Age-Related Left Ventricular Remodeling and Associated Risk for Cardiovascular Outcomes
The Multi-Ethnic Study of Atherosclerosis

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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 (\( R>0.0001 \)) as well as diastolic (\( R>0.01 \)) 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 (\( P_{\text{interaction}}=0.013 \)).

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
Methods

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.30 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.31 Of the 5004 participants who underwent cardiac MRI, 1099 received additional tissue tagging as described previously.31 Institutional review boards at each center approved the study protocol.

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.

For the 1099 participants with tissue tagging performed, 3 tagged short-axis slices were obtained, uniformly spaced, from base to apex. Parallel stripe tags were prescribed separately in 2 orthogonal orientations (0°, 90°) using spatial modulation of magnetization. Parameters for tagged images were field of view, 40 cm; slice thickness, 8 to 10 mm; repetition time, 6 ms (range, 3.5 to 7.2 ms); echo time, 3.0 ms (range, 2.0 to 4.2 ms); flip angle, 12°; matrix size, 256×96 to 140; phase-encoding views per segment, 4 to 9; tag spacing, 7 mm; and temporal resolution, 20 to 40 ms. Myocardial strain was analyzed by harmonic phase imaging.

Parameters of Ventricular Structure and Function

Indices of LV structure and function included LV mass, end-diastolic volume (LVEDV), end-systolic volume (LVESV), stroke volume (SV), and ejection fraction (EF), obtained using commercially available software (MASS 4.2, MEDIS, Leiden, The Netherlands). Mass-to-volume (M/V) ratio was calculated as LV mass divided by LVEDV. Myocardial midwall circumferential strain was measured as \( \varepsilon_c = (L_d - L_r)/L_r \), where \( L_d \) is length in the deformed state and \( L_r \) is length in the relaxed state. By convention, positive strain denotes lengthening and negative strain denotes shortening. Peak systolic strain (Ecc) and early diastolic strain rate (SRE) were determined in each of 4 LV wall regions (anterior, lateral, septal, and inferior); mean midwall Ecc and SRE were calculated for each individual.

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.32 Medical records from approximately 98% of hospitalizations for cardiovascular events and from 95% of outpatient cardiovascular diagnostic encounters were obtained. A cardiovascular event was defined as: a new diagnosis of coronary artery disease (CAD) including myocardial infarction, definite or probable angina if revascularized at the same time or afterward, resuscitated cardiac arrest, or CAD death; heart failure (HF); stroke; stroke death; other atherosclerotic death; or, other cardiovascular death as previously described.32 Diagnosis of HF required symptoms, a physician diagnosis, medical treatment for HF, and (1) pulmonary edema/congestion by chest radiography and/or (2) ventricular dilatation, poor LV function, or evidence of LV diastolic dysfunction by echocardiography or ventriculography.

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
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<0.00001, 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 this age-associated decline in LV volumes (Table 2; Figures 2B, 2C, and 2D). 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 (Pinteraction =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 markedly increased M/V ratio, consistent with the age-associated LV hypertrophic remodeling and increase in relative wall thickness found in prior studies. However, the increased M/V ratio in this study was not due to increased LV mass, as suggested by some prior population studies, but instead driven by a substantial decline in LV volumes out of proportion to any alterations in mass. Earlier investigations used echocardiographic methods for estimating LV mass, including M-mode, which are less able than cardiac MRI to distinguish between concentric remodeling and concentric hypertrophy. On the other hand, prior MRI studies in smaller samples have found similarly preserved or reduced LV mass in older compared with younger adults. An explanation for age-associated hypertrophy, in the absence of increased mass, is offered by histomorphometric studies in humans and animals showing that as the absolute number of myocytes decreases in older age, remaining myocytes tend to hypertrophy in size and number. These studies also found that the number of collagen fibers and nonenzymatic cross-linking in myocardium increases with age. Therefore, despite progressive myocyte dropout in aging, myocyte hypertrophy and increased collagen concentration appear to relatively preserve but not increase LV mass. This type of age-based ventricular remodeling is likely also related to the well-described coupling of ventricular and vascular stiffening processes that can occur over a life course. Indeed, our ventricular findings were observed independent from, but also in the setting of a concurrent age-associated rise in pulse pressure, a recognized index of arterial stiffness.

![Image of graphs showing age-related changes in LV structure and function](image-url)
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.27 Conversely, other reports have described increased fractional shortening34 or at least preserved EF40 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.41–43 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.44

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,45,46 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 adults34 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.47 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.48

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

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### Table 3. Relation of Selected LV Indices With Total CV Events By Age Group

<table>
<thead>
<tr>
<th></th>
<th>Age &lt;65 y</th>
<th>Age ≥65 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>LV mass (1 SD=39.5 g)</td>
<td>1.45 (1.11, 1.90)</td>
<td>0.007</td>
</tr>
<tr>
<td>LVEDV (1 SD=31.5 mL)</td>
<td>0.89 (0.66, 1.21)</td>
<td>0.470</td>
</tr>
<tr>
<td>LV mass (1 SD=39.5 g)†</td>
<td>1.86 (1.33, 2.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDV (1 SD=31.5 mL)†</td>
<td>0.65 (0.46, 0.92)</td>
<td>0.015</td>
</tr>
<tr>
<td>M/V ratio (1 SD=0.25 g/mL)</td>
<td>1.51 (1.23, 1.85)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

M/V ratio quintiles

<table>
<thead>
<tr>
<th></th>
<th>Age &lt;65 y</th>
<th>Age ≥65 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st quintile</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>2nd quintile</td>
<td>1.67 (0.56, 4.93)</td>
<td>0.350</td>
</tr>
<tr>
<td>3rd quintile</td>
<td>0.75 (0.21, 2.63)</td>
<td>0.650</td>
</tr>
<tr>
<td>4th quintile</td>
<td>2.68 (0.96, 7.49)</td>
<td>0.060</td>
</tr>
<tr>
<td>5th quintile</td>
<td>3.69 (1.34, 10.10)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

*Hazard ratio (and 95% confidence interval) are shown per standard deviation increment in continuous variables.
†All models are adjusted for age, sex, race/ethnicity, height, weight, hypertension status, LDL cholesterol, diabetes, and smoking. HRs are for 1 SD change. Both LV mass and LVEDV were included in these models.

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**Figure 3.** Fitted curves represent hazards ratio (95% CI) of M/V ratio with respect to total CV events across increasing age while adjusting for age, sex, race/ethnicity, height, weight, hypertension status, LDL cholesterol, diabetes, and smoking. As shown, the risk is greater for those individuals who develop the “typical” age-associated LV remodeling phenotype at a younger compared with older age (arrows).
volumes. Prior studies have reported on the relation of LV hypertrophy with a variety of important cardiovascular outcomes.\textsuperscript{3,3,4} 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.

Sources of Funding

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

Age-related alterations of left ventricular (LV) structure and function that may predispose to cardiovascular events are not well understood. Therefore, we used cardiac MRI to examine age-related differences in LV structure and function among 5004 participants of the Multi-Ethnic Study of Atherosclerosis who had no cardiovascular disease at baseline; additional strain analyses were performed for 1099 of these participants. We also assessed the relation of age-associated remodeling with cardiovascular outcomes while adjusting for traditional risk factors. In multivariable regression models, age was associated with a decrease in LV mass but also a marked increased in the LV mass-to-volume ratio driven by substantial reduction in LV end-diastolic volume. Age was also associated with a significant fall in stroke volume along with strain patterns reflecting systolic as well as diastolic myocardial dysfunction, despite a modestly enhanced ejection fraction. Higher mass-to-volume ratio conferred a significant risk for total cardiovascular events, and this trend was strongest among younger (<65 years; hazard ratio, 3.69; P=0.011) versus older (≥65 years; hazard ratio, 1.68; P=0.190) individuals with the highest compared with lowest mass-to-volume ratio quintile (Pinteraction=0.013). These findings suggest that 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 appears to confer significant cardiovascular risk, especially when present earlier in life.
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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
Figure 2.

A) LV Mass Index, Est. Marginal Means
P=0.092

B) LVEDV Index, Est. Marginal Means
P=0.497

C) LVESV Index, Est. Marginal Means
P=0.212

D) M/V Ratio, Est. Marginal Means
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 Strain Rate, Est. Marginal Means

Age Group, y

Women □ Men

P=0.202

P=0.043

P=0.292

P=0.966
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) SV, Est. Marginal Means

F) EF, Est. Marginal Means

G) Peak Systolic Strain, Est. Marginal Means

H) Diastolic Strain Rate, Est. Marginal Means