echocardiography at their tertiary center and showed that these patients had

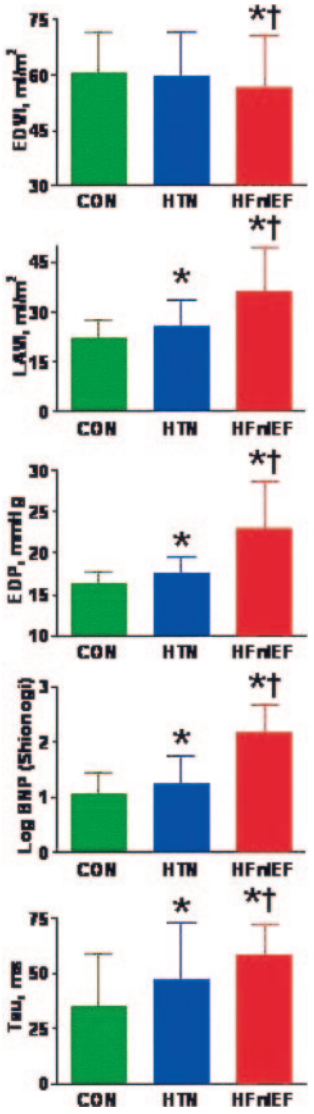

Figure 2. Bar graphs of EDVI, indexed left atrial volume (LAVI), EDP, plasma brain natriuretic peptide (BNP), and derived τ by subject group. Data are mean±SD. *$P<0.05$ vs CON; †$P<0.05$ vs HTN.

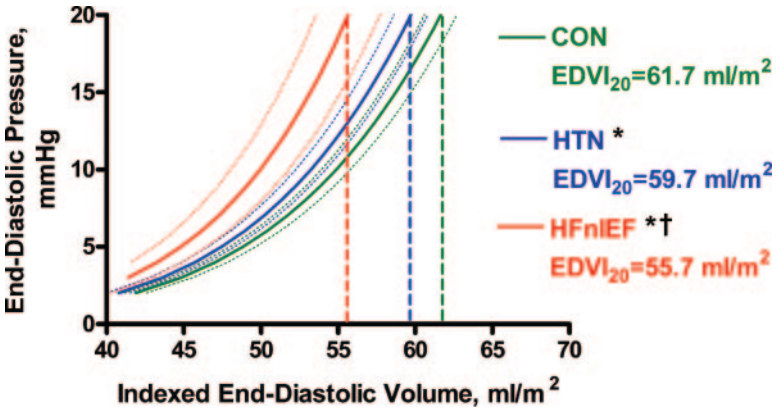

Figure 3. Schematic of group-averaged EDPVR, where $EDP=\alpha EDV^{\beta}$ (α=curve-fitting constant, β=diastolic stiffness constant). Solid lines represent the mean EDPVR; dotted lines, 95% CI for each group. For comparison of $EDVI_{20}$ between groups, *$P<0.05$ vs CON; † $P<0.05$ vs HTN.

more severe diastolic dysfunction than 39 nonhypertensive control, 14 hypertensive control, and 23 control subjects with LVH but no HF.[6] The inclusion of hypertensive control subjects was a strength of this study, which focused on HFnlEF patients with LVH.

In the present study, consecutive cases of HFnlEF identified in both the inpatient and outpatient settings, not preselected for any geometric characteristics, were compared with large, randomly selected, and prospectively enrolled control populations from the same community, with all subjects studied in a similar manner using analyses adjusted for potential effects of age, sex, and body size. The present results are consistent with the aforementioned studies in that relaxation and passive diastolic stiffness were impaired in HFnlEF compared with disease-free control subjects. Furthermore, the present data confirm that compared with HTN subjects, HFnlEF patients have more severe diastolic dysfunction. Although the predominant cardiovascular abnormalities and contributing comorbidities in HFnlEF patients may vary according to a number of demographic parameters, it is noteworthy that the presence of diastolic dysfunction is a consistent finding in HFnlEF patients identified in this community and in the diverse settings included in previous studies.[2,5–9,25,26]

In contrast, Kawaguchi et al,[4] using either invasive (conductance catheters and multiple-beat model) or noninvasive (single-beat model) measurements, found that relaxation was not significantly different in HFnlEF patients (n=10) compared with young control subjects (n=9) and age- and blood pressure–matched control subjects (n=25), except during stress (isometric handgrip). Additionally, although higher EDPs were observed in HFnlEF, this was due to a parallel upward shift of the diastolic pressure–volume curve rather than to a steeper curve (ie, β stiffness coefficients were similar), suggesting that exaggerated external forces, rather than increased passive diastolic stiffness, was present in HFnlEF. However, the large variability in β observed in the HFnlEF group (range, ≈0.01 to 0.05 mm Hg/mL) may have prevented demonstration of differences in β in the small numbers of subjects enrolled. Importantly, this study showed that HFnlEF patients had increased Ea and Ees, suggesting that vascular and LV systolic stiffening may contribute to the pathophysiology of HFnlEF by exaggerating systolic load and diastolic dysfunction during exercise. These patients were studied over a 14-year period at a referral center, and although the patients were predominantly female, the mean age was lower than that observed in most population-based studies. Although we also found that Ea and Ees were increased in HFnlEF compared with healthy control subjects, these indexes were not further increased in HFnlEF compared with hypertensive controls in the this study and others.[5,6,9] Nonetheless, these data do not exclude a role for increased vascular and LV systolic stiffening in the pathophysiology of HFnlEF, particularly during exercise or other stressors in which such changes exaggerate hypertensive responses and induce further load-dependent diastolic dysfunction.

The potential for a subgroup of HFnlEF patients to have LV dilatation and a "high-output" form of HF has been

TABLE 3. Subgroup Analysis in Subjects 60 to 95 Years of Age

	CON (n=211)	HTN (n=519)	HFnlEF (n=214)
EDVI, mL/m^2			
Teichholz	59.4±12.1	60.0±12.7	56.7±14.2*†
Area-length	63.7±12.8	64.7±14.0	60.8±15.6†
Doppler	72.0±13.4	73.4±16.0	68.1±16.6*†
Ea, mm Hg/mL	1.35±0.32	1.53±0.43*	1.54±0.43*
Ees, mm Hg/mL	2.12±0.64	2.37±0.83*	2.42±0.88
$EDVI_{20}$, mL/m^2	60.5±12.8	60.0±12.3	55.7±14.3*†
τ, ms	41.3±27.7	49.1±28.0	59.5±13.1*†

Data are mean±SD. Comparisons were adjusted for age, sex, and body surface area when appropriate.

*$P<0.05$ vs CON; †$P<0.05$ vs HTN.

TABLE 4. Analysis Adjusted for Renal Function, Diabetes Mellitus, Age, Sex, and Body Size

	CON (n=617)	HTN (n=719)	HFnlEF (n=244)
Ea, mm Hg/mL	1.30±0.30	1.50±0.41*	1.53±0.43*
Ees, mm Hg/mL	1.99±0.59	2.30±0.80*	2.39±0.87*
$EDVI_{20}$, mL/m^2	61.7±11.4	59.7±11.9	55.7±14.5*†
τ, ms	35.2±23.4	46.8±26.0*	58.1±14.3*†

Data are mean±SD. Comparisons were adjusted for glomerular filtration rate, diabetes mellitus, age, sex, and body surface area.

*$P<0.05$ vs CON; †$P<0.05$ vs HTN.

reported.[3] Maurer et al[3] used 3-dimensional and Doppler echocardiography to characterize LV volumes and pressures noninvasively at a tertiary referral center in the New York metropolitan area. Among 35 patients with hypertension and HFnlEF, a subgroup (n=29) of younger, more obese subjects had increased LV volumes associated with increased EDP but no change in Ees or Ea compared with healthy control subjects. These investigators concluded that many (most in their series) HFnlEF patients may have volume overload, without intrinsic diastolic dysfunction as a mechanism for increased filling pressures. In contrast, our data show that on average, compared with healthy or hypertensive controls, HFnlEF patients have normal or decreased LV volumes, respectively. Because ventricular volumes vary with body size, sex, and possibly age in persons without cardiovascular disease, we were careful to adjust for these parameters in all volume comparisons. We accounted not only for the short-axis but also for the long-axis LV dimension when calculating volumes. A further Doppler-based method was used to estimate volumes independently of geometric assumptions. All 3 methods gave the consistent picture that ventricular enlargement was not present in most HFnlEF patients despite their more impaired renal function. In fact, stroke volume and cardiac index were lower in HFnlEF than in HTN subjects. As emphasized previously, however, the present analysis is restricted to group comparisons; because LV volume is a continuous variable with a fairly normal distribution in the HFnlEF population, some patients with HFnlEF will have increased LV volume even though the distribution curve as a whole was not shifted toward larger volumes. Indeed, our findings underscore the variable LV geometric patterns present in HFnlEF.

More recently, Melenovsky et al[9] used noninvasive methods to study 37 HFnlEF patients, 40 hypertensive control subjects, and 56 nonhypertensive age-, sex-, and race-matched control subjects recruited from an urban setting in Baltimore, Md. This population was largely black, and HFnlEF patients were younger (by a decade) than observed here, more obese, and more predominantly female. As in our study, LV volume did not vary significantly among groups, estimated filling pressures were highest in HFnlEF, and both Ees and Ea were similarly increased in hypertensive control subjects and HFnlEF patients compared with disease-free controls. However, both the HFnlEF and hypertensive groups had much more dramatic LVH than we observed, and although estimated LV diastolic pressures were higher in HFnlEF, many parameters displayed substantial overlap, with little disparity between these 2 groups. Although LV diastolic stiffness was not estimated, the prior study found left atrial enlargement and impaired atrial function in HFnlEF, leading the authors to speculate that impaired atrial function also may play a key role in the transition to HFnlEF among patients with cardiovascular disease. This hypothesis is consistent with clinical studies documenting that new-onset atrial fibrillation is a common precipitant of episodes of acutely decompensated HF, regardless of EF.[28,29] We also found increased left atrial volume in HFnlEF patients compared with either control group. Melenovsky et al[9] further found that total epicardial cardiac volume was highest in HFnlEF patients and speculated that external forces may contribute to the elevation in filling pressures.

The variable LV geometry patterns observed in HFnlEF patients in our study is noteworthy and consistent with several[2,4,28,30] prior studies, underscoring that despite traditional teaching, concentric LVH or concentric remodeling is not invariably present in HFnlEF. Indeed, there may be important geographic and race-specific differences, with marked concentric LVH being more common in some populations such as blacks, as seen in studies in which these groups are more prominently represented.[9] Finally, the similar relative wall thickness and ratio of LV mass to volume observed in HTN and HFnlEF suggest that factors other than chamber geometry additionally mediate increased diastolic stiffness in HFnlEF. Changes in the cardiomyocytes themselves[26] and/or the extracellular matrix[31,32] may mediate diastolic stiffening and represent potential therapeutic targets in the treatment and/or prevention of HFnlEF.

Study Limitations

Our data are purely observational and cannot prove causality. The more impaired diastolic dysfunction in HFnlEF could be a marker for, rather than a mediator of, progression to HF. Although invasive measurements were not performed, each of the methods used to characterize pressure–volume relationships was validated against gold-standard invasive techniques.

Future Directions

Although total vascular load and indirect measures of vascular stiffness were obtained here, further study is needed to evaluate more direct and perhaps regional measures of vascular stiffening and other assessments of arterial impedance and its impact such as characteristic impedance, wave reflections, and pulse-wave velocity. Hemodynamic data obtained during exercise and other stresses may be key in differentiating HFnlEF and HTN subjects. The study population was mainly white, and potential differences in other racial groups should be examined. Finally, the functional significance of different geometric patterns in HFnlEF deserves further study.

Conclusions

In this large, population-based study, HFnlEF patients had reduced LV volumes and cardiac output compared with hypertensive controls despite more renal impairment. Although HFnlEF patients displayed vascular and LV systolic stiffening compared with normal controls, HFnlEF was distinguished from hypertensive heart disease by the presence of more severe diastolic dysfunction and increased left atrial size. Thus, these data support efforts to ameliorate diastolic dysfunction in order to prevent or treat HFnlEF. Although we speculate that progression of diastolic dysfunction plays a key role in the development of HF symptoms in persons with hypertensive heart disease and a normal EF, further studies characterizing potential differential responses to exercise and other stressors may reveal additional pathophysiological mechanisms and therapeutic targets.

Appendix

A recognized limitation of the original predictions used in the single-beat EDPVR method[15] was the breakdown of the equations as measured EDP approached 30 mm Hg. This limitation was due to the arbitrary choice of V_{30} (estimated EDV at 30 mm Hg) as a starting point in the original derivation equations for α and β, which therefore became unstable as measured EDP approached 30 mm Hg (>28 mm Hg). This mathematical instability was overcome simply by use of an estimate of EDV at a pressure of 15 mm Hg (V_{15}) instead of V_{30} for cases when measured EDP was >28 mm Hg. V_{15} was derived from the EDV-normalized curve in the same fashion[15] as V_{30} (D. Burkoff, MD, PhD, personal communication, 2006). Similar to the original derivations, α and β were then calculated by solving the following simultaneous equations: $Pm=\alpha Vm^{\beta}$ and $15=\alpha V_{15}{}^{\beta}$, where Pm is measured pressure (measured EDP) and Vm is measured volume (measured EDV). Dividing the first equation by the second and solving for β gives the following: $\beta=\log(Pm/15)/\log(Vm/V_{15})$. Substituting into the first equation yields this: $\alpha=Pm/Vm^{[\log (Pm/15)/\log (Vm/V_{15})]}$. EDPVR curves derived using V_{15} and V_{30} were well correlated at multiple parts of the curves.

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Disclosures

None.

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CLINICAL PERSPECTIVE

In this large, population-based study, patients with heart failure and normal ejection fraction (HFnlEF) were compared with both healthy and hypertensive control subjects with normal EF. The HFnlEF patients had worse renal function than the healthy or hypertensive control subjects and displayed variable left ventricular geometry. However, on average, HFnlEF patients had reduced left ventricular volumes and cardiac output compared with hypertensive control subjects. Although HFnlEF patients displayed vascular and ventricular systolic stiffening compared with healthy control subjects, HFnlEF was distinguished from hypertensive heart disease by the presence of more severe diastolic dysfunction and increased left atrial size. These data provide further evidence that diastolic dysfunction plays a key role in the development of heart failure symptoms in persons with hypertensive heart disease and a normal ejection fraction. Thus, strategies to ameliorate diastolic dysfunction may prove efficacious in the prevention or treatment of HFnlEF. Further studies, however, are warranted to characterize the heterogeneity among HFnlEF patients and to investigate differential responses to exercise and other stressors that may contribute to the pathophysiology of this syndrome.