Age- and Gender-Related Ventricular–Vascular Stiffening
A Community-Based Study

Margaret M. Redfield, MD; Steven J. Jacobsen, MD, PhD; Barry A. Borlaug, MD; Richard J. Rodeheffer, MD; David A. Kass, MD

Background—Increases in vascular (Ea), ventricular systolic (Ees), and ventricular diastolic (Ed) elastance (stiffness) may contribute to the pathogenesis of heart failure (HF) with preserved ejection fraction (HFnLFE). The prevalence of HFnLEF increases strikingly with age, particularly in women. We hypothesized that ventricular–vascular stiffening may occur with age and be more pronounced in women in the general community.

Methods and Results—In a cross-sectional sample of Olmsted County, Minn, residents ≥45 years old (n=2042), clinical data, Doppler echocardiography, and blood pressure (BP) measurements were obtained. Ea was calculated from stroke volume and systolic BP and indexed to body size (EaI). Ees was calculated by a modified single-beat method using systolic and diastolic BP, stroke volume, ejection fraction, timing intervals, and an estimated normalized ventricular elastance at arterial end diastole. Operant Ed was calculated from Doppler indices reflective of atrial pressures and the diastolic filling volume. EaI, Ees, and Ed all increased with age in men and in women (P<0.0001 for all). Ees increased more steeply with age in women (P=0.002). Adjusted for age, EaI, Ees, and Ed were higher in women than in men (P<0.0001 for all). Findings were similar in those without known or suspected cardiovascular disease (n=623).

Conclusions—In the community, advancing age and female gender are associated with increases in vascular and ventricular systolic and diastolic stiffness even in the absence of cardiovascular disease. We speculate that this combined ventricular–vascular stiffening may contribute to the increased prevalence of HFnLEF in elderly persons and particularly in elderly women.

Key Words: aging ■ diastole ■ epidemiology ■ heart failure ■ hypertension

Epidemiology studies report that 40% to 50% of patients with heart failure (HF) have preserved ejection fraction (EF). The pathogenesis of HF with preserved EF (HFnLEF) remains controversial. Some studies report left ventricular (LV) diastolic dysfunction in patients with HFnLEF. Other studies suggest that vascular and LV end-systolic elastance are increased in HFnLEF and potently contribute to increased volume sensitivity, labile hypertension, and load-dependent diastolic dysfunction without necessitating intrinsic LV diastolic stiffening. Patients with HFnLEF are older than those with HF and reduced EF (systolic HF) and are more often female. Indeed, the prevalence of HFnLEF increases more sharply with age than does systolic HF, especially in women. These observations suggest that ventricular or vascular function might change with age or be different in women, thus predisposing elderly persons and particularly elderly women to HFnLEF. Age-dependent ventricular–vascular stiffening has been reported in a small hospital-based study. Data from the community and analysis of the interplay between gender and age remain notably lacking. Accordingly, the objective of the present study was to determine whether vascular or LV stiffness increased with age or was different in men and women in a large cross-sectional sample of a community. To determine whether age- or gender-related differences are independent of cardiovascular disease, we also analyzed a subset of the community without known or suspected cardiovascular disease.

Methods

Study Setting
In 1990, the population of Olmsted County, Minn, was 106 470 and 96% white. Other characteristics of this community, the unique aspects of community-based research in Olmsted County, and the methods used to sample and characterize the population have been described previously. This study was approved by the Mayo Foundation Institutional Review Board.

Community Sampling, Subject Recruitment, and Enrollment
Using the resources of the Rochester Epidemiology Project, a random sample of Olmsted County residents ≥45 years old on January 1, 1997, was identified. Subjects were enrolled and studied...
over a 3-year period. Of the 4203 subjects invited, 2042 (47%) participated. Characteristics of participants and nonparticipants have been described.10

Medical Record Review
Medical records for each participant were reviewed by trained nurse abstractors using established criteria for hypertension,11 myocardial infarction,12 or HF.13 In addition, a clinical diagnosis of coronary artery disease, atrial fibrillation, transient ischemic attack or stroke, cardiomyopathy, valvular disease, and diabetes mellitus were recorded. Subjects with a diagnosis of hypertension or HF who did not meet established criteria were considered to have possible hypertension or HF. A subset of the study participants without known or suspected cardiovascular disease was defined as those subjects who had none of the above validated or suspected diagnoses, a systolic blood pressure <140 mm Hg at the time of the echocardiogram, and a body mass index <30 kg/m² (n=625).

Doppler Echocardiography
All echocardiograms were performed by 1 of 3 registered diagnostic cardiac sonographers with the same echocardiographic instrument (HP-2500) according to a standardized protocol and interpreted by a single echocardiologist (M.M.R.) who was masked to any clinical data. All parameters were measured in triplicate and averaged. M-mode echocardiograms were performed as previously described.14 Systolic and diastolic blood pressure was measured by automated cuff at the time of the M-mode echocardiogram. The time from the peak of the QRS to the onset and to the cessation of aortic flow measured by continuous-wave Doppler was used to screen for hemo- dynamically significant (more than moderate regurgitation or more than mild stenosis or prosthetic valve) valve disease. We identified 86 patients (4.2%) with valve disease. These patients were included in the analysis of the entire population but excluded from the analysis of subjects without cardiovascular disease.

In each subject, measurement of EF by M-mode, quantitative two-dimensional, and semiquantitative two-dimensional methods was performed as previously described.15 Because values for EF by these 3 methods were highly correlated and because the semiquan- titative method was available in >99% of participants, it was used for this analysis.

End-systolic pressure (Pes) was estimated as systolic pressure ×0.90. Previous studies have demonstrated that this estimation and directly measured Pes correlate very well in patients of widely varied ages and vascular properties.15,16 Stroke volume (SV) was measured from the LV outflow tract diameter and the pulse wave Doppler signal as previously described17 and was used to calculate cardiac output (SV × heart rate) and cardiac index (cardiac output/body surface area [BSA]). The effective arterial elastance index (EaI) was estimated as Pes/SV normalized to BSA. This index models the arterial system as if it were an elastance receiving ejected volume from the heart and is affected principally by systemic vascular resistance, heart rate, and central aortic stiffness. EaI correlates very well with measures of arterial load derived from aortic input impedance data.15 Because SV (and input impedance) varies directly with body size, Ea was adjusted for BSA to better reflect differences in arterial properties with age and between the genders adjusted for differences in body size.

End-diastolic LV volumes (LVEDVs) were calculated by use of the Teichholz formula.18 Systemic vascular resistance index (SVRI) was estimated as [(mean arterial pressure/cardiac index) ×80]. End-systolic wall stress (σes, g/cm²) was estimated as [(Pes) × (Des)/1.35]/[(4 × hes) × (1 + hes/Des)], where Des is the end-systolic LV dimension and hes is the average of the septal and posterior wall end-systolic wall thickness.18 Fractional shortening (FS) was calculated as [(Ded − Des)/Ded]. The ratio of FS to σes (stress-corrected FS) was used as a load-independent measure of systolic performance. End-systolic elastance (Ees) was calculated by the modified single-beat method using arm-cuff pressures, echo Doppler SV, pre-ejection and total systolic periods, EF, and an estimated normalized ventricular elastance at arterial end-diastole as previously described and validated against invasive assessment.4,7,16

Assessment of Diastolic Function
Pulsed-wave Doppler examination of mitral inflow as well as Doppler tissue imaging of the lateral mitral annulus was performed in each subject.9,19–21 To provide a continuous variable that might estimate diastolic elastance (Ed), the ratio of the mitral inflow early diastolic filling velocity (E) to the mitral annular early diastolic velocity measured by tissue Doppler (E′) was used as an estimation of mean left atrial pressure (E/E′).20,22,23 Operant Ed was then estimated as E/E′ divided by the volume of filling during diastole, assuming the absence of significant aortic regurgitation (SV). The E′ was used as a measure of the speed of LV relaxation, because E′ has been shown to correlate inversely with the time constant of isovolumic relaxation and is considered relatively preload-independent.20,22

Plasma Brain Natriuretic Peptide and Clinical Function Assessment
Plasma brain natriuretic peptide (BNP) levels were measured on the same day as the echocardiogram, as previously described.24 The Goldman Specific Activity Scale (GSAS) was administered to all subjects as part of a questionnaire and applies a set of structured questions to assess the interviewee’s ability to perform specific commonly performed daily activities the metabolic exercise equivalents of which have been previously quantified.25 On the basis of the algorithm by Goldman, responses to the GSAS are used to classify subjects on a 4-point ordinal scale: class I, can perform at least 7 metabolic equivalents of exercise; class II, can perform at least 5 but fewer than 7 metabolic equivalents; class III, can perform at least 2 but fewer than 5 metabolic equivalents; and class IV, cannot perform more than 2 metabolic equivalents. No participants were classified as class IV.

Statistical Methods
The association between indices of cardiovascular function or structure and age was investigated with linear regression and linear least-squares regression with adjustment for both age and gender. An interaction term with age and gender was also evaluated to determine whether associations with age differed between the genders. Because the relationship between indices and age frequently varied by gender, the association with gender was illustrated by the value of the parameter calculated from the regression equation at 2 different ages in men and in women.

Results

Study Participant Characteristics
Characteristics of the study participants and the subgroup without known cardiovascular disease are provided in Table 1.

Age- and Gender-Related Alterations in Vascular Function
EaI, Pes, and pulse pressure increased with age (Figure 1; Table 2) in both men and women in the community. The association of Pes and pulse pressure with age was steeper, and the association of EaI with age tended to be steeper in women. Adjusted for age, EaI and pulse pressure were higher in women than in men, whereas Pes was similar in men and women. EaI is reflective of both mean resistive and pulsatile load and is influenced by heart rate. Although EaI increased with age and was higher in women, SVRI did not vary with age and was higher in men, indicating that age and gender differences in EaI were a result of differences in either pulsatile load or heart rate. When adjusted for potential
differences in heart rate, EaI still increased with age and was higher in women (EaI = 0.081 + (0.006 × age) + (0.004 × heart rate) – 0.107 if male; r = 0.55; P < 0.0001 for age, heart rate, and gender). The lack of altered mean resistive load and the independent effect of age and gender when adjusted for heart rate suggest that age- and gender-dependent vascular changes are principally reflective of altered oscillatory properties (i.e., stiffness). The association of arterial elastance with age and female gender was still noted when not indexed to body size (data not shown).

Similar results were observed in persons without cardiovascular disease (Table 3). EaI increased similarly with age in men and women. EaI and pulse pressure were higher in women, whereas Pes was higher in men when adjusted for age. As in the total study population, SVRi did not vary with age and was higher in men, whereas pulse and end-systolic pressures increased with age and more steeply so in women. Increases in EaI with age and in women were independent of changes in heart rate (EaI = 0.188 + (0.003 × age) + (0.006 × heart rate) – 0.108 if male; r = 0.60; P < 0.0004 for age, heart rate, and gender).

**Age- and Gender-Related Alterations in Ventricular Systolic Function**

Ees increased with age in men and women (Figure 2; Table 2). Stress-corrected FS increased with age in women but not men. Both measures of systolic function increased more steeply with age in women than men and were higher in women after adjustment for age.

Arterial and end-systolic elastances are coupled to optimize cardiovascular performance and efficiency. Ea and Ees
were strongly correlated both in the entire study population ($r=0.72, P<0.0001$) and in those without cardiovascular disease ($r=0.75, P<0.0001$). As expected, Ees was inversely related to chamber size (LVEDV) in men ($r=-0.171, P<0.0001$) and in women ($r=-0.266, P<0.0001$). To determine whether gender- or age-related differences in Ees were attributable to differences in chamber size, Ees was normalized to LVEDV ($Ees\times LVEDV$) and the association of indexed Ees to age and gender was retested. $Ees\times LVEDV$ also increased with age ($Ees\times LVEDV=147+1.55\times age; r=0.19; P<0.0001$); however, when gender was added to this model, it was not significant ($P=0.55$).

### Table 2. Effect of Age and Gender on Vascular and Ventricular Structure and Function in the Entire Population (n=2042)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men</th>
<th>Women</th>
<th>Age–Gender Interaction*</th>
<th>Men</th>
<th>Women</th>
<th>Men vs Women†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial elastance, Eal, mm Hg · mL/m²</td>
<td>0.28 &lt;0.0001</td>
<td>0.28 &lt;0.0001</td>
<td>0.09</td>
<td>0.61</td>
<td>0.83</td>
<td>0.73</td>
<td>0.97</td>
</tr>
<tr>
<td>End-systolic pressure, mm Hg</td>
<td>0.33 &lt;0.0001</td>
<td>0.42 &lt;0.0001</td>
<td>&lt;0.0001</td>
<td>116</td>
<td>113</td>
<td>126</td>
<td>129</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>0.43 &lt;0.0001</td>
<td>0.47 &lt;0.0001</td>
<td>0.002</td>
<td>52</td>
<td>56</td>
<td>65</td>
<td>72</td>
</tr>
<tr>
<td>Systemic vascular resistance index, dyne · s · cm⁻² · m²</td>
<td>0.03 0.41 0.02 0.54</td>
<td>0.81</td>
<td>2657</td>
<td>2453</td>
<td>2690</td>
<td>2473</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>End systolic elastance, Ees, mm Hg/mL</td>
<td>0.21 &lt;0.0001</td>
<td>0.28 &lt;0.0001</td>
<td>0.002</td>
<td>1.86</td>
<td>2.21</td>
<td>2.05</td>
<td>2.58</td>
</tr>
<tr>
<td>Stress-corrected fractional shortening, cm²/g</td>
<td>0.03 0.46 0.15 &lt;0.0001</td>
<td>0.0002</td>
<td>0.0083</td>
<td>0.0094</td>
<td>0.0081</td>
<td>0.0106</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vascular ventricular coupling, Ea/Ees</td>
<td>−0.02 0.64 −0.08 0.04</td>
<td>0.08</td>
<td>0.70</td>
<td>0.69</td>
<td>0.72</td>
<td>0.68</td>
<td>0.001</td>
</tr>
<tr>
<td>Left atrial pressure, E/A′</td>
<td>0.39 &lt;0.0001</td>
<td>0.38 &lt;0.0001</td>
<td>0.66</td>
<td>6.06</td>
<td>6.63</td>
<td>7.85</td>
<td>8.53</td>
</tr>
<tr>
<td>LV relaxation, E′, m/s</td>
<td>−0.48 &lt;0.0001</td>
<td>−0.54 &lt;0.0001</td>
<td>0.31</td>
<td>0.11</td>
<td>0.11</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Diastolic elastance, Ed</td>
<td>0.38 0.0003 0.34 &lt;0.0001</td>
<td>0.72</td>
<td>0.065</td>
<td>0.085</td>
<td>0.086</td>
<td>0.106</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-diastolic volume/BSA, mL/m²</td>
<td>0.13 0.0003 0.00 0.99</td>
<td>0.0003</td>
<td>62</td>
<td>60</td>
<td>66</td>
<td>60</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass/BSA, g/m²</td>
<td>0.21 &lt;0.0001</td>
<td>0.38 &lt;0.0001</td>
<td>0.173</td>
<td>1.00</td>
<td>0.87</td>
<td>1.12</td>
<td>1.02</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.15 0.0005 0.34 &lt;0.0001</td>
<td>0.0001</td>
<td>0.413</td>
<td>0.399</td>
<td>0.434</td>
<td>0.456</td>
<td>0.340</td>
</tr>
</tbody>
</table>

*P value indicates whether the association of parameters with age differs in men and women.
†P value indicates whether parameter varies between genders independent of age effect.
‡Pearson’s correlation coefficients.

### Table 3. Effect of Age and Gender on Vascular and Ventricular Structure and Function in Those Without Cardiovascular Disease (n=623)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men</th>
<th>Women</th>
<th>Age–Gender Interaction*</th>
<th>Men</th>
<th>Women</th>
<th>Men vs Women†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial elastance, Eal, mm Hg · mL/m²</td>
<td>0.18 0.004 0.13 0.02</td>
<td>0.71</td>
<td>0.60</td>
<td>0.83</td>
<td>0.67</td>
<td>0.89</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>End-systolic pressure, mm Hg</td>
<td>0.20 0.0008 0.31 &lt;0.0001</td>
<td>0.04</td>
<td>107</td>
<td>103</td>
<td>113</td>
<td>113</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>0.27 &lt;0.0001</td>
<td>0.34 &lt;0.0001</td>
<td>0.02</td>
<td>49</td>
<td>52</td>
<td>59</td>
<td>67</td>
</tr>
<tr>
<td>Systemic vascular resistance index, dyne · s · cm⁻² · m²</td>
<td>0.01 0.82 −0.04 0.50</td>
<td>0.56</td>
<td>2479</td>
<td>2339</td>
<td>2497</td>
<td>2301</td>
<td>0.0005</td>
</tr>
<tr>
<td>End systolic elastance, Ees, mm Hg/mL</td>
<td>0.16 0.0008 0.23 &lt;0.0001</td>
<td>0.14</td>
<td>1.74</td>
<td>2.13</td>
<td>1.91</td>
<td>2.46</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stress-corrected fractional shortening, cm²/g</td>
<td>0.18 0.0007 0.27 &lt;0.0001</td>
<td>0.13</td>
<td>0.0087</td>
<td>0.0095</td>
<td>0.0102</td>
<td>0.0121</td>
<td>0.007</td>
</tr>
<tr>
<td>Vascular ventricular coupling, Ea/Ees</td>
<td>−0.02 0.76 −0.19 0.0005</td>
<td>0.04</td>
<td>0.69</td>
<td>0.68</td>
<td>0.69</td>
<td>0.62</td>
<td>0.03</td>
</tr>
<tr>
<td>Left atrial pressure, E/A′</td>
<td>0.42 &lt;0.0001</td>
<td>0.46 &lt;0.0001</td>
<td>0.71</td>
<td>5.72</td>
<td>6.05</td>
<td>7.47</td>
<td>7.93</td>
</tr>
<tr>
<td>LV relaxation, E′, m/s</td>
<td>−0.51 &lt;0.0001</td>
<td>−0.54 &lt;0.0001</td>
<td>0.72</td>
<td>0.12</td>
<td>0.12</td>
<td>0.08</td>
<td>0.09</td>
</tr>
<tr>
<td>Diastolic elastance, Ed</td>
<td>0.41 &lt;0.0001</td>
<td>0.39 &lt;0.0001</td>
<td>0.72</td>
<td>0.063</td>
<td>0.081</td>
<td>0.084</td>
<td>0.105</td>
</tr>
<tr>
<td>LV end-diastolic volume/BSA, mL/m²</td>
<td>−0.09 0.16 −0.12 0.04</td>
<td>0.89</td>
<td>62</td>
<td>61</td>
<td>59</td>
<td>58</td>
<td>0.28</td>
</tr>
<tr>
<td>LV mass/BSA, g/m²</td>
<td>0.17 0.01 0.18 0.002</td>
<td>0.90</td>
<td>96</td>
<td>83</td>
<td>103</td>
<td>90</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.28 &lt;0.0001</td>
<td>0.29 &lt;0.0001</td>
<td>0.61</td>
<td>0.412</td>
<td>0.389</td>
<td>0.448</td>
<td>0.434</td>
</tr>
</tbody>
</table>

Symbols as in Table 2.
In those without cardiovascular disease, both Ees and stress-corrected FS increased similarly with age in men and in women (Table 3). As in the total study population, both indices were higher in women after adjustment for age. Furthermore, Ees was inversely related to LVEDV in men ($r=-0.193$, $P=0.003$) and in women ($r=-0.312$, $P<0.0001$). When indexed to chamber size ($\text{Ees} \times \text{LVEDV}$), Ees was associated with age ($\text{Ees} \times \text{LVEDV}=172+0.77 \times \text{age}; r=0.11; P<0.0001$). When gender was added to this model, it was not significant ($P=0.26$).

Age- and Gender-Related Alterations in Arterial Ventricular Coupling

Arterial ventricular coupling (Ea/Ees) did not change with age in men but declined slightly with age in women both in the entire study population and in those without cardiovascular disease. Adjusted for age, the coupling ratio was lower in women than in men (Tables 2 and 3).

Age- and Gender-Related Alterations in Ventricular Diastolic Function

Mean left atrial pressures ($\text{E/E}'$) and Ed increased similarly with age in men and women in the entire study population (Figure 3; Table 2). Both indices were greater in women than in men when adjusted for age. Ed was correlated with Ees ($r=0.43$, $P<0.0001$). As with Ees, Ed was inversely related to LVEDV in men ($r=-0.125$, $P=0.003$) and in women ($r=-0.197$, $P<0.0001$). When Ed was indexed for LVEDV ($\text{Ed} \times \text{LVEDV}$), there was still a positive association between Ed and age ($\text{Ed} \times \text{LVEDV}=2.80+0.11 \times \text{age}; r=0.27; P<0.0001$). When gender was added to this model, it was significant ($\text{Ed} \times \text{LVEDV}=2.89+0.08 \times \text{age} -0.23$ if male; $r=0.28; P<0.0001$ for age and $P=0.02$ for gender), showing somewhat higher indexed Ed in women. LV relaxation ($E'$) declined similarly with age in men and in women and was similar in men and in women when adjusted for age.

In the group with no cardiovascular disease (Table 3), findings were similar to those observed in the general community. Mean left atrial pressures and Ed increased similarly with age in men and women and were higher in women than in men when adjusted for age. Ed was inversely associated with LVEDV in women ($r=-0.219$, $P=0.003$) but not in men ($r=-0.129$, $P=0.08$). When indexed to LVEDV ($\text{Ed} \times \text{LVEDV}$), Ed was associated with age ($\text{Ed} \times \text{LVEDV}=3.04+0.09 \times \text{age}; r=0.27; P<0.0001$). When gender was added to this model, it was significant ($\text{Ed} \times \text{LVEDV}=3.30+0.08 \times \text{age} -0.41$ if male; $r=0.31; P<0.0001$ for age and $P=0.001$ for gender). LV relaxation decreased similarly with age in men and in women and was similar in men and in women when adjusted for age.

Age- and Gender-Related Alterations in Ventricular Structure

In the entire study population, the LV diastolic volume indexed to BSA increased with age in men but not in women
and was smaller in women after adjustment for age (Figure 4; Table 2). LV mass index increased similarly with age in men and in women and was higher in men after adjustment for age. Relative wall thickness increased with age in both men and women. Similar findings were observed in those without cardiovascular disease (Table 3).

**Association of Increased Arterial and Ventricular Elastance With Plasma BNP and Functional Status**

Plasma BNP concentration and the percentage of subjects with functional impairment (functional class II or III as defined by the GSAS) were compared in subjects with values for EaI, Ees, and Ed that were less than or greater than the 97.5th percentile in subjects without cardiovascular disease. Compared with those without elevated EaI, Ees, or Ed, subjects with increased vascular or ventricular elastance had higher plasma BNP concentrations and more functional impairment (Table 4).

**Discussion**

This study represents the largest and the first community-based analysis of indices reflecting combined vascular–ventricular stiffness to date. We confirm previous studies showing that arterial stiffening increases with age, is higher in women than in men, and is observed in subjects without cardiovascular disease. The accompanying age-dependent rise in both ventricular systolic and diastolic stiffness observed here and their correlation with vascular stiffening supports an earlier invasive study in a small hospital-based cohort. However, the present findings importantly extend that study by clarifying gender differences, age–gender interactions, and the contribution of age and gender to LV stiffening after adjustment for heart size. Because combined vascular–ventricular stiffening was most apparent in that segment of the community most at risk for HFnlEF, a role for cardiovascular stiffening in the pathogenesis of HFnlEF is supported.

**Association of Altered Vascular Function With Age and Gender**

Previous studies using a variety of indices have established that large-artery stiffness increases with age, is higher in women, and increases with age even in the absence of vascular disease or risk factors. The present findings confirm and extend these studies by demonstrating that EaI, a valuable means to index net ventricular afterload that combines mean and oscillatory components of the arterial load, also increases with age and is higher in women in a large cross-sectional sample of the adult community. EaI incorporates resistance, pulsatile load, and systolic and diastolic time intervals, which are influenced by heart rate. Elevated blood pressure related to peripheral vasoconstriction increases aortic stiffness. Thus, it was important to note that SVRi did not increase with age and was not increased in women. These data suggest that age- and gender-related differences in EaI are a result of increases in oscillatory load, a concept further supported by the observed increases in pulse pressure with age and in women. The differences in pulse pressure with age and gender noted here are consistent with some but not all previous studies. The larger sample size, community setting, and age distribution may have influenced our ability to demonstrate these differences. Multiple mechanisms have been proposed to explain age-dependent vascular stiffening, including alterations in endothelial function, structural protein composition, collagen cross-linking, geometric changes, and neurohumoral signaling. The cause of gender differences in vascular stiffening is unclear, although both the present and earlier data indicate that this is not simply a matter of differences in body size and vasculature length.

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**TABLE 4. Association of Elevated Arterial or Ventricular Systolic or Diastolic Elastance With Plasma BNP and Functional Status**

<table>
<thead>
<tr>
<th></th>
<th>Arterial Elastance, EaI</th>
<th>End-Systolic Elastance, Ees</th>
<th>Diastolic Elastance, Ed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1.23 (n=1662)</td>
<td>≥1.23 (n=109)</td>
<td>&lt;0.13 (n=1428)</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>47±77</td>
<td>98±132</td>
<td>42±66</td>
</tr>
<tr>
<td>Functional status II or III</td>
<td>14.30%</td>
<td>30.30%</td>
<td>12.70%</td>
</tr>
</tbody>
</table>

n indicates number of subjects.
Association of Systolic Performance Indices With Age and Gender

Hearts coupled to a stiffer vascular system are subjected to higher systolic stresses as well as wider pulse pressures that can adversely influence the regulation of coronary flow. To maintain optimal interaction with the arterial system, the LV itself must develop greater systolic stiffness. A previous invasive study reported tandem increases in Ees and Ea with aging, and the present analysis supports this observation, but in a much larger, community-based population. Gender differences were not found in the earlier investigation, most likely a reflection of the small sample size (57 subjects, with 17 women). In this regard, both the findings that Ees was increased in women and that Ees increased more steeply with age in women than in men are novel and are supported by similar findings with an additional index of systolic performance, stress-corrected FS. The similarity of findings in subjects free of cardiovascular disease suggests that the enhanced systolic performance observed in women and with aging is not because of a lower prevalence of cardiovascular disease.

The chronic changes in LV systolic stiffness that couple with changes in vascular stiffness may represent cardiovascular adaptations to maintain optimal ventricular–vascular matching and thus optimal cardiac performance. Whether this is mediated by increases in inotropic state or by structural remodeling such as those caused by hypertrophy, concentric remodeling, or fibrosis cannot be ascertained here, but altered chamber geometry with age and between genders seems to play a role. Interestingly, the present analysis found concordant changes in the stress-corrected FS. This ratio, however, is also dependent on chamber geometry and cannot separate intrinsic inotropy from structural remodeling. However, the presence of concomitant diastolic LV stiffening, which is consistent with previous data, does suggest some role for structural changes.

Although vascular–ventricular coupling helps to maintain SV and mechanical efficiency, increases in Ees may have adverse effects. Increases in Ees result in increased sensitivity of systolic pressure to changes in volume. Together, increases in arterial and systolic stiffness promote load-induced impairment in LV relaxation. Thus, age-related vascular–ventricular stiffening could contribute to exercise intolerance and could predispose to HFnlEF as recently reported. Although longitudinal studies and studies in patients with incident HFnlEF will be needed to determine the role of vascular–ventricular stiffening in the pathogenesis of HFnlEF, the higher plasma BNP concentrations and more severe functional impairment observed in subjects with elevated Eal, Ees, and Ee lend some support to this concept.

Association of Diastolic Function Parameters With Age and Gender

Our finding that E’ , a preload-independent index of LV relaxation, decreased with age is consistent with studies reporting that other Doppler indices reflective of the speed of LV relaxation decrease with increasing age. Whereas the concept of age-dependent impairment in relaxation is consistent with animal studies, a small study that measured the time constant of isovolumic relaxation invasively in humans did not find an association with age. Subsequent studies using MRI have reported conflicting data with studies refuting and supporting age-related decreases in LV relaxation.

Novel to this study is our observation that estimates of atrial pressure and Ed increased with age and were higher in women. The association of diastolic and systolic LV stiffening observed here is consistent with previous invasive studies and with the concept of time-varying elastance, which mandates that increases in Ees are coupled to increases in Ed. Although E/E ’ is well established to correlate well with pulmonary capillary wedge pressure, use of E/E’/SV as an index of Ed has not been reported previously. However, use of a continuous variable to characterize operant Ed offers advantages in examining the relationship between age and gender and Ed. Traditional Doppler indices reflective of increased diastolic stiffness, such as deceleration time and E/A ratio, are limited by directionally opposite changes, with changes in relaxation and stiffness limiting their value in populations with variable relaxation and potentially concomitant changes in relaxation and diastolic stiffness with age.

Association of Ventricular Structure Indices With Age and Gender

Because increases in arterial stiffness with age and female gender may stimulate LV remodeling and because structural changes may contribute to the increases in Ees and Ed, we examined the relationship between LV age and gender and chamber geometry. LV volume indexed to BSA increased modestly with age in men in the entire population but was not associated with age in women or in men without cardiovascular disease. As previously reported, LV mass index increased with age in the community and in those without cardiovascular disease. This appeared to represent concentric remodeling, because relative wall thickness increased with age, most dramatically in women. These findings are consistent with the recognized adverse effects of age-related arterial stiffening even in the absence of clinical hypertension. We speculate that other aspects of remodeling, such as LV fibrosis, may vary with age and between genders and contribute to the changes in systolic and diastolic elastance. Indeed, in elderly hypertensive dogs in which Ees was increased compared with young nonhypertensive dogs, Ees correlated more closely with the degree of LV fibrosis than the degree of LV hypertrophy.

Strengths and Potential Limitations

This study is strengthened by the large sample size, community-based setting, and comprehensive assessment of conventional and novel indices of vascular and ventricular function and ventricular structure. Limitations include the cross-sectional nature of the data, which limits conclusions about causality; the lack of data in persons of diverse ethnic backgrounds or in younger persons; and the noninvasive nature of the indices assessed.

We acknowledge that to assess effective arterial and ventricular systolic and diastolic elastances without using...
invasive measures of pressure and simultaneous volume, one must make some simplifying assumptions. However, this study could not have been performed by use of an invasive approach. Importantly, each of the assumptions made was based on previously published invasive validation data as outlined above. Furthermore, these assumptions are not systematically biased so that they would predict the age/gender disparities that are reported.

The subjects with HF may not be representative of most patients with HF because of the impact of “survival bias” in studies such as these. Indeed, the diagnosis of HF preceded the study echo by an average of 4.8 ± 4.0 years. This factor, along with the very small number of subjects with HFnEF, limits our ability to test the role of altered vascular and ventricular elastance in contributing to the pathogenesis of HFnEF. Although higher plasma BNP concentrations and more severe functional impairment assessed by the GSAS in subjects with increased EaI, Ees, and Ed suggest that increases in vascular and ventricular stiffness predispose to HF, studies in patients with incident HF and longitudinal study of subjects with increased elastance are needed to test this hypothesis. Participation bias may also affect the observed association between age and gender and indices of vascular and ventricular function. Cardiovascular medications (including diuretics) were used by 39.5% of subjects, and these medications may alter indices of vascular and ventricular function.

Conclusions
The epidemiology of HFnEF is unique in the potent association of advanced age and female gender with development of HFnEF. Paradigms defining the pathogenesis of HFnEF must account for the unique demographic profile of afflicted individuals. Because increased vascular and LV systolic and diastolic stiffness are purported to contribute to the pathogenesis of HFnEF, the present findings may provide insight into the natural history of HFnEF by documenting increased vascular and ventricular stiffness in those persons most at risk.

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Margaret M. Redfield, Steven J. Jacobsen, Barry A. Borlaug, Richard J. Rodeheffer and David A. Kass

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