Heart Failure

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

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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 = 11005, n = 617), with hypertension but no heart failure (n = 11005, n = 719), or with HFnlEF (n = 11005, 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 = αEDV²). 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 LV11 and effective arterial elastance (elastance),12 LV relaxation,13,14 and diastolic elastance15 to compare cardiac structure and ventricular–vascular function in consecutive patients with HFnlEF with those observed in

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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. 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. 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 (HTN), and patients with HFnlEF. To recruit the first 2 groups, a random sample of the population favoring population-based hypertensive control subjects without HF in this community.

Assessment of Cardiac Volume

LV volume was determined in each subject by 3 methods. The Teichholz method was used to determine 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. 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.

Determination of Vascular Function

Effective arterial elastance (Ea) was estimated as end-systolic pressure divided by SV. End-systolic pressure was estimated as systolic pressure times 0.9, as previously validated. Total arterial compliance was estimated by the SV-to-pulse-pressure ratio 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 and used in recent studies. 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]. Early transmirtal 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.

Determination of LV Diastolic Stiffness

The recently developed and validated single-beat approach proposed by Klotz et al was used to characterize the EDP–diastolic volume (EDV) relationship (EDPVR, where EDP=α·EDVβ; 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, 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 (EDV0). Comparison of EDV0 indexed to BSA (EDV0/BSA) was then used as an comparison of overall diastolic stiffness between groups.

Statistical Analysis

Categorical variables were compared by use of Pearson’s χ2 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-
The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the

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

$P < 0.05$.

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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 $\tau$) and higher $\beta$ compared with CON and HTN (Table 2). After adjusting for age and sex and controlling for covariance in $\alpha$ and $\beta$, overall diastolic LV
TABLE 2. Measures of Cardiovascular Structure and Function

<table>
<thead>
<tr>
<th></th>
<th>CON (n = 617)</th>
<th>HTN (n = 719)</th>
<th>HFnlEF (n = 244)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LV structure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDV, mL</td>
<td>110.6±23.6</td>
<td>113.3±26.1</td>
<td>110.2±32.6</td>
</tr>
<tr>
<td>Teichholz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area-length</td>
<td>123.2±30.3</td>
<td>125.9±32.9</td>
<td>119.4±39.3†</td>
</tr>
<tr>
<td>Doppler</td>
<td>134.4±31.4</td>
<td>141.1±35.5</td>
<td>132.8±37.7†</td>
</tr>
<tr>
<td>EDVI, mL/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teichholz</td>
<td>60.6±10.9</td>
<td>59.7±12.2</td>
<td>56.4±14.4†</td>
</tr>
<tr>
<td>Area-length</td>
<td>66.6±12.3</td>
<td>64.9±13.9</td>
<td>60.9±16.1†</td>
</tr>
<tr>
<td>Doppler</td>
<td>72.5±12.9</td>
<td>72.2±15.5</td>
<td>68.1±16.6†</td>
</tr>
<tr>
<td>Stroke volume index, mL/m²</td>
<td>45.8±7.5</td>
<td>46.3±9.5</td>
<td>42.3±10.0†</td>
</tr>
<tr>
<td>Cardiac index, L· min⁻¹· m⁻²</td>
<td>4.5±0.65</td>
<td>3.0±0.70</td>
<td>2.95±0.79†</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>164.2±38.8</td>
<td>195.0±53.2</td>
<td>200.4±67.1*</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>88.8±16.3</td>
<td>100.2±22.7†</td>
<td>102.1±29.0*</td>
</tr>
<tr>
<td>LV mass/EDVI, mg/mL</td>
<td>1.50±0.28</td>
<td>1.75±0.39*</td>
<td>1.85±0.47*</td>
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<td>Relative wall thickness</td>
<td>0.38±0.06</td>
<td>0.42±0.07*</td>
<td>0.45±0.10*</td>
</tr>
<tr>
<td>LV hypertrophy, %</td>
<td>18</td>
<td>40*</td>
<td>42*</td>
</tr>
<tr>
<td>Normal geometry, %</td>
<td>66</td>
<td>39*</td>
<td>31*</td>
</tr>
<tr>
<td>Concentric remodeling, %</td>
<td>16</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>Concentric hypertrophy, %</td>
<td>5</td>
<td>21*</td>
<td>26*</td>
</tr>
<tr>
<td>Eccentric hypertrophy, %</td>
<td>13</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td><strong>Vascular function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ea, mm Hg/mL</td>
<td>1.30±0.30</td>
<td>1.50±0.41*</td>
<td>1.53±0.43*</td>
</tr>
<tr>
<td>Systemic vascular resistance index, dyne·s·cm⁻¹·m⁻²</td>
<td>2424±521</td>
<td>2703±657*</td>
<td>2588±873*</td>
</tr>
<tr>
<td>Arterial compliance, mL/mm Hg</td>
<td>1.86±0.58</td>
<td>1.45±0.55*</td>
<td>1.41±0.93*</td>
</tr>
<tr>
<td><strong>LV systolic function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ees, mm Hg/mL</td>
<td>1.99±0.59</td>
<td>2.30±0.80*</td>
<td>2.39±0.87*</td>
</tr>
<tr>
<td>Ees·LV mass</td>
<td>319.7±96.4</td>
<td>439.6±163.7*</td>
<td>461.8±209.7*</td>
</tr>
<tr>
<td>Ees·EDV</td>
<td>215.5±60.7</td>
<td>256.3±86.3*</td>
<td>254.0±105.3*</td>
</tr>
<tr>
<td>Ea/Ees</td>
<td>0.68±0.13</td>
<td>0.68±0.17</td>
<td>0.69±0.22</td>
</tr>
<tr>
<td><strong>LV diastolic function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E, m/s</td>
<td>0.660±0.131</td>
<td>0.671±0.169*</td>
<td>0.979±0.347†</td>
</tr>
<tr>
<td>A, m/s</td>
<td>0.561±0.161</td>
<td>0.722±0.203*</td>
<td>0.848±0.267†</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.25±0.38</td>
<td>0.99±0.37*</td>
<td>1.21±0.69†</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>222±33</td>
<td>239±43</td>
<td>208±54†</td>
</tr>
<tr>
<td>e', m/s</td>
<td>0.094±0.035</td>
<td>0.077±0.039*</td>
<td>0.060±0.021†</td>
</tr>
<tr>
<td>τ, ms</td>
<td>35.2±23.4</td>
<td>46.8±26.0*</td>
<td>58.1±14.3*†</td>
</tr>
<tr>
<td>E/e' ratio</td>
<td>7.55±2.29</td>
<td>9.43±3.32*</td>
<td>18.43±9.65†</td>
</tr>
<tr>
<td>LV EDP, mm Hg</td>
<td>16.5±1.4</td>
<td>17.6±2.0*</td>
<td>22.9±5.7†</td>
</tr>
<tr>
<td>β</td>
<td>5.96±0.06</td>
<td>6.05±0.41*</td>
<td>7.09±3.35†</td>
</tr>
<tr>
<td>EDVI₃₀, mL/m²</td>
<td>61.7±11.4</td>
<td>59.7±11.9*</td>
<td>55.7±14.5†</td>
</tr>
<tr>
<td>EDP/EDV, mm Hg/mL</td>
<td>0.16±0.04</td>
<td>0.16±0.05</td>
<td>0.23±0.11†</td>
</tr>
</tbody>
</table>

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 EDVI₃₀) 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.
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 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 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 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. Ahmed et al identified 26 patients with LVH and HFnlEF undergoing echocardiography at their tertiary center and showed that these patients had...
more severe diastolic dysfunction than 39 nonhypertensive control, 14 hypertensive control, and 23 control subjects with LVH but no HF. 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.

In contrast, Kawaguchi et al., 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. 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**

<table>
<thead>
<tr>
<th></th>
<th>CON (n=211)</th>
<th>HTN (n=519)</th>
<th>HFnlEF (n=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDVI, mL/m²</td>
<td>59.4±12.1</td>
<td>60.0±12.7</td>
<td>56.7±14.2†</td>
</tr>
<tr>
<td>Teichholz</td>
<td>63.7±12.8</td>
<td>64.7±14.0</td>
<td>60.8±15.6‡</td>
</tr>
<tr>
<td>Area-length</td>
<td>72.0±13.4</td>
<td>73.4±16.0</td>
<td>68.1±16.6†</td>
</tr>
<tr>
<td>Doppler</td>
<td>1.35±0.32</td>
<td>1.53±0.43*</td>
<td>1.54±0.43*</td>
</tr>
<tr>
<td>Ea, mm Hg/mL</td>
<td>2.12±0.64</td>
<td>2.37±0.83*</td>
<td>2.42±0.88</td>
</tr>
<tr>
<td>Ees, mm Hg/mL</td>
<td>60.5±12.8</td>
<td>60.0±12.3</td>
<td>55.7±14.3‡</td>
</tr>
<tr>
<td>τ, ms</td>
<td>41.3±27.7</td>
<td>49.1±28.0</td>
<td>59.5±13.1†</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th>CON (n=617)</th>
<th>HTN (n=719)</th>
<th>HFnlEF (n=244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ea, mm Hg/mL</td>
<td>1.30±0.30</td>
<td>1.50±0.41*</td>
<td>1.53±0.43*</td>
</tr>
<tr>
<td>Ees, mm Hg/mL</td>
<td>1.99±0.59</td>
<td>2.30±0.80*</td>
<td>2.39±0.87*</td>
</tr>
<tr>
<td>EDVI0, mL/m²</td>
<td>61.7±11.4</td>
<td>59.7±11.9</td>
<td>55.7±14.5‡</td>
</tr>
<tr>
<td>τ, ms</td>
<td>35.2±23.4</td>
<td>46.8±26.0*</td>
<td>58.1±14.3‡</td>
</tr>
</tbody>
</table>

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. Maurer et al 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 HFnIEF, 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) HFnIEF 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, HFnIEF 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 HFnIEF patients despite their more impaired renal function. In fact, stroke volume and cardiac index were lower in HFnIEF 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 HFnIEF population, some patients with HFnIEF 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 HFnIEF.

More recently, Melenovsky et al used noninvasive methods to study 37 HFnIEF 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 HFnIEF 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 higher in HFnIEF, and both Ees and Ea were similarly increased in hypertensive control subjects and HFnIEF patients compared with disease-freecontrols. However, both the HFnIEF and hypertensive groups had much more dramatic LVH than we observed, and although estimated LV diastolic pressures were higher in HFnIEF, 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 HFnIEF, leading the authors to speculate that impaired atrial function also may play a key role in the transition to HFnIEF 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. We also found increased left atrial volume in HFnIEF patients compared with either control group. Melenovsky et al further found that total epicardial cardiac volume was highest in HFnIEF patients and speculated that external forces may contribute to the elevation in filling pressures.

The variable LV geometry patterns observed in HFnIEF patients in our study is noteworthy and consistent with several prior studies, underscoring that despite traditional teaching, concentric LVH or concentric remodeling is not invariably present in HFnIEF. 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. Finally, the similar relative wall thickness and ratio of LV mass to volume observed in HTN and HFnIEF suggest that factors other than chamber geometry additionally mediate increased diastolic stiffness in HFnIEF. Changes in the cardiomyocytes themselves and/or the extracellular matrix may mediate diastolic stiffening and represent potential therapeutic targets in the treatment and/or prevention of HFnIEF.

**Study Limitations**

Our data are purely observational and cannot prove causality. The more impaired diastolic dysfunction in HFnIEF 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 HFnIEF 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 HFnIEF deserves further study.

**Conclusions**

In this large, population-based study, HFnIEF patients had reduced LV volumes and cardiac output compared with hypertensive controls despite more renal impairment. Although HFnIEF patients displayed vascular and LV systolic stiffening compared with normal controls, HFnIEF 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 HFnIEF. 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 was the breakdown of the equations as measured EDP approached 30 mm Hg. This limitation was due to the arbitrary choice of V30 (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 (V15) instead of V30 for cases when measured EDP was >28 mm Hg. V15 was derived from the EDV-normalized curve in the same fashion as V30 (D. Burkoff, MD, PhD, personal communication, 2006). Similar to the original derivations, α and β were then calculated by solving the following simultaneous equations: 

\[ \log \left( \frac{P_m}{15} \right) / \log \left( \frac{V_m}{V_{15}} \right) = \alpha \] 

EDPVR curves derived using V15 and V30 were well correlated at multiple parts of the curves.

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Disclosures
None.

References
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.
Cardiac Structure and Ventricular–Vascular Function in Persons With Heart Failure and Preserved Ejection Fraction From Olmsted County, Minnesota
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In the article by Lam et al, “Cardiac Structure and Ventricular–Vascular Function in Persons With Heart Failure and Preserved Ejection Fraction From Olmsted County, Minnesota,” which appeared in the April 17, 2007, issue of the journal (Circulation. 2007;115:1982–1990), the following corrections should be made.

On page 1982, the β symbol in the equation should be superscripted so that the equation would read, “EDP=αEDV⁺.” This change should also be made to the same equation in the legend to Figure 3 on page 1987.

These errors have been corrected in the current online version of the article. The publisher regrets these errors.

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