Age-Related Left Ventricular Remodeling and Associated Risk for Cardiovascular Outcomes

The Multi-Ethnic Study of Atherosclerosis

Susan Cheng, MD; Verônica R.S. Fernandes, MD, PhD; David A. Bluemke, MD, PhD; Robyn L. McClelland, PhD; Richard A. Kronmal, PhD; João A.C. Lima, MD

Background—Age-related alterations of left ventricular (LV) structure and function that may predispose to cardiovascular events are not well understood.

Methods and Results—We used cardiac MRI to examine age-related differences in LV structure and function in 5004 participants without overt cardiovascular disease when enrolled in the Multi-Ethnic Study of Atherosclerosis; 1099 participants received additional strain analyses by MRI tagging. We also assessed the relation of age-associated remodeling with cardiovascular outcomes using Cox proportional hazard models adjusting for cardiovascular risk factors. Although LV mass decreased with age (−0.3 g per year), the mass-to-volume ratio markedly increased (+5 mg/mL per year, P<0.0001), driven by a substantial reduction in end-diastolic volume (−0.8 mL per year, P<0.0001). Age was also associated with a significant fall in stroke volume (−0.4 mL per year, P<0.0001), along with strain patterns reflecting systolic (P<0.0001) as well as diastolic (P<0.01) myocardial dysfunction—despite a modestly enhanced ejection fraction (+0.1% per year, P<0.0001). Increased mass-to-volume ratio conferred a significant risk for total cardiovascular events; this trend was strongest among younger (<65 years; hazard ratio, 3.69 [CI, 1.34 to 10.10]) versus older (≥65 years; hazard ratio, 1.68 [CI 0.77 to 3.68]) individuals with the highest compared to lowest mass-to-volume ratio quintile (Pinteraction=0.013).

Conclusions—Age is associated with a phenotype of LV remodeling marked by increased mass-to-volume ratio and accompanied by systolic as well as diastolic myocardial dysfunction that is not reflected by preserved ejection fraction. This pattern of ventricular remodeling confers significant cardiovascular risk, particularly when present earlier in life. (Circ Cardiovasc Imaging. 2009;2:191-198.)

Key Words: aging ■ MRI ■ myocardium ■ remodeling

While age is one of the most powerful risk factors for cardiovascular disease, the mechanisms by which aging predisposes to cardiovascular morbidity and mortality remain incompletely understood.1–3 It is well known that age is associated with left ventricular (LV) hypertrophy, but less clear is the degree to which this remodeling is accompanied by age-specific relative changes in LV mass,4–11 volumes,11–17 chamber performance,13,15,16 and intrinsic myocardial function in humans.10,11,14,18 Recent work has described aging-related cellular8,19,20 and molecular21–23 processes that likely contribute to myocardial dysfunction. Although the relation of advancing age with diastolic dysfunction is widely recognized, associated changes in systolic function are less clear.11,16,24–27 Conventional diagnostic methods may be limited in their ability to detect intrinsic age-associated changes in human myocardial function in relation to structural chamber remodeling. Furthermore, their link to cardiovascular morbidity and mortality remains elusive.

Clinical Perspective on p 198

In a large cohort of ethnically diverse individuals free of cardiovascular disease at baseline, we sought to comprehensively assess age-associated changes in LV structure and function using cardiac MRI and to determine whether these changes predict cardiovascular outcomes. Cardiac MRI with myocardial tagging is considered the reference standard for assessing LV structural abnormalities and offers the ability to assess myocardial function in fine detail. However, cardiac MRI tagging has not previously been used in large studies to concurrently investigate structural and functional aspects of LV
Study Population
The original cohort included 6814 community-dwelling individuals enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA). The design and objectives of MESA have been described elsewhere. In brief, study participants were 45 to 84 years of age, represented 4 racial/ethnic groups (non-Hispanic white, black, Hispanic, and Chinese), and had no history of clinical cardiovascular disease (diagnosed coronary artery disease, peripheral arterial disease, cerebrovascular disease, or heart failure) at enrollment. As part of the baseline examination, consenting participants underwent cardiac MRI studies at 6 centers across the United States. Of the 5004 participants who underwent cardiac MRI, 1099 received additional tissue tagging as described previously. Institutional review boards at each center approved the study protocol.

Magnetic Resonance Imaging Studies
Participants underwent MRI at 1.5- to 3.0-T MR scanners with a 1.5-T system (Signa or CVi, GE Medical Systems, Waukesha, Wis) and a 3.0-T system (Sonata, Siemens Medical Systems, Erlangen, Germany).

Clinical Events
Participants were followed via telephone interviews for incident cardiovascular events at intervals of 9 to 12 months from baseline. Details regarding the MESA processes and criteria for verifying, classifying, and adjudicating cardiovascular events have been reported. MRI studies at 6 centers across the United States. Of the 5004 participants who underwent cardiac MRI, 1099 received additional tissue tagging as described previously. Institutional review boards at each center approved the study protocol.

Statistical Analysis
Mean (95% CI) values of all LV structural and functional indices were calculated in the sample divided into 8 equal groups by age. We considered mass and volumes as absolute measures and as indexed to body size (body surface area [BSA], body mass index [BMI], and height). We also quantified mean Ecc and SRE across age quartiles. Independent associations between increasing age and all LV indices were performed using linear regression with multivariable

Methods
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MRI Standard and Tagging Acquisition Protocols
Cardiac MRI images were obtained using 1.5-T MR scanners: Signa LX or CVi (GE Medical Systems, Waukesha, Wis) and Somatom Vision or Sonata (Siemens Medical Systems, Erlangen, Germany). Images were acquired using segmented k-space, ECG-triggered gradient echo pulse sequence during breath-holds lasting 12 to 18 seconds. Two- and 4-chamber cine-MR images and short-axis cine images were obtained from above the mitral valve plane to the LV apex.

Table 1. Baseline Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age &lt;65 y (n=3129)</th>
<th>Age ≥65 y (n=1879)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, %</td>
<td>52.7</td>
<td>52.9</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>37.9</td>
<td>41.3</td>
</tr>
<tr>
<td>Chinese American</td>
<td>12.9</td>
<td>13.4</td>
</tr>
<tr>
<td>Black</td>
<td>25.5</td>
<td>26.1</td>
</tr>
<tr>
<td>Hispanic</td>
<td>23.8</td>
<td>19.2</td>
</tr>
<tr>
<td>BMI, kg/m²†</td>
<td>28.1±5.2</td>
<td>27.2±4.6</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.9±0.2</td>
<td>1.8±0.2</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>120.6±19.1</td>
<td>133.4±22.4</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>72.4±10.2</td>
<td>70.8±10.3</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>48.2±13.7</td>
<td>62.6±17.7</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>26.7</td>
<td>49.7</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>10.4</td>
<td>17.3</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>32.7</td>
<td>40.9</td>
</tr>
<tr>
<td>Current</td>
<td>15.8</td>
<td>7.5</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>195.3±35.6</td>
<td>192.6±34.9</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>133.3±90.7</td>
<td>127.9±75.0</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>118.6±31.6</td>
<td>114.9±30.8</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>50.5±14.7</td>
<td>52.4±15.3</td>
</tr>
<tr>
<td>Taking medication for hypertension, %</td>
<td>24.8</td>
<td>43.1</td>
</tr>
<tr>
<td>Taking medication for cholesterol, %</td>
<td>11.6</td>
<td>22.4</td>
</tr>
<tr>
<td>Taking medication for diabetes, %</td>
<td>7.4</td>
<td>11.4</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>147.2±39.3</td>
<td>142.1±39.6</td>
</tr>
<tr>
<td>LV mass index, g/m²†</td>
<td>77.9±15.9</td>
<td>78.0±17.0</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>131.8±31.0</td>
<td>117.4±30.3</td>
</tr>
<tr>
<td>LVESV index, mL/m²†</td>
<td>70.1±13.0</td>
<td>64.8±14.0</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>42.5±17.1</td>
<td>35.8±16.3</td>
</tr>
<tr>
<td>LV mass-to-volume ratio, g/mL</td>
<td>22.5±7.9</td>
<td>19.6±8.1</td>
</tr>
<tr>
<td>LV stroke volume, mL</td>
<td>89.3±19.5</td>
<td>81.6±19.5</td>
</tr>
<tr>
<td>LV stroke volume index, mL/m²†</td>
<td>47.6±8.7</td>
<td>45.2±9.4</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>68.3±7.2</td>
<td>70.2±7.6</td>
</tr>
<tr>
<td>Peak systolic strain‡</td>
<td>-17.4±2.6</td>
<td>-17.0±2.7</td>
</tr>
<tr>
<td>Diastolic strain rate‡</td>
<td>1.6±0.5</td>
<td>1.6±0.6</td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD or %. †Values are indexed to BSA. **Strain measures assessed in a subset of 1099 participants: 449 age <65 years and 650 age ≥65 years.

Therefore, we used a range of MRI techniques to characterize the phenotype of age-specific LV remodeling in detail and to determine whether prominent aspects of such a phenotype are related to incident cardiovascular events.
adjustments for demographic characteristics and risk factors: model 1 was unadjusted; model 2 adjusted for sex, race/ethnicity, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure, and BMI; and model 3 included the variables from model 2 and also further adjusted for total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, diabetes (fasting plasma glucose ≥7.0 mmol/L [126 mg/dL]), smoking status (current, former, or never), and taking medications to control hypertension, dyslipidemia, and/or diabetes. All analyses were also performed by sex, racial/ethnic group, and hypertension status (blood pressure ≥140/90 or taking antihypertensive medication); 2-way ANOVA was used to assess for the possible interaction of sex, race/ethnicity, or hypertension status on the relation of age to each of the LV indices.

For outcomes analyses, Cox proportional hazard models were calculated for each LV measure separately as continuous variables (per standard deviation increments) and then for LV mass and LVEDV jointly in the same model. All models were adjusted for age, sex, race/ethnicity, baseline height and weight, hypertension status, LDL cholesterol, diabetes, and smoking status. Analyses were repeated for incident cardiovascular events using M/V ratio quintiles, and then repeated again by age group (<65 and ≥65 years). All analyses were performed using SPSS 13.0 and Stata 10.0. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Table 1 shows the demographic and clinical characteristics of the 5004 study participants in this analysis by age group. Notably, older adults had higher SBP, lower DBP, and higher pulse pressure when compared with younger adults; these trends were more pronounced across increasing age (supplemental Figure 1).

Left Ventricular Structure and Aging
In age-based analyses, absolute LV mass incrementally decreased across increasing age group by ~0.3 g per year (P<0.0001), and this trend was observed in both sexes (Figure 1A). When LV mass was indexed to BSA, this inverse relationship was diminished but remained statistically significant after adjusting for multiple variables including...
sex, race/ethnicity, and blood pressure (Table 2). Whereas LV mass slightly declined across increasing age groups, M/V ratio substantially increased by 5 mg/mL (0.005 g/mL) for every year increase in age (P<0.0001, Figure 1B). The mean M/V ratio was almost 25% higher in the oldest compared with youngest age group (1.25 versus 1.08 g/mL).

The marked age-associated increase in M/V ratio was driven by a proportionately greater magnitude of age-associated decline in LVEDV (0.8 to 0.9 mL per year) compared with that of LV mass (0.2 to 0.5 g per year, Table 2, Figures 1C and 1D). Moreover, LVEDV index declined at similar rates in individuals of different race/ethnicity (Figure 1E), and, correspondingly, the M/V ratio increased across all race/ethnic groups with a nonsignificant trend toward a sharper incline among blacks (Figure 1F). In addition, when LV mass and volumes were normalized to indices of body size other than BSA (Table 2), such as BMI and height, these age-based trends remained the same. All age-associated differences in LV mass and volumes remained highly significant (P<0.00001) after adjustment for multiple variables including cardiovascular risk factors (Table 2).

**Left Ventricular Function and Aging**

The age-associated decline in LVEDV exceeded that of LVESV (0.3 to 0.4 mL per year), generating a corresponding age-associated decline in the SV (Table 2, Figure 2A). Conversely, EF increased modestly with age in the face of age-associated decline in the SV (Table 2, Figure 2A). Age-associated differences in SV and EF remained significant in multivariable analyses.

The effect of hypertension status on LV indices of structure and function was independent of age. Similarly, the effects of sex and race/ethnicity (Figure 1E and 1F) were also independent. Age did appear to augment differences in EF between women and men, but this heterogeneity was not statistically significant (supplemental Figure 2). Similarly, the relations of age with LV indices of structure and function were not significantly different in hypertensive compared with normotensive individuals (supplemental Figure 3).

Finally, among the 1099 participants who had LV strain analysis performed, older age was associated with impaired systolic strain, represented by reduced circumferential shortening and less negative mean Ecc, particularly after multivariable adjustment (Table 2, Figure 2E). As well, mean early diastolic strain rate (SRE) significantly decreased with age in both unadjusted and adjusted models, consistent with lower rates of early circumferential lengthening (SRE) during diastole in older compared with younger adults (Table 2, Figure 2F).

**Age-Associated Ventricular Remodeling and Outcomes**

Of the 5004 participants who had baseline MRI studies, 36 participants were lost to follow-up after the baseline examination and so were excluded from outcomes analyses. Over the 5.2 years of MESA cohort follow-up (median, 4.0 years) for the remaining 4968 participants, there were 180 total cardiovascular events: 45 myocardial infarctions, 71 anginal episodes, 48 HF cases, 39 strokes, and 13 CAD deaths.

Structural LV features were significantly associated with total cardiovascular events; in particular, the M/V ratio was consistently associated with a higher rate of cardiovascular events in the total sample (hazards ratio, 1.23; 95% CI, 1.09 to 1.39; P=0.001). Moreover, we observed significant age-based heterogeneity with respect to the relation of structural indices to cardiovascular events. When comparing outcomes between age groups, elevated M/V ratio was associated with a higher hazards ratio for total cardiovascular events, with wider confidence intervals, in younger compared with older adults (P interaction =0.013). This finding remained unchanged in models adjusting for multiple risk factors (Table 3, Figure 3).
Discussion

This study demonstrates marked age-associated differences in LV structure and function in the largest cohort of multi-ethnic individuals studied to date with cardiac MRI. In this cohort, age was associated with a phenotype of LV remodeling marked by several specific structural features and coincident with impaired systolic as well as diastolic myocardial function. Furthermore, this LV remodeling conferred significant risk for cardiovascular events. Taken together, these findings suggest that processes related to biological aging likely contribute to alterations in LV structure and function that, in turn, predispose to greater cardiovascular risk.

The major age-associated differences in LV structure and function found in this study were 3-fold. First, age was associated with a phenotype of LV remodeling marked by several specific structural features and coincident with impaired systolic as well as diastolic myocardial function. Furthermore, this LV remodeling conferred significant risk for cardiovascular events. Taken together, these findings suggest that processes related to biological aging likely contribute to alterations in LV structure and function that, in turn, predispose to greater cardiovascular risk.

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Figure 2. SV declines across increasing age group (A). Conversely, EF progressively rises (B). The relation of age to these global functional indices are summarized by showing age-associated changes in standardized values for LVEDV, LVESV, and EF (C). A schematic overview depicts changes in LV volumes and EF with increasing age (D). Although SV progressively falls, EF paradoxically increases; this appears due to the progressive decline in all LV volumes, particularly LVESV. Peak systolic strain (Ecc), reflecting the magnitude of myocardial systolic deformation across increasing age quartiles, is shown (E). As age increases, midwall circumferential shortening becomes less negative, that is, decreases because systolic strain is conventionally negative during systole. Because diastolic strain rate is conventionally a positive value, reduction of its magnitude reflects slower circumferential lengthening during LV filling or progressively reduced myocardial relaxation with age (F). Values in A, B, E, and F are presented as mean (95% CI).
Second, we found an age-associated decline in SV that was accompanied, paradoxically, by a modestly enhanced EF. Physiological studies have previously documented an age-associated deterioration in global LV function as represented by indices of SV but not EF. Conversely, other reports have described increased fractional shortening or at least preserved EF in older compared with younger subjects. In our study, the apparent paradox of rising EF in the face of a falling SV appeared driven by the overall decline in LV chamber volumes, particularly in LVESV despite a correspondingly greater reduction in LVEDV across all age groups (Table 2, Figure 2C). Given that EF is the ratio of SV over LVEDV, we were able to observe that as SV decreased, EF actually increased (see hatched bars in Figure 2D). Prior studies have suggested that age is associated with preserved EF but greater LV volumes. However, these earlier studies assessed LV volumes using radionuclide ventriculography, which is limited by varying attenuation between anterior and posterior walls, background subtraction errors, and geometric assumptions when compared with cardiac MRI.

Finally, in the setting of falling SV and rising EF, age was also associated with abnormal systolic and diastolic strain, representing early myocardial dysfunction. Age-related myocyte depletion, combined with increased myocardial collagen deposition, may well contribute to impaired contractility and abnormal diastolic function as well as reduced LV volumes. Additionally, the discrepancy between the age-associated increase in EF and decline in circumferential shortening may be in part due to the phenomenon of cross-fiber shortening, whereby the ventricle compensates for impaired contractile function through concentric hypertrophy and associated reliance on shortening of cross-fibers to maintain systolic wall thickening and EF. Prior studies have found abnormal relaxation and diastolic strain in older adults but overall myocardial systolic function was generally thought to remain intact. On the other hand, reduced systolic strain in the presence of LV hypertrophy and preserved EF has been found in association with hypertension and, in the MESA cohort, systolic circumferential strain was progressively lower in participants with increasing M/V ratios. This study suggests that these same features are associated with age even after adjusting for hypertension and blood pressure indices. Age-associated abnormalities in myocardial strain may be yet another sign of abnormal coupling of ventricular and vascular remodeling, particularly as we have previously observed abnormal myocardial strain in the setting of increased arterial stiffness.

The most representative feature of age-associated remodeling was increased M/V ratio, reflective of a hypertrophic process occurring in the setting of progressively reduced LV volume.
volumes. Prior studies have reported on the relation of LV hypertrophy with a variety of important cardiovascular outcomes.\textsuperscript{33,49} Interestingly, we found that an increased M/V ratio conferred a higher hazard for total cardiovascular events in younger compared with older age. This finding may reflect survivor bias in the MESA population and/or suggest that individuals who develop hypertrophic remodeling earlier in life have greater risk. This higher risk in younger adults may be related to subclinical coronary artery disease and/or hypertensive heart disease. However, the relation of M/V ratio to cardiovascular outcomes was significant even after adjustment for risk factors including hypertension.

The generalizability of our results may be limited by selection and survivor biases. Since MESA participants had no known cardiovascular disease at baseline, older individuals in this cohort represent a particularly healthy sample; therefore, the present findings may underestimate true age-related differences. Our sample did not include persons <45 or >84 years of age. Additionally, analyses of age-associated LV remodeling were cross-sectional across a large cohort of individuals of varying age groups and did not account for the possible influence of birth cohort. Therefore, temporal relationships cannot be inferred for analyses of age-associated LV remodeling, although these may be the subject of future longitudinal investigations using serial cardiac MRI. We also were not able to adjust measures of peak systolic and diastolic strain for wall stress, which should ideally be considered in detailed investigations of myocardial contractile function and relaxation.\textsuperscript{50}

Our findings suggest that human aging is associated with specific alterations of LV structure and function marked by an increase in M/V ratio, driven by a reduction in LV volumes out of proportion to declining LV mass. Moreover, age is independently associated with a parallel reduction in SV and progressive systolic and diastolic myocardial dysfunction, despite a modestly enhanced EF. Additionally, this study demonstrates a significant relationship between this phenotype of LV remodeling and adverse cardiovascular outcomes. Further investigations are needed to elucidate the etiology of such age-associated processes.

Acknowledgments
We thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

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Disclosures
None.

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SUPPLEMENTAL MATERIAL

Figures Legend

Figure 1. Across increasing age groups, women and men demonstrate an increase in systolic blood pressure (Panel A), decrease in diastolic blood pressure (Panel B), and increase in pulse pressure (Panel C). Values are presented as means (95% CI).

Figure 2. Panels A through H show the relation of age to indices of LV structure and function by sex. P values are for interaction between age and sex. For EF, shown in Panel F, Levene’s test of equality for error variances was <0.05; therefore, the interaction between age group and hypertension status was not considered statistically significant since the P value was not <0.01.

Figure 3. Panels A through H show the relation of age to indices of LV structure and function by hypertension status, where the presence of hypertension is defined by BP≥140/90 or taking anti-hypertensive medications. P values are for interaction between age and hypertension status.
Figure 1.

A) Systolic Blood Pressure, mmHg

B) Diastolic Blood Pressure, mmHg

C) Pulse Pressure, mm Hg

Age Group, y

Women  Men

≥ 75 70-74 67-69 62-66 58-61 54-57 50-53 ≤ 49

≥ 75 70-74 67-69 62-66 58-61 54-57 50-53 ≤ 49

Pulse Pressure, mm Hg

≥ 75 70-74 67-69 62-66 58-61 54-57 50-53 ≤ 49
Figure 2.

A) LV Mass Index, Est. Marginal Means

Age Group, y

≥ 75
70-74
67-69
62-66
58-61
54-57
50-53
≤ 49

Women
Men

P=0.092

B) LVEDV Index, Est. Marginal Means

Age Group, y

≥ 75
70-74
67-69
62-66
58-61
54-57
50-53
≤ 49

Women
Men

P=0.497

C) LVESV Index, Est. Marginal Means

Age Group, y

≥ 75
70-74
67-69
62-66
58-61
54-57
50-53
≤ 49

Women
Men

P=0.212

D) M/V Ratio, Est. Marginal Means

Age Group, y

≥ 75
70-74
67-69
62-66
58-61
54-57
50-53
≤ 49

Women
Men

P=0.161
Figure 2. (continued)

E) SV, Est. Marginal Means

F) EF, Est. Marginal Means

G) Peak Systolic Strain, Est. Marginal Means

H) Diastolic Systolic Rate, Est. Marginal Means

Age Group, y

Age Group, y

Age Group, y

Age Group, y
Figure 3.

A) LV Mass Index, Est. Marginal Means

B) LVEDV Index, Est. Marginal Means

C) LVESV Index, Est. Marginal Means

D) M/V Ratio, Est. Marginal Means
Figure 3. (continued)

E) P=0.134

F) P=0.113

G) P=0.229

H) P=0.630