Longitudinal Changes in Left Ventricular Stiffness
A Community-Based Study

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Background—Cross-sectional studies suggest that left ventricular (LV) and arterial elastance (stiffness) increase with age, but data examining longitudinal changes within human subjects are lacking. In addition, it remains unknown whether age-related LV stiffening is merely a reaction to arterial stiffening or caused by other processes.

Methods and Results—Comprehensive echo-Doppler cardiography was performed in 1402 subjects participating in a randomly selected community-based study at 2 examinations separated by 4 years. From this population, 788 subjects had adequate paired data to determine LV end-systolic elastance (Ees), end-diastolic elastance (Eed), and effective arterial elastance. Throughout 4 years, blood pressure, arterial elastance, and LV mass decreased, coupled with significantly greater use of antihypertensive medications. However, despite reductions in arterial load, Ees increased by 14% (2.10±0.67–2.26±0.70 mm Hg/mL; P<0.0001) and Eed increased by 8% (0.13±0.03–0.14±0.04 mm Hg/mL; P<0.0001). Increases in Eed were greater in women than men, whereas Ees changes were similar. Age-related increases in Ees and Eed were correlated with changes in body weight, but were similar in subjects with or without cardiovascular disease. Changes in Ees were correlated with Eed (r=0.5; P<0.0001), but not with other measures of contractility, indicating that the increase in Ees was reflective of passive stiffening rather than enhanced systolic function.

Conclusions—Despite reductions in arterial load with medical therapy, LV systolic and diastolic stiffness increase over time in humans, particularly in women. In addition to blood pressure control, therapies targeting load-independent ventricular stiffening may be effective to treat and prevent age-associated cardiovascular diseases, such as heart failure. (Circ Heart Fail. 2013;6:944-952.)

Key Words: aging ■ arterial stiffness ■ heart failure ■ hemodynamics ■ ventricular function

Cross-sectional data suggest that ventricular and arterial stiffness increase with normal aging. This phenomenon is thought to contribute to or underlie multiple age-related cardiovascular diseases, including isolated systolic hypertension, stroke, and heart failure with preserved ejection fraction (HFpEF). Although ventricular-arterial stiffness increases with age in cross-sectional analyses, longitudinal data examining within-subject changes over time are lacking. Furthermore, it remains unclear how much of the age-related changes in ventricular properties are because of chronic load alteration (eg, arterial stiffening, systemic hypertension) versus other changes that may be independent of load.

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It is widely assumed that increased ventricular stiffness with age is driven by arterial stiffening, as suggested by acute load-altering experiments and trials documenting improvements in ventricular structure and function with blood pressure (BP) control. An alternative hypothesis is that the heart and arteries stiffen in parallel with age in a partially independent fashion because of shared exposures to age-related stresses, such as profibrotic and proinflammatory milieu, cellular senescence, and oxidative stress. Improved understanding of serial changes in ventricular-arterial properties with aging is crucial to the development of therapies to prevent and treat age-related diseases associated with ventricular-arterial stiffening, such as HFpEF.

Accordingly, we aimed to examine longitudinal changes in ventricular-arterial stiffness over 4 years among subjects participating in the prospective, community-based Olmsted County Heart Function Study, contrasting changes in ventricular-arterial stiffness with alterations in BP, and comorbidity burden during the study period.

Methods

Study Population

In 1997, a random sample of individuals residing in Olmsted County, aged ≥45 years, was identified by applying a sampling fraction of...
7% within 5-year sex- and age-specific strata. A total of 4203 persons were invited and 2042 participated in examination 1 (1997–2000), which consisted of physical examination, echocardiography, and medical record abstraction. Comparison of invited participants with invited nonparticipants disclosed no difference in the prevalence of cardiovascular disease, diabetes mellitus, or Charlson index.11 Four years later all participants were invited to return and 1402 participated in examination 2 (2001–2004). Diabetes mellitus history was based on physician diagnosis and treatment. Myocardial infarction and hypertension were diagnosed according to criteria from the World Health Organization and the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, respectively. Some clinical and echocardiographic data from this population have been reported previously,2–11 but the current study findings on ventricular-arterial stiffening over time have not been reported. The institutional review boards of Mayo Clinic and Olmsted Medical Center approved this study. Participants provided written informed consent for evaluation and medical record follow-up.

Healthy Subject Subset
Subjects were identified who had no hypertension, coronary artery disease, heart failure, or diabetes mellitus, and who were taking no cardiovascular medications at examinations 1 and 2. These subjects were considered to be free of apparent cardiovascular disease and were evaluated separately to control to provide an assessment of age-related changes in cardiovascular stiffening independent of potential effects of antihypertensive therapies or other cardiovascular medications.

Assessment of Left Ventricular Structure and Function
Comprehensive echocardiographic assessment was performed by registered diagnostic cardiac sonographers using standardized instruments and techniques as previously described.2–11 Examination 1 and 2 echocardiograms were performed by the same 3 sonographers and reviewed by 2 cardiologists (B.L.K. and M.M.R.), each of whom was blinded to clinical and examination 1 echocardiogram findings. Ventricular dimensions, wall thickness, and chamber volumes were determined in triplicate from 2-dimensional echocardiography. Left ventricular (LV) EF was determined by the biplane Simpson method. LV stroke volume (SV) was determined from pulse wave Doppler of the LV outflow tract. Cardiac output was determined as the product of SV and heart rate. Brachial BP was determined by sphygmomanometry. End-systolic pressure (ESP) was determined from the product of 0.9×systolic BP.

LV diastolic function was assessed by pulse wave Doppler examination of mitral inflow (E, A velocities, E/A ratio) and tissue Doppler examination of septal mitral anular velocities (e’ velocity). The ratio of echo-Doppler and tissue-Doppler early diastolic velocities (E/e’) was used to estimate LV end-diastolic pressure (LVEDP) as previously validated (≥11.96+0.596E/e’). Operating LV end-diastolic chamber stiffness (end-diastolic elastance [Eed]) was estimated by the ratio of LVEDP and end-diastolic volume.16 LV end-systolic elastance (Ees) was determined by the single-beat technique of Chen et al on the basis of measured SV, EF, BP, and systolic time intervals as previously reported.2–14 To adjust for differences in LVEDP at the 2 examinations, Ees was also determined using developed pressure during systole (DP=ESP−EEDP) in place of ESP. This is referred to as Ees(DP). In addition to contractile state, passive stiffness and EDP, Ees may be influenced by chamber remodeling and geometry. Accordingly, Ees was also normalized for the LV mass/volume ratio as previously described,16 and alternative load-independent measures of contractility were determined, including LV stroke work (SW=DP×SV) divided by end-diastolic volume, and single-beat preload recruitable SW.37 LV endocardial fractional shortening was plotted against circumferential endocardial wall stress to provide another independent assessment of LV contractility at examinations 1 and 2, as previously described.11

Assessment of Arterial Function and Ventricular-Arterial Interaction
Effective arterial elastance (Ea), a measure of total arterial load that incorporates both mean and pulsatile components, was determined as ESP/SV. Systemic vascular resistance (=mean BP×80/cardiac output) and total arterial compliance (=SV/pulse pressure) were determined as additional measures of arterial load. The ratio Ea/Ees was used to assess ventricular-arterial coupling.16

Statistical Methods
Data are expressed as mean±SD or number (percentage). Categorical variables were compared by the χ² test, and continuous variables were log transformed as necessary and compared using 1-way ANOVA. Longitudinal changes in categorical variables were assessed with McNemar test and continuous variables by paired t test or Wilcoxon signed-rank test. Analyses were performed with JMP version 8.0 (SAS Institute, Cary, NC). Analyses were 2 sided, and significance judged at P<0.05.

Results
Of 1402 Olmsted County residents participating in examination 2, 788 had complete echocardiographic data to allow for assessment of Ees and Ea at both examinations. The mean age of the subjects at examination 1 was 60 years and 48% were men (Table 1). Obesity and hypertension were present in roughly one quarter of patients and 40% were treated with cardiovascular medicines. Two hundred forty nine of the 788 subjects were free of cardiovascular disease at examinations 1 and 2.

Examination 2 was performed 4.0±0.3 years after examination 1. Body mass index increased slightly at examination 2 as did the prevalence of comorbidities, including hypertension, diabetes mellitus, and coronary artery disease. The use of antihypertensive agents, including angiotensin antagonists, β-blockers, diuretics, and calcium channel blockers, increased over time, with the proportion of patients receiving any cardiovascular medicine increasing from 40% to 55% at examination 2.

From examinations 1 and 2, systolic, diastolic, and mean BPs decreased by 4.5±18.4, 4.1±10.3, and 4.3±11.3 mm Hg, respectively (all P<0.0001; Table 1; Figure 1). In contrast, pulse pressure did not change (+0±14 mm Hg; P=0.4). Systolic BP was elevated (>140 mm Hg) in 232 subjects (29%) at examination 1 and 157 subjects (20%) at examination 2 (P<0.0001). Systemic BP reduction was coupled with reduction in LV mass, with no change in LV end-diastolic volume or EF (Table 2). LV diastolic function worsened from examinations 1 and 2 as reflected by increased E and A velocities, lower mean E/A ratio, and increased left atrial volume. LV early diastolic relaxation velocity (e’) decreased by 11% (~1±5 cm/s; P<0.0001), whereas estimated LV filling pressures (E/e’ ratio) increased by 27% (+2.3±4.8; P<0.0001). Estimated LV operant diastolic stiffness (Eed) increased by 8% (+0.01±0.04; P<0.0001) in association with an increase in LVEDP.

From examinations 1 and 2, Ea decreased slightly but significantly, consistent with net reduction in arterial load (Table 2; Figure 1). This was related exclusively to reduction in mean systemic vascular resistance because total arterial compliance was unchanged and heart rate (which varies
directly with $E_a$) increased slightly. Despite reductions in BP and wall stress, and regression in LV mass, $E_{es}$ increased by 14% ($+0.17±0.71$ mmHg/mL; $P<0.0001$) during the 4-year interval from examinations 1 and 2. Age-related increases in $E_{es}$ were independent of the elevation in filling pressures, as evidenced by the increase in $E_{es}/LV$ mass/volume ratio (both $P<0.0001$; Table 2). Given the opposing changes in $E_{es}$ and $E_a$, the arterial-ventricular coupling ratio ($E_a/E_{es}$) decreased from $0.69±0.15$ to $0.62±0.14$ ($P<0.0001$).

Similar to cross-sectional data reported in this population from examination 1,$^2$ $E_{es}$, $E_a$, and $E_{ed}$ each correlated directly with age, and all were again consistently higher in women than men at examination 2 (Figure 2A–2C). $E_{es}$ increased in both men and women from examinations 1 and 2, and the magnitude of increase was similar (Figure 2D). In contrast, although $E_{ed}$ increased in both men and women, the magnitude of increase was greater in women (Figure 2E). From examinations 1 and 2, $E_a$ decreased in men but not in women, although the difference between the sexes was not significant (Figure 2F).

Age-related changes in body mass were positively correlated with changes in $E_{es}$ ($r=0.12$; $P<0.0001$), $E_{ed}$ ($r=0.25$; $P<0.0001$), and $E_a$ ($r=0.14$; $P<0.0001$). However, in other subgroup analyses, changes in $E_{es}$, $E_a$, and $E_{ed}$ from examinations 1 and 2 were similar in older versus younger subjects (analyzed as quartiles or above/below 65 years at examination 1), in hypertensives versus normotensives, and in patients with diabetes mellitus versus patients without diabetes mellitus.

$E_{es}$ is an established measure of LV contractility, but it is also affected by passive ventricular stiffening.$^{14}$ In contrast to $E_{es}$, preload recruitable SW and SW/end-diastolic volume, alternative load-independent measures of LV chamber contractility, decreased slightly at examination 2 compared with examination 1 (Table 2). Despite reductions in wall stress coupled with BP reduction, there was no change in the slope or intercept of the stress-shortening plot (Figure 3A).

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**Table 1. Patient Characteristics at Study Entry and After 4 Years**

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<tr>
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<tbody>
<tr>
<td>Men, n (%)</td>
<td>375 (48)</td>
<td>375 (48)</td>
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<tr>
<td>Age, y</td>
<td>60±9</td>
<td>64±9</td>
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<tr>
<td>BMI, kg/m²</td>
<td>27.9±4.9</td>
<td>28.1±4.8</td>
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<td>BSA, m²</td>
<td>1.90±0.23</td>
<td>1.90±0.23</td>
<td>0.6</td>
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<td>Comorbidities</td>
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<td>Obese, n (%)</td>
<td>214 (27)</td>
<td>213 (27)</td>
<td>0.9</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>204 (26)</td>
<td>327 (41)</td>
<td>&lt;0.0001</td>
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<td>Diabetes mellitus, n (%)</td>
<td>45 (6)</td>
<td>70 (9)</td>
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<td>Coronary disease, n (%)</td>
<td>79 (10)</td>
<td>128 (16)</td>
<td>0.0003</td>
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<td>Heart failure, n (%)</td>
<td>5 (0.6)</td>
<td>8 (1)</td>
<td>0.6</td>
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<tr>
<td>Medications</td>
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<tr>
<td>ACEI/ARB, n (%)</td>
<td>88 (12)</td>
<td>172 (22)</td>
<td>&lt;0.0001</td>
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<td>β-Blocker, n (%)</td>
<td>123 (16)</td>
<td>206 (26)</td>
<td>&lt;0.0001</td>
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<td>Calcium channel blocker, n (%)</td>
<td>56 (7)</td>
<td>76 (10)</td>
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<td>Diuretic, n (%)</td>
<td>142 (19)</td>
<td>194 (25)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Cardiovascular medication, n (%)</td>
<td>312 (40)</td>
<td>433 (55)</td>
<td>&lt;0.0001</td>
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<td>Vital signs</td>
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<tr>
<td>Heart rate, bpm</td>
<td>65±10</td>
<td>66±12</td>
<td>0.04</td>
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<tr>
<td>Systolic BP, mmHg</td>
<td>130±20</td>
<td>126±19</td>
<td>&lt;0.0001</td>
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<tr>
<td>Diastolic BP, mmHg</td>
<td>73±10</td>
<td>69±10</td>
<td>&lt;0.0001</td>
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<tr>
<td>Mean BP, mmHg</td>
<td>92±12</td>
<td>88±12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>57±16</td>
<td>57±17</td>
<td>0.4</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; bpm, beats per minute; and BSA, body surface area.

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*S* indicates statistically significant differences at $P<0.0001$ and † indicates statistically significant differences at $P<0.05$. $E_a$ indicates arterial elastance; EDV, end-diastolic volume; $E_{ed}$, end-diastolic elastance; $E_{es}$, end-systolic elastance; LVM, left ventricular mass; and SBP, systolic blood pressure.
indicative of similar chamber contractility at examinations 1 and 2. Finally, longitudinal changes in Ees were correlated with changes in Eed within subjects, but not with changes in preload recruitable SW (Figure 3B and 3C), suggesting that the increase in Ees was not reflective of enhanced contractility but rather increases in passive ventricular stiffness.

Changes in Subjects Free of Cardiovascular Disease
The addition of antihypertensive or other cardiovascular medications represents an important potential source of confounding regarding changes in ventricular-arterial properties during the study period. To address this, we next evaluated changes in cardiovascular structure and function in subjects with no cardiovascular disease at any time point during the study (n=249; Table 3). In this healthy subgroup, there were similar increases in LV Ees and Eed from examinations 1 and 2, despite lower BP and wall stress. Also similar to the broader population, there was no change in EF but reductions in preload recruitable SW and SW/end-diastolic volume, with no shift in the stress-shortening relationship. In contrast to the total study population, there were no reductions in Ea or in LV mass and no increases in left atrial volume or pulmonary artery pressure.

Discussion
This is the first large-scale population-based study to examine longitudinal changes of LV systolic and diastolic stiffness, as well as arterial stiffness in humans. We show that on average, despite lower BP, regression of ventricular mass, and reduction in arterial load, LV stiffness during both systole and diastole increases over 4 years in patients with and without cardiovascular disease. An important implication of this finding is that a significant component of ventricular stiffening seems to be mediated by processes that are independent of elevations in arterial load. Increases in systolic and diastolic LV stiffness were correlated with one another, yet changes in Ees were not correlated with other measures of contractility.
and there was no shift in the LV stress-shortening plot over time, suggesting that the increase in Ees is reflective of passive stiffening rather than enhanced systolic function. Diastolic LV stiffness increased more dramatically in women than in men, which may partly explain greater risk of HFpEF in women. Ventricular stiffening was directly correlated with increases in body mass, consistent with the prior observations of obesity as a risk factor for diastolic dysfunction and HF. Collectively these data suggest that in addition to aggressive control of BP, novel therapies and interventions targeting the nonhemodynamic components of age-related ventricular stiffening, including obesity, may provide further benefit in treating and preventing cardiovascular disorders associated with ventricular stiffening, such as HFpEF.

Ventricular Stiffness and Aging
Prior studies examining changes in ventricular and arterial stiffness with normal aging have been predominantly cross-sectional in nature. In a small-sized invasive study, Chen et al1 showed that Ea, Ees, and Eed increase across the age spectrum, and that each of these increases was correlated with one another, suggesting that arterial and ventricular stiffening may be mechanistically intertwined. Subsequently, our group reported cross-sectional data from examination 1 in this population, again showing that Ees, Ea, and Eed increased across the age spectrum in the cohort, and that the age-related increase in Ees was steeper in women than in men.2 However, cross-sectional analyses do not provide an accurate picture of true age-related longitudinal changes in ventricular-arterial properties. This is because there is selection for healthier individuals in the upper age ranges; individuals that agree to participate in studies are in general healthier, particularly when older, and this results in a selection bias wherein each older aged cohort represents an increasingly selected group that is relatively healthier than their younger aged predecessors.

Here, we show for the first time using longitudinal assessments in the same subject that ventricular systolic and diastolic stiffness increase in tandem with normal aging, even as arterial stiffness decreases or remains stable (Figure 4). The magnitude of the increase in stiffness was not related to age at index examination or to the presence of cardiovascular disease or other comorbidities. BP and LV mass decreased from examinations 1 and 2. This is likely, in part, because of increased prescription of efficacious medical therapy, as evidenced by the 35% increase in the use of cardiovascular medications. This major improvement in BP control is concordant

Figure 2. Cross-sectional relationships between age and end-systolic elastance (Ees, A), end-diastolic elastance (Eed, B), and arterial elastance (Ea, C) at examination 2. Bar graphs show mean within-subject changes (±SE) in men and women over 4 years in Ees (D), Eed (E), and Ea (F). *P<0.0001 for paired comparison within group vs examination 1; †P<0.05 for paired comparison within group vs examination 1.

Figure 3. A, Stress-shortening plot of endocardial fractional shortening (FS) vs circumferential end-systolic wall stress (cESS) reveals no change in chamber contractility from examination 1 (black) and examination 2 (gray). Dotted lines show 95% prediction bands. B, Correlations between 4-year longitudinal changes in left ventricular end-systolic elastance (Ees) and changes in end-diastolic elastance (Eed, left) and (C) changes in preload recruitable stroke work (PRSW, right).
with a recent report from a similar cohort in the Minnesota Heart Study, where the prevalence of uncontrolled hypertension fell from 20.3% to 5.8% for men and from 13.1% to 2.7% for women from 1980 to 2009. However, not all of the BP reduction is explainable by improved treatment because pressure also dropped in the subgroup of subjects free of cardiovascular disease. This may be related to secular trends in BP and cardiovascular risk as recently reported. Importantly, despite reductions in BP, wall stress, and thus hemodynamic load, LV systolic and diastolic elastance increased by 14% and 8%, respectively, over 4 years. These changes are much greater than what would be predicted from the linear least squares slopes of the cross-sectional age regressions in our previous study, emphasizing how longitudinal data provide more insight into age-related changes compared with cross-sectional analysis. These data extend on a recent report showing that such as LV stiffness, LV diastolic dysfunction progresses over time. As observed in previous studies, ventricular-arterial stiffening was greater in women than in men at any age (Figure 2).
were not sex differences in the age-related changes in Ees or Ea, but there was a greater increase in Eed in women in the current study. This finding may help explain part of the greater predilection for elderly women to develop HFpEF as compared with men.

An older natural history study from the Framingham group showed that systolic BP increases strikingly with age in the absence of treatment, highlighting the dramatic impact of antihypertensive therapy in the current study population, where systolic and diastolic pressure dropped on average over 4 years. BP control is well known to reduce HF incidence by 25% to 50%, even when initiated after the age of 80 years, and BP control according to contemporary guidelines has not been associated with reductions in incident HFpEF.

Increases in LV systolic stiffness (Ees), also commonly observed in HFpEF, enhance BP lability with preload or afterload alteration and limit contractile reserve. This partly explains the greater susceptibility of older patients to hypotension with postural fluid shifts or diuresis, and to hypertension with excess sodium intake or medication non-adherence. Thus, strategies to reduce systolic and diastolic stiffness would allow for easier control of BP with less risk of toxicity in older adults.

The cardiovascular structural and functional changes observed in HFpEF compared with controls are qualitatively similar to alterations observed during normal aging and with hypertensive heart disease compared with younger healthy controls. Acute changes in Ees are reflective of alterations in chamber contractility, but chronically, Ees is influenced by passive stiffening and changes in geometry and heart size. We observed that Ees increased with time when substituting developed pressure for ESP, indicating that this finding was not simply because of an elevation in EDP. Further, Ees increased after normalizing for chamber mass:volume ratio, indicating that this change is not ascribable to alterations in chamber size or geometry. The current findings showing the coexistence of increased Ees and slightly depressed chamber contractility with aging are similar to cross-sectional differences that have been described comparing patients with HFpEF to hypertensive and healthy controls. Uninterrupted progressive stiffening of the ventricle may partly explain why afterload-targeting therapies have failed to improve outcomes in HFpEF trials, and why BP reduction with lisinopril or amlodipine has not been associated with reductions in incident HFpEF in ancillary analyses from the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) trial. Because ventricular stiffening is a key process driving progression to HFpEF, and because 10-year outcomes after diagnosis are dismal, future research should identify the mechanisms underlying load-independent, age-related ventricular stiffening to better treat and prevent HFpEF.

**Limitations**

The noninvasive methods used to assess ventricular stiffness and function are each validated against gold-standard invasive methods, but echo-Doppler data inherently have greater variability compared with invasive measurements. However, a longitudinal study of this type could not be performed using invasive assessments. Although sampling bias was minimal in this population-based study, our study cohort was almost exclusively white, and these results may not be applicable to other ethnic groups. Survival bias and participation bias may contribute to underestimation of the impact of LV stiffening in the cohort.
Conclusions

LV stiffness increases with normal aging, despite excellent control of BP and reductions in LV mass. These data indicate that ventricular stiffening with aging is not exclusively ascribable to progression in systemic hypertension and arterial stiffening, and they further suggest that novel therapies targeting age-related ventricular stiffening may help to treat and prevent diseases associated with ventricular-arterial stiffening, including HFpEF.

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

Cross-sectional studies have shown that ventricular and arterial elastance (stiffness) increase across the age spectrum, but little data are available about serial, within-patient changes in cardiovascular mechanics over time. In addition, although it is widely thought that the ventricle becomes stiffer in response to pressure overload from age-related increases arterial hypertension, it is possible that other load-independent processes may contribute. To explore these questions, we measured ventricular systolic and diastolic elastance, as well as arterial elastance, in a community-based study at 2 time points separated by 4 years. Although the prevalence of hypertension increased during the study period, blood pressure and arterial stiffness decreased in tandem with greater use of antihypertensive medications. However, despite lowering of blood pressure, regression in left ventricular mass, and reduction in arterial stiffness, left ventricular systolic and diastolic elastance increased significantly. Age-related increases in ventricular-arterial stiffness were correlated with increases in body mass, suggesting that adiposity and its associated sequelae may contribute to age-related stiffening. Ventricular-arterial stiffness was higher in women than in men, and the increase in diastolic ventricular elastance with aging was also greater in women, which may partly underlie the greater predilection for older women to develop heart failure with preserved ejection fraction. Collectively, these findings show that not all age-related ventricular stiffening is ascribable to increases in blood pressure, and that novel therapies targeting nonhemodynamic components of ventricular stiffening may hold promise to treat and prevent age-related cardiovascular diseases, such as heart failure with preserved ejection fraction.
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