Association of Longitudinal Changes in Left Ventricular Structure and Function With Myocardial Fibrosis
The Multi-Ethnic Study of Atherosclerosis Study

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Abstract—The association of longitudinal changes in left ventricular (LV) structure and function with myocardial fibrosis is unclear. We relate temporal changes in body size–indexed LV mass (LVMi) and end-diastolic volume indexed to body surface area, LV mass-to-volume ratio, and LV ejection fraction (LVEF) from cine cardiac magnetic resonance for 10 years, with replacement scar assessed from late gadolinium enhancement, and lower postcontrast T1 times reflecting greater diffuse myocardial fibrosis measured at the end of the follow-up period. All participants (n=1813) who underwent cardiac magnetic resonance twice as part of the Multi-Ethnic Study of Atherosclerosis 10 years apart were included. Multivariable logistic and linear regression models adjusted for cardiovascular risk factors measured the association of 10-year changes in LV structure and function, with fibrosis measured at follow-up. The presence of LV scar at year 10 was cross-sectionally associated with higher LVMi (≥10 g/m²), higher mass-to-volume ratio (0.1–0.2 g/mL), but lower LVEF (≤4%) and longitudinally with 3% decrease in LVEF and 0.7% greater end-diastolic volume indexed to body surface area in men for 10 years. Lower postcontrast T1 times at year 10 were associated cross-sectionally with lower LVMi (≥0.33), end-diastolic volume indexed to body surface area (r=0.25), and LVEF (in men only: r=0.14) and longitudinally with a decrease in LVMi (r=0.20) and reduction in LVEF (in men only: r=0.15). Sustained hypertension for 10 years was associated with increased LVMi and higher diffuse and replacement fibrosis at follow-up. During a 10-year period, increased concentric hypertrophy in women and LV dilatation in men were associated with replacement fibrosis, whereas decreasing LVMi was associated with diffuse fibrosis. Hypertension-induced remodeling was related to enhanced replacement and diffuse fibrosis, as well as hypertrophy. (Hypertension. 2014;64:508-515.) • Online Data Supplement

Key Words: fibrosis ■ hypertension ■ hypertrophy ■ magnetic resonance imaging ■ ventricular function, left ■ ventricular remodeling

Left ventricular (LV) structural and functional changes in response to, or in association with, myocardial fibrosis are important components of cardiac disease. Myocardial fibrosis is considered as 1 of the chief factors that influence the process of cardiac remodeling, conceptualized as the structural and functional cardiac alterations that accompany exposure to pathogenic processes and cardiovascular risk factors. Previous studies have shown the association of myocardial fibrosis with alterations of myocardial structure and function, as well as with indices of impaired myocardial tissue deformation in varied cardiomyopathies. Sex dependency of these alterations of structure and function has also been demonstrated, reflecting different mechanisms of cardiac morbidity and associated LV remodeling.

Cardiac magnetic resonance (CMR) imaging can be used to quantify LV mass and volume accurately throughout the cardiac cycle and is considered as the standard of reference for assessment of structure and function. CMR has also been used to characterize focal and diffuse myocardial fibrosis through late gadolinium enhancement (LGE) and longitudinal relaxation time (T1) mapping, respectively. In previous studies, T1 mapping times and related parameters have been shown to correlate well with collagen content of the myocardium as measured through biopsy, whereas LGE has long been used to measure replacement myocardial fibrosis.

The goals of this study were to understand how LV structure and function and its 10-year change relate to diffuse and replacement myocardial fibrosis measured at the end of the follow-up period in a multiethnic population. We relate CMR measures...
of structure—LV mass, volume, and mass-to-volume ratio—and function with measures of replacement fibrosis detected by myocardial scar from LGE and diffuse myocardial fibrosis indexed by T1 mapping. We also study the variation LV structure and function and fibrosis in conjunction with hypertension.

Methods

Population Characteristics

The design and population characteristics of the Multi-Ethnic Study of Atherosclerosis (MESA) have been described previously. Briefly, MESA is a prospective, population-based observational cohort study of 6814 men and women representing 4 racial/ethnic groups, aged 45 to 84 years, and free of clinical cardiovascular disease at enrollment. As part of the baseline examination, between 2000 and 2002 (year 0), a total of 5004 (73%) participants received cine CMR examinations at 6 field centers. Of the 5004 individuals who underwent CMR at baseline, 2981 participants underwent a follow-up CMR between 2010 and 2012 (year 10). The follow-up scan included LGE imaging and T1 mapping. Participants undergoing CMR scans were screened for gadolinium eligibility. Participants with glomerular filtration rate ≥60 mL/min (60 mL/min for 1 site) and without history of allergic reaction to contrast agents were qualified to receive gadolinium. Of the eligible participants, 1814 agreed to a gadolinium injection and underwent LGE imaging. One thousand three hundred twenty of the participants who were injected with gadolinium also had T1 mapping as part of the protocol. After exclusion for participants with either wrong or unavailable administered gadolinium dose and for those where the images acquired had artifacts (51 participants), a total of 1223 participants were included in the T1 analysis. During the 10-year follow-up period, a telephone interviewer contacted each participant (or representative) every 6 to 9 months to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. Two physicians reviewed all records for independent end point classification (criteria provided in the online-only Data Supplement) and assignment of event dates. The institutional review boards of all MESA field centers approved the study protocol, and all participants gave informed consent.

Cardiac Magnetic Resonance

LV mass and LV end-diastolic volumes were indexed to body surface area (LVMi and EDVi). LV mass-to-volume ratio (MVR) and ejection fraction (LVEF) were obtained as previously described. In addition to indexing the LV mass by body surface area, an allometric approach to indexing the LV mass as used in the same population was also implemented. A detailed explanation of the acquisition methods is provided in the online-only Data Supplement.

LGE was used to detect presence of regional scar replacement. Delayed contrast enhancement images were obtained 15 minutes after an intravenous bolus injection of gadolinium-dihydric trinitrinate (0.15 mmol/kg, Magnevist, Bayer Healthcare Pharmaceuticals, NJ) to identify regional fibrosis. Short-axis slices, 1 horizontal and 1 vertical long axis, all at the same positions as the cine images were acquired. The images were analyzed using QMass (Medis, The Netherlands). The region of interest for myocardium was manually placed on short-axis slices, and the scar replacement area was then detected as the area with increased intensity manually by the user for each slice.

For evaluation of diffuse fibrosis, 1 short-axis precontrast modified look-locker inversion recovery image at the midslide position was acquired and repeated at 12 and 25 minutes after contrast injection (5 of the 6 centers; all Siemens 1.5-T scanners). The imaging has been described in detail before. All images were acquired with the same trigger delay time in end diastole. T1 maps were constructed offline using QMass research. On each T1 map (precontrast and postcontrast), a region of interest was manually drawn around the core myocardium to calculate the myocardial T1 time. Lower postcontrast T1 times have been associated with greater diffuse myocardial fibrosis.

Statistical Analysis

Statistical analysis was performed with STATA, version 12 (Stata Corp, TX), LV structure and function, T1 mapping parameters, presence of myocardial scar, and participants’ baseline data were evaluated using the Student t test for continuous variables and the χ² test for categorical variables. We stratified the cohort by sex in all analyses.

The associations of LV structure and function parameters from year 0 and year 10 examinations with presence of myocardial scar at year 10 and T1 mapping parameters at year 10 were assessed using multivariable logistic and linear regression analyses, respectively, with fibrosis markers as dependent variables. Participants who had scar detected from the LGE assessment were excluded for analysis with T1 mapping parameters. The models adjusted for the following covariates: demographics (age and ethnicity) and traditional cardiovascular risk factors (body mass index, systolic blood pressure, hypertension medication, diabetes mellitus, smoking, high-density lipoprotein, and total cholesterol). In addition, when T1 times were the dependent variable, adjustment was performed for factors affecting acquisition—heart rate during CMR acquisition for precontrast T1 times and exact gadolinium dose and glomerular filtration rate for postcontrast T1 times. In addition to LV mass indexed by body surface area, LV mass indexed using an allometric approach was also used to clarify that the relationships were independent of the indexing method.

In the assessment of association with year 10 LV structure and function variables, the models adjusted for year 10 covariates. In the assessment of association with change in structure and function, the models adjusted for 10-year change in covariates and year 0 value of the parameter studied, as well as year 0 value of the covariates. The associations explored with change include both categorical (coded as decrease of >1 SD=0, change of <1 SD=1, and increase of >1 SD=2) and continuous change.

Further analysis was performed to check for variation of hypertension status and LV structure and function and fibrosis. Hypertension categories were defined based on hypertension status based on Joint National Committee VI criteria at year 0 and year 10. Four categories were defined: without hypertension at year 0 and year 10, with hypertension at year 0 but no hypertension at year 10, with hypertension at year 10 but not at year 0, and those with hypertension at year 0 and year 10. Values of LV structure and function and diffuse myocardial fibrosis were compared across categories using 1-way ANOVA. Presence of scar was compared across categories using the χ² test.

Results

Table 1 shows the baseline and follow-up population characteristics by sex. The mean age of women and men at baseline was 58 and 59 years, respectively. The number of participants on lipid-lowering and antihypertensive medication increased significantly for 10 years. The proportion of participants with impaired fasting glucose and treated diabetes mellitus increased significantly during the 10-year follow-up period in association with a significant increase in body mass index. During the 10-year follow-up period, 83 participants had a cardiovascular event (18 women, 65 men), 26 had a myocardial infarction (3 women, 23 men), and 13 had congestive heart failure (4 women, 9 men). CMR-defined LVMi increased significantly for men, whereas EDVi decreased significantly in both women and men during the 10-year follow-up period. In women, there was also a decrease in end-systolic volume index and no change in LVEF, whereas in men, there was no significant change in end-systolic volume index and consequently a small but significant reduction in LVEF. The LV MVR increased between baseline and follow-up in both women and men, although men had a higher mean MVR compared with women in both examinations. Postcontrast T1 times at 12 and 25 minutes were lower in women compared with men. Conversely, the proportion of participants with myocardial scar in men (12.9%) was 5× greater than that in women (2.5%).
Late Gadolinium Enhancement

Table 2 shows the coefficients for logistic regression analyses of structural and functional variables for the presence of LGE-defined scar at the year 10 follow-up examination. Cross-sectional analysis (versus year 10 structural and functional LV parameters) showed that the presence of myocardial scar was associated with greater LVMi and MVR, as well as lower LVEF with coefficients greater in women than in men. LGE-defined myocardial scar was also associated with higher EDVi in men but not in women. Greater LVMi and MVR at year 0, as well as their increase for 10 years, were also associated with the presence of myocardial scar at year 10 after adjustment for covariates. A lower LVEF at year 0 and a further decrease during the 10-year follow-up period were also associated with the presence of LGE-defined myocardial scar. When LV mass was indexed using the allometric approach, the results remained consistent and similar with what was observed for LVMi (indexed to body surface area) as shown in Table S3.

Participants who had scar detected from the LGE assessment were excluded for analysis with T1 mapping parameters because the presence of LGE-defined scar was significantly associated with precontrast and postcontrast T1 times. Precontrast T1 times were significantly higher and postcontrast T1 times significantly lower in the group with CMR scar defined by LGE (Table S1).

Precontrast and Postcontrast T1 Times

Table 3 (Table S2) shows association of T1 times with LV structural and functional parameters. Cross-sectional analyses at follow-up (year 10 examination) revealed that lower LVMi and EDVi were associated with lower postcontrast T1 times, reflecting greater interstitial fibrosis. Regression coefficients were greater in women versus men as indicated in adjusted linear regression plots in Figure 1. Approximately 1 g/m² lower LVMi was related to 1.0 to 1.2 ms lower postcontrast T1 times in women, whereas the corresponding value was 0.35 to 0.45 ms in men. In men also, lower LVEF was associated with lower postcontrast T1, reflecting greater fibrosis. Greater concentric remodeling indexed as higher MVR was related to higher precontrast T1 times (greater fibrosis) in both univariable (coefficient: 15.67, P=0.021) and multivariable (coefficient: 17.46, P=0.018) analyses but in men only. Precontrast T1 times showed weak inverse correlations with LVMi and EDVi but not with LVEF and only in univariate analyses. None of the other parameters showed any statistically significant relationship with precontrast T1 times even after sex-specific analysis.
Longitudinal analyses revealed that a decrease in LVMi (in both men and women), EDVi (in women only), and LVEF (in men only) was related to a lower postcontrast T1 times. These relationships remained significant after repeating the analysis stratified by sex. In men only, higher baseline MVR (coefficient: 28.95; $P<0.005$) but not its change was related to increased precontrast T1 times. None of the other baseline parameters or their change showed a statistically significant relationship with precontrast T1 times. When LV mass was indexed using the allometric approach, the results remained consistent and

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable</th>
<th>Multivariable</th>
<th>$r^2$</th>
<th>Univariable Δ</th>
<th>BL</th>
<th>Multivariable</th>
<th>$r^2$</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LVMi</td>
<td>0.07 (0.04 to 0.10)*</td>
<td>0.07 (0.03 to 0.11)*</td>
<td>0.14</td>
<td>0.03 (−0.02 to 0.07)</td>
<td>0.06 (0.01 to 0.11)†</td>
<td>0.08 (0.02 to 0.13)*</td>
<td>0.19</td>
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<td>EDVi</td>
<td>−0.01 (−0.05 to 0.03)</td>
<td>0.001 (−0.04 to 0.04)</td>
<td>0.07</td>
<td>0.003 (−0.04 to 0.05)</td>
<td>−0.001 (−0.05 to 0.04)</td>
<td>−0.002 (−0.05 to 0.05)</td>
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<td>MVR</td>
<td>3.45 (1.94 to 4.96)*</td>
<td>3.17 (1.51 to 4.83)*</td>
<td>0.14</td>
<td>1.9 (−0.25 to 4.04)</td>
<td>4.54 (1.54 to 7.54)*</td>
<td>2.30 (0.26 to 4.34)†</td>
<td>0.2</td>
</tr>
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<td>LVEF</td>
<td>−0.09 (−0.15 to 0.03)*</td>
<td>−0.06 (−0.14 to −0.02)†</td>
<td>0.11</td>
<td>−0.06 (−0.12 to −0.00)†</td>
<td>−0.10† (−0.19 to −0.01)†</td>
<td>−0.08 (−0.15 to −0.01)†</td>
<td>0.18</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>LVMi</td>
<td>0.05 (0.03 to 0.06)*</td>
<td>0.05 (0.04 to 0.07)*</td>
<td>0.12</td>
<td>0.04 (0.02 to 0.06)*</td>
<td>0.05 (0.03 to 0.07)*</td>
<td>0.05 (0.03 to 0.07)*</td>
<td>0.13</td>
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<tr>
<td>EDVi</td>
<td>0.02 (0.00 to 0.03)†</td>
<td>0.02 (0.01 to 0.03)*</td>
<td>0.08</td>
<td>0.02 (0.01 to 0.03)*</td>
<td>0.02 (0.01 to 0.04)*</td>
<td>0.02 (0.01 to 0.04)*</td>
<td>0.08</td>
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<tr>
<td>MVR</td>
<td>1.29 (0.58 to 2.01)*</td>
<td>0.93 (0.15 to 1.71)†</td>
<td>0.07</td>
<td>0.3 (−0.47 to 1.07)</td>
<td>1.21 (0.06 to 2.35)†</td>
<td>0.81 (−0.02 to 1.64)</td>
<td>0.07</td>
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<tr>
<td>LVEF</td>
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<td>−0.06 (−0.09 to −0.04)*</td>
<td>0.09</td>
<td>−0.04 (−0.06 to −0.02)*</td>
<td>−0.09 (−0.13 to −0.05)*</td>
<td>−0.06 (−0.09 to −0.03)*</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Coefficients and 95% confidence intervals in brackets for multivariable logistic regression models to assess the cross-sectional associations and baseline and change associations of CMR variables with T1 postcontrast 12’ times at year 10. Multivariable models adjusted for risk factor values at year 10 for cross-sectional associations. For associations with baseline (BL) and change (Δ) in values, models adjusted for baseline value and change in value of covariates. CMR indicates cardiac magnetic resonance; EDVi, end-diastolic volume indexed to body surface area (ml/m²); LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction (%); LVMi, LV mass indexed to body surface area (g/m²); and MVR, mass-to-volume ratio (g/mL). *if $P<0.001$, †if $P<0.05$.
similar with what was observed for LVMi (indexed to body surface area) as shown in Table S4.

**Hypertension Status, Fibrosis, and LV Structure and Function**

LVMi and MVR were greater in those with hypertension at both the baseline (year 0) and follow-up (year 10) MESA examinations. LVEF was greater in women with hypertension compared with those without hypertension. The percentage of participants with myocardial scar was significantly higher in those with hypertension compared with those without hypertension. Postcontrast T1 times were also lower, reflecting greater interstitial fibrosis in those with hypertension compared with those without hypertension. However, this was statistically significant in men only (Table S4). Eight women and 24 women were categorized as having hypertension at year 0 but not at year 10. Because the number of participants in this group was small, it was omitted from analysis.

**Discussion**

This study investigates the relationship between LV remodeling characterized by alterations of LV structure and function that occurred during a 10-year period, with CMR-derived parameters of replacement and interstitial myocardial fibrosis measured at follow-up. Our study shows that in a large multiethnic population of middle-to-older aged women and men followed for 10 years, (1) LV structural and functional correlates of replacement fibrosis from LGE are different from those of diffuse myocardial fibrosis from T1 mapping, (2) there are differences in these correlations of myocardial fibrosis with LV remodeling in women versus men, and (3) hypertension is related to myocardial hypertrophy and both replacement and interstitial fibrosis.

**Replacement Myocardial Fibrosis**

Previous studies have shown cross-sectional associations of replacement myocardial fibrosis with systolic and diastolic dysfunction, adverse LV remodeling, and mortality. Our study shows similar cross-sectional associations of replacement fibrosis with LV structural and functional indices in the MESA follow-up examination. In addition, LV structural and functional parameters measured 10 years previously, as well as their 10-year change, were related to presence of replacement fibrosis in the MESA follow-up examination. Increased myocardial mass and concentricity and decreased function were associated with the presence of LGE-defined scar defined follow-up. Importantly, in men only, presence of replacement fibrosis was also associated with LV dilatation during the follow-up period.

Progressive LV remodeling arising from hypertension, diabetes mellitus, and other cardiovascular risk factors may lead to hypertrophied myocytes and increased LV concentric remodeling. Myocardial overload coupled with impaired microvascular circulation can result in focal myocyte necrosis, leading to focal replacement fibrosis. However, sudden loss of myocardial tissue because of myocardial infarction, as well as progressive replacement fibrosis induced by the mechanisms mentioned above, may induce eccentric remodeling characterized by lengthened myocytes, greater volume, and reduced LVEF. Therefore, as demonstrated, focal/replacement fibrosis as cause or consequence of myocardial injury is associated with compensatory mechanisms known to influence the residual myocardium, leading to concentric or eccentric hypertrophy accompanied by dilatation or LV volume reduction.

**Diffuse Myocardial Fibrosis**

In our study, postcontrast T1 mapping of the myocardium, with lower values indicating greater fibrosis, showed the strongest and most consistent relationships with parameters of LV remodeling. In women, lower LV mass and chamber volumes at baseline, and their further longitudinal decrease during a 10-year follow-up period, were related to greater interstitial fibrosis. In men, lower LV chamber volume at baseline and a reduction during the 10-year follow-up period of time in LV mass and LVEF were consistently related to greater diffuse interstitial fibrosis. Interestingly, in men, concentric
remodeling at baseline was associated with greater interstitial fibrosis 10 years later, but the cross-sectional association at the end of the follow-up period was not statistically significant. Moreover, precontrast T1 times were positively associated with MVR only. This is perhaps indicative of precontrast T1 times being representative of both intracellular and extracellular alterations that become prominent only with advanced cardiac disease and greater hypertrophic concentricity.

The process of death and regeneration of myocytes continues through the entire cardiac life. Studies have shown that with aging the process of cell regeneration slows down, leading to noncompensated myocyte loss and progressively diffuse myocardial fibrosis. Ventricular remodeling secondary to exposure to cardiovascular risk factors places increased demands on this process of myocyte death and regeneration and shifts this homeostasis further, in addition to the effects of structural and functional changes associated with aging alone. This is evidenced in this study by the relationship of baseline concentric remodeling, as well as decreased LVMi and chamber volume with diffuse interstitial fibrosis.

Therefore, although focal/replacement fibrosis, indicative of more extensive myocyte loss, is easily detectable using LGE and is associated with increased LV mass and chamber size, cardiac aging, characterized by diffuse interstitial fibrosis in the same population was studied in detail previously. Ventricular remodeling secondary to exposure to cardiovascular risk factors places increased demands on this process of myocyte death and regeneration and shifts this homeostasis further, in addition to the effects of structural and functional changes associated with aging alone. This is evidenced in this study by the relationship of baseline concentric remodeling, as well as decreased LVMi and chamber volume with diffuse interstitial fibrosis.

Table 4. Hypertension Status, Fibrosis, and LV Hypertrophy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women (n=866)</th>
<th>Men (n=915)</th>
<th>P Value</th>
</tr>
</thead>
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<td>Year 10</td>
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<tr>
<td>LVMi</td>
<td>56±8</td>
<td>60±10</td>
<td>63±10</td>
</tr>
<tr>
<td>EDVi</td>
<td>63±11</td>
<td>61±11</td>
<td>62±11</td>
</tr>
<tr>
<td>MVR</td>
<td>0.92±0.2</td>
<td>1.01±0.2</td>
<td>1.03±0.2</td>
</tr>
<tr>
<td>LVEF</td>
<td>63.1±6</td>
<td>63.8±7</td>
<td>64.5±7</td>
</tr>
<tr>
<td>Year 0</td>
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<td></td>
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<td>56±8</td>
<td>58±8</td>
<td>63±9</td>
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<tr>
<td>EDVi</td>
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<td>68±10</td>
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<td>0.94±0.1</td>
</tr>
<tr>
<td>LVEF</td>
<td>63.1±5</td>
<td>63.6±6</td>
<td>64.6±5</td>
</tr>
</tbody>
</table>

Fibrosis measures

| T1 pre  | 986±45       | 984±48      | 989±45  | 0.74   | 966±37  | 970±38  | 969±53  | 0.65   |
| T1 12'  | 444±43       | 437±40      | 438±39  | 0.11   | 471±33  | 467±32  | 460±37  | 0.002  |
| T1 25'  | 508±42       | 501±41      | 501±39  | 0.11   | 536±35  | 530±37  | 523±37  | <0.001 |
| Scar %  | 1.06         | 2.55        | 4.44    | 0.022  | 8.67   | 14.42   | 18.49   | 0.001  |

Mean±SD for cardiac magnetic resonance variables among 3 groups for men and women in those without hypertension at year 0 and year 10 (group 0), those with hypertension at year 10 but not at year 0 (group 1), and those with hypertension at both year 0 and year 10 (group 2). Hypertension was determined based on Joint National Committee VI criteria. P value shown is for 1-way ANOVA based on the 3 defined categories. EDVi indicates end-diastolic volume indexed to body surface area (mL/m²); LV, left ventricular; LVEF, LV ejection fraction (%); LVMi, LV mass indexed to body surface area (g/m²); MVR, mass-to-volume ratio (g/mL); and T1 pre, T1 at 12’, T1 at 25’, T1 time at T1 precontrast injection, 12 and 25 min postcontrast injection, respectively (ms).
fibrosis detected by T1 mapping, may be associated with both decreased LV mass and chamber size.

**Sex Differences in Myocardial Fibrosis and Ventricular Remodeling**

Sex-related differences in adaptations to increased load and myocardial dysfunction have been studied before. These results support the concept that in population studies women and men undergo different patterns of LV remodeling either because of different exposures to injurious mechanisms or different responses to cardiovascular risk factors over time. For associations with replacement fibrosis, subtle sex differences were observed (higher magnitude of coefficients in women), indicating that replacement fibrosis is associated with larger changes in structure and function in women compared with men. Figure 1 illustrates associations of LV structure and function with diffuse fibrosis. Higher coefficients in women compared with men were observed in relationship with LV mass. The magnitude of concentric remodeling was also considerably lower among women versus men. This perhaps results from a combination of processes: (1) adverse remodeling is more common in men; (2) reduction in the number of myocytes is faster in men compared with women, and myocyte turnover is also slower in men than women; (3) the size of myocytes is on average larger in men compared with women; and, (4) the coefficients also reflect the fact that average LV mass and LV volumes are higher in men compared with women even after body size indexing. Lower LV chamber volume during a 10-year period was strongly related to diffuse interstitial fibrosis with fewer myocytes (related to aging and remodeling) could explain the enhanced prevalence of diastolic heart failure seen in older men and especially women. Although there was a nonsignificant relationship between diffuse fibrosis and LVEF in women, increasing fibrosis had a strong association with reduced LVEF in men reflecting greater systolic dysfunction.

**Hypertension, Fibrosis, and Hypertrophy**

We also demonstrate in this study that in those with continued hypertension (baseline and follow-up examination), there is significantly greater concentric remodeling and greater fibrosis (both replacement and diffuse). Increased blood pressure is related to increased myocyte hypertrophy, as well as concentric remodeling, so that LV chamber performance can be maintained (as evidenced by either maintained or increased LVEF). The process of increased reactive fibrosis linked to the activation of the renin–angiotensin–aldosterone system might potentially be at play, enhancing alterations in those with hypertension. The relationship of the presence of replacement fibrosis assessed with delayed enhancement in particular was strong. There was a 2-fold (men) to 4-fold (women) increase in the percent of participants who had replacement fibrosis in the group with sustained hypertension compared with those without hypertension.

Those with sustained hypertension also had increased diffuse myocardial fibrosis compared with those without hypertension in this population; however, this relationship was weaker than that observed for replacement fibrosis and hypertension. The quantification of diffuse or interstitial fibrosis using T1 times provides us with a measure of diffuse fibrosis/volume of extracellular matrix relative to that of the volume of the whole myocardium. This definition has an inherent disadvantage: with increasing myocyte hypertrophy (and hence total myocardial volume), as seen in hypertension, the sensitivity of this method of quantification to detect small changes in diffuse fibrosis might be reduced. This could potentially be among the reasons that interstitial fibrosis was only modestly increased in those with sustained hypertension compared with those without hypertension. The effective change in the amount of diffuse fibrosis in addition to hypertrophy concurrently with hypertension status in a longitudinal fashion would perhaps shed more light on this relationship.

**Perspective**

Temporal changes in LV structure and function help in studying the complex process of remodeling of the left ventricle with aging and hypertension. Myocardial fibrosis is considered as 1 of the chief factors that influence the process of cardiac disease and remodeling. This study explores the relationship between temporal changes in LV structure and function and diffuse and interstitial myocardial fibrosis.

**Limitations**

To our knowledge, this is the first study associating longitudinal changes in LV structure and function to myocardial fibrosis in a large multiethnic population. This population was free of any cardiovascular disease at baseline, and hence the conclusions from this study may be limited by survival bias. An analysis of changes in myocardial fibrosis concomitantly with LV remodeling could not be performed because fibrosis indices were available only at follow-up. In this study, we assess the association of temporal changes of LV structure and function with cross-sectional data with respect to fibrosis measures; inferences with respect to longitudinal changes in fibrosis with changes in LV structure and function could not be made. In the process of a 10- to 12-year longitudinal study such as one in our study, it is a reality that there would be changes in personnel, technology, and methodology. To calibrate and account for changes that occur because of changes in pulse sequences and readers between the baseline and follow-up examinations, utmost care was taken. A detailed explanation of this process has been provided in the online-only Data Supplement; however, we do acknowledge that this introduces additional variability in the measurement of temporal changes.

**Conclusions**

This study shows that while increasing LV hypertrophy and decreasing ejection fraction for 10 years are associated with replacement fibrosis, decreasing LV mass for 10 years, perhaps related to age- and risk factor–mediated myocyte loss, was associated with diffuse myocardial fibrosis. Increased concentricity in women only and LV dilatation in men only were associated with replacement fibrosis, indicating sex differences in remodeling mechanisms. In addition, ejection fraction was preserved with increased diffuse myocardial...
fibrosis in women but was reduced in men. Finally, hypertension-induced remodeling is related to enhanced replacement and interstitial fibrosis, as well as hypertrophy in a multiethnic population of free-living individuals.

Acknowledgments

We thank the other investigators, the staff, and the participants of the Multi-Ethnic Study of Atherosclerosis study for their valuable contributions. A full list of participating Multi-Ethnic Study of Atherosclerosis investigators and institutions can be found at http://www.mesa-nhlbi.org/ (http://www.clinicaltrials.gov. Unique identifier: NCT00005487).

Sources of Funding

This research was supported by contracts N01-HC-95159 through N01-HC-95168 from the National Heart, Lung, and Blood Institute.

Disclosures

None.

References


Novelty and Significance

What Is New?

- Exploration of the relationship of changes in left ventricular (LV) structure and function during 10 years with fibrosis at the end of follow-up in multiethnic free-living individuals.
- The LV structural and functional correlates of replacement and diffuse interstitial fibrosis are different.
- Sex-specific associations.

What Is Relevant?

- The longitudinal study of LV remodeling, an important component in hypertensive heart disease.

- The relationship of LV remodeling and sustained hypertension with fibrosis.

Summary

During a 10-year period, increased concentric hypertrophy in women and LV dilatation in men were associated with replacement fibrosis, whereas decreasing LVMI was associated with diffuse fibrosis. Hypertension-induced remodeling is related to enhanced replacement and diffuse fibrosis, as well as hypertrophy.
Association of Longitudinal Changes in Left Ventricular Structure and Function With Myocardial Fibrosis: The Multi-Ethnic Study of Atherosclerosis Study

Bharath Ambale Venkatesh, Gustavo J. Volpe, Sirisha Donekal, Nathan Mewton, Chia-Ying Liu, Steven Shea, Kiang Liu, Gregory Burke, Colin Wu, David A. Bluemke and João A.C. Lima

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Association of Longitudinal Changes in Left Ventricular Structure and Function with Myocardial Fibrosis: The MESA study

Bharath Ambale Venkatesh, PhD; Gustavo J. Volpe, MD; Sirisha Donekal, MD; Nathan Mewton, MD, PhD; Chia-Ying Liu, PhD; Steven J. Shea, MD, MS; Kiang Liu, PhD; Gregory Burke, MD, MS; Colin Wu, PhD; David A. Bluemke, MD, PhD; Joao A.C. Lima, MD.

The authors would like to thank Dr. John Eng (Johns Hopkins University, Baltimore, MD) for performing the correction detailed below that allowed us to compare year-0 and year-10 MRI variables, and for the preparation of this document.

BACKGROUND

The MESA cardiac MRI protocol was established in 1999 and implemented in 2000 at all sites. The protocol used the fast gradient echo (FGRE) MRI pulse sequence to obtain cine images of the heart at year-0. This pulse sequence was well validated at the time and was available at all MESA sites.

In 2001, Carr et al. published a new method for cardiac cine MRI, the steady-state free precession (SSFP) pulse sequence. The new method was 2.7 times faster than the prior FGRE approach, resulting in shorter breath-hold times for the MESA participants. SSFP’s other advantage is that it is not dependent on flowing blood (as is the case for FGRE). The definition between myocardial wall and blood pool is greater with SSFP compared to FGRE since fluid is intrinsically bright on SSFP images. SSFP has since replaced FGRE for routine cine cardiac MRI. The SSFP technique has been subsequently validated and found to be more reproducible with better image quality than FGRE. Thus, MESA year-10 study used SSFP cine MRI.

Unfortunately, quantification of SSFP MRI results in different left ventricular mass and volumes than using FGRE. There are also less significant, but important differences regarding the software and readers. Newer, more rapid software methods for quantification of the MRI data were developed between 2000 and 2010. MESA year-10 used CIM 6.0 software (UniServices, Auckland, New Zealand) while MESA year-0 used MASS 4.0 software (Medis, Leiden, Netherlands). Year-10 also used different readers than year-0. Therefore, in order to compare MESA year-0 and year-10 MRI data, it was necessary to use correction equations to account for these differences.

METHODS

At baseline, Cardiac MRI was performed with 1.5-T scanners with determination of LV mass and volumes as previously described. Briefly, a stack of short-axis images covering the entire LV was acquired using a fast gradient recalled echo sequence. The endocardial and epicardial myocardial borders were contoured using a semi-automated method (MASS 4.2, Medis, Leiden, the Netherlands). The difference between the epicardial and endocardial
areas for all slices was multiplied by the slice thickness and section gap, and then multiplied by the specific gravity of myocardium (1.04 g/ml) to determine the ventricular mass. Papillary muscle mass was included in the LV cavity and excluded from the LV mass.

At follow-up, MESA participants without contraindications underwent CMR exams using 1.5T scanners (Avanto and Espree, Siemens Medical Systems; Signa LX, GE Healthcare) with a six-channel anterior phased-array torso coil and corresponding posterior coil elements. LV function, dimensions and myocardial mass were assessed by a cine steady-state free precession sequence. Twelve short axis slices, one 4-chamber view and one 2-chamber view were acquired as described previously\textsuperscript{22}. LV structural parameters (LV mass and volumes) and LV ejection fraction were measured using commercially available software (CIM v6.2, Auckland, New Zealand)\textsuperscript{28}.

For derivation of the longitudinal conversion coefficients, data were used from the following additional readings performed.

<table>
<thead>
<tr>
<th>Data source</th>
<th>Pulse sequence</th>
<th>Reader</th>
<th>N</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 0</td>
<td>FGRE</td>
<td>Current</td>
<td>500</td>
<td>Calibration for different readers/software</td>
</tr>
<tr>
<td>Year 10</td>
<td>FGRE</td>
<td>Current</td>
<td>500</td>
<td>Calibration for different pulse sequences</td>
</tr>
<tr>
<td>Year 0</td>
<td>FGRE</td>
<td>Past</td>
<td>~75</td>
<td>Estimate of reader variability</td>
</tr>
<tr>
<td>Year 10</td>
<td>FGRE</td>
<td>Current</td>
<td>100</td>
<td>Estimate of reader variability</td>
</tr>
</tbody>
</table>

**READER CALIBRATION**

Errors-in-variables linear regression between original Exam 1 FGRE readings and re-readings of Exam 1 by current readers was performed. This gave a calibration equation that corrected for reader and software differences between year-0 and year-10 for each of the major MRI outcome variables. The errors-in-variables regression required an estimate of variability of the original year-0 FGRE readings, and this was obtained from conventional ANOVA of the year-0 reproducibility data\textsuperscript{1}.

**PULSE SEQUENCE CALIBRATION**

Errors-in-variables linear regression between FGRE and SSFP readings for year-10 participants was performed. This gave a calibration equation that corrected for pulse sequence differences between year-0 and year-10 for each of the major MRI outcome variables – left ventricular (LV) mass, end-systolic volume (EDV) and end-diastolic volume (ESV). The errors-in-variables regression required an estimate of variability of the year-10 FGRE readings, and this is obtained from conventional ANOVA.

**COMBINED CALIBRATION**

Reader and pulse sequence calibration equations were algebraically combined to obtain overall equations for each of the major MRI outcome variables. This equation was used to correct original year-0 readings to be comparable to year-10 readings.
EQUATIONS

The correction equations used in this paper following the above methodology were:

\[
LV\ Mass(\text{SSFP @ year0}) = olvedm1(\text{FGRE @ year0}) \times 0.7491541082777 + 11.55746667761
\]

\[
LV\ EDV(\text{SSFP @ year0}) = olvedv1(\text{FGRE @ year0}) \times 0.9576837658703 + 7.589499318002
\]

\[
LV\ ESV(\text{SSFP @ year0}) = olvesv1(\text{FGRE @ year0}) \times 0.8945541670171 + 12.72954664005
\]

Please note that ejection fraction was calculated after the correction is performed from LV ESV and EDV.

REFERENCES


### Supplemental Table S1: LV structure and function variables from MRI and in women and men without scar (LGE –ve) and with scar (LGE+–ve) at year 10 defined by late gadolinium enhancement (LGE).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women (n=874)</th>
<th>Men (n=939)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LGE –ve</td>
<td>LGE +ve</td>
</tr>
<tr>
<td>LVMi (g/m²) at year-10</td>
<td>59.2±9.3</td>
<td>70±14.4</td>
</tr>
<tr>
<td>LVMi (g/m²) at year-0</td>
<td>58.8±8.4</td>
<td>65.6±16.6</td>
</tr>
<tr>
<td>ΔLVMi (g/m²)</td>
<td>0.4±8.4</td>
<td>2.3±11.8</td>
</tr>
<tr>
<td>EDVi (ml/m²) at year-10</td>
<td>62.2±10.8</td>
<td>61±14.4</td>
</tr>
<tr>
<td>EDVi (ml/m²) at year-0</td>
<td>67.5±10.4</td>
<td>66±12.9</td>
</tr>
<tr>
<td>ΔEDVi (ml/m²)</td>
<td>-5.3±9.7</td>
<td>-5±10.4</td>
</tr>
<tr>
<td>MVR (g/ml) at year-10</td>
<td>0.97±0.18</td>
<td>1.18±0.38</td>
</tr>
<tr>
<td>MVR (g/ml) at year-0</td>
<td>0.88±0.14</td>
<td>1.02±0.29</td>
</tr>
<tr>
<td>Δ MVR (g/ml)</td>
<td>0.09±0.18</td>
<td>0.16±0.26</td>
</tr>
<tr>
<td>LVEF (%) at year-10</td>
<td>63.8±6.2</td>
<td>59.8±8.4</td>
</tr>
<tr>
<td>LVEF (%) at year-0</td>
<td>63.8±5.2</td>
<td>62.7±7.1</td>
</tr>
<tr>
<td>Δ LVEF (%)</td>
<td>0.1±6.9</td>
<td>-2.9±9.4</td>
</tr>
<tr>
<td>T1 pre-contrast (ms) at year-10</td>
<td>985±45</td>
<td>1015±49</td>
</tr>
<tr>
<td>T1 at 12’ (ms) at year-10</td>
<td>442±42</td>
<td>419±39</td>
</tr>
<tr>
<td>T1 at 25’ (ms) at year-10</td>
<td>505±42</td>
<td>489±39</td>
</tr>
</tbody>
</table>

LVMi: left ventricular mass indexed to body surface area. EDVi: end-diastolic volume indexed to body surface area. ESVi: end-systolic volume indexed to body surface area. MVR: left-ventricular mass to end-diastolic volume ratio. LVEF: left ventricular ejection fraction. T1 at 12’: T1 time at 12 minutes post contrast injection. T1 at 25’: T1 time at 25 minutes post contrast injection.
**Supplemental Table S2:** Coefficients for cross-sectional multivariable linear regression of T1 25’ times at year-10 with LV size and function at year-10, as well as T1 times at year-10 with 10-year change in LV size and function between the baseline (year 0) and follow up (year 10) CMR exams.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cross-sectional</th>
<th>Longitudinal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uni</td>
<td>Multi</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOMEN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMi</td>
<td><strong>0.95†</strong></td>
<td><strong>1.07†</strong></td>
</tr>
<tr>
<td></td>
<td>(0.58,1.32)</td>
<td>(0.75,1.4)</td>
</tr>
<tr>
<td>EDVi</td>
<td><strong>0.84†</strong></td>
<td><strong>0.60†</strong></td>
</tr>
<tr>
<td></td>
<td>(0.54,1.13)</td>
<td>(0.36,0.84)</td>
</tr>
<tr>
<td>MVR</td>
<td>-14.665</td>
<td>-1.16</td>
</tr>
<tr>
<td></td>
<td>(-33.25,3.92)</td>
<td>(-17.20,14.87)</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.38</td>
<td>0.099</td>
</tr>
<tr>
<td></td>
<td>(-0.16,0.92)</td>
<td>(-0.32,0.52)</td>
</tr>
</tbody>
</table>

| MEN       |     |       |       |     |       |       |
| LVMi     | **0.44†** | **0.46†** | 0.22 | **0.47†** | **0.35*** | **0.73†** | 0.33 |
|          | (0.19,0.70) | (0.19,0.73) |       | (0.17,0.76) | (0.05,0.65) | (0.43,1.03) |       |
| EDVi     | **0.22*** | 0.16 | 0.2 | -0.001 | 0.16 | 0.16 | 0.31 |
|          | (0.02,0.42) | (-0.04,0.36) |       | (-0.22,0.21) | (-0.08,0.37) | (-0.07,0.38) |       |
| MVR      | -1.45 | 2.52 | 0.2 | 9.68 | -0.57 | 6.63 | 0.31 |
|          | (-13.66,10.76) | (-10.16,15.20) |       | (-2.00,21.36) | (-17.11,15.98) | (-5.87,19.14) |       |
| LVEF     | **0.82†** | 0.36 | 0.21 | **0.60†** | **0.07** | **0.45*** | 0.31 |
|          | (0.41,1.23) | (-0.06,0.79) |       | (0.23,0.97) | (-0.48,0.63) | (0.03,0.86) |       |

Coefficients and 95% confidence intervals (in brackets) for multivariable linear regression models to assess the cross-sectional associations, and baseline and change associations of CMR variables with T1 post-contrast 25’ times at year 10. Multivariable models adjusted for risk factor values at year-10 for cross-sectional associations. For associations with baseline (BL) and change ($\Delta$) in values, models adjusted for baseline value and change in value of covariates. Additionally, models adjusted for gadolinium dose and glomerular filtration rate at year-10 for post-contrast T1 times. * if $p<0.05$, † if $p<0.001$.

LVMi: left ventricular mass indexed to body surface area (g/m$^2$). EDVi: end-diastolic volume indexed to body surface area (ml/m$^2$). MVR: left-ventricular mass to end-diastolic volume ratio (g/ml). LVEF: left-ventricular ejection fraction (%).
**Supplemental Table S3:** Coefficients for multivariable logistic regression relating presence of scar defined by LGE at the follow up year-10 exam with LV mass indexed (allometric approach).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cross-Sectional Associations with Baseline and Change</th>
<th>Uni</th>
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<th>Multi</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BL</td>
<td></td>
<td>Δ</td>
<td>BL</td>
<td></td>
<td>Δ</td>
</tr>
<tr>
<td>WOMEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMIa</td>
<td>0.05†</td>
<td>0.05†</td>
<td>0.14</td>
<td>0.02</td>
<td>0.08*</td>
<td>0.04*</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>(0.02,0.07)</td>
<td>(0.02,0.08)</td>
<td></td>
<td>(-0.01,0.05)</td>
<td>(0.02,0.09)</td>
<td>(0.01,0.08)</td>
<td></td>
</tr>
<tr>
<td>MEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMIa</td>
<td>0.04†</td>
<td>0.04†</td>
<td>0.13</td>
<td>0.03†</td>
<td>0.04†</td>
<td>0.05†</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>(0.03,0.05)</td>
<td>(0.03,0.06)</td>
<td></td>
<td>(0.02,0.05)</td>
<td>(0.03,0.06)</td>
<td>(0.03,0.06)</td>
<td></td>
</tr>
</tbody>
</table>

Coefficients and 95% confidence intervals (in brackets) for multivariable logistic regression models to assess the cross-sectional associations, and baseline and change associations of LV mass indexed (allometric approach) with the presence of scar as assessed by LGE at year 10. Multivariable models adjusted for risk factor values at year-10 for cross-sectional associations. For associations with baseline (BL) and change (Δ) in values, models adjusted for baseline value and change in value of covariates. * if p<0.05, † if p<0.001.
**Supplemental Table S4:** Coefficients for cross-sectional multivariable linear regression of T1 12’ times at year-10 with LV mass indexed (allometric approach) at year-10, as well as T1 times at year-10 with 10-year change in LV mass indexed (allometric approach) between the baseline (year 0) and follow up (year 10) CMR exams.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cross-sectional</th>
<th>Longitudinal</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uni</td>
<td>Multi</td>
<td>r²</td>
<td>Uni</td>
</tr>
<tr>
<td></td>
<td>Δ</td>
<td>BL</td>
<td>Δ</td>
<td></td>
</tr>
<tr>
<td>WOMEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMIa</td>
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<td>0.79†</td>
<td>0.46</td>
<td>0.50†</td>
</tr>
<tr>
<td></td>
<td>(0.74,1.25)</td>
<td>(0.57,1.01)</td>
<td></td>
<td>(0.23,0.77)</td>
</tr>
<tr>
<td>MEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMIa</td>
<td>0.43</td>
<td>0.37†</td>
<td>0.28</td>
<td>0.38*</td>
</tr>
<tr>
<td></td>
<td>(0.23,0.63)</td>
<td>(0.16,0.57)</td>
<td></td>
<td>(0.14,0.61)</td>
</tr>
</tbody>
</table>

Coefficients and 95% confidence intervals (in brackets) for multivariable linear regression models to assess the cross-sectional associations, and baseline and change associations of LV mass indexed (allometric approach) with T1 post-contrast 12’ times at year 10. Multivariable models adjusted for risk factor values at year-10 for cross-sectional associations. For associations with baseline (BL) and change (Δ) in values, models adjusted for baseline value and change in value of covariates. Additionally, models adjusted for gadolinium dose and glomerular filtration rate at year-10 for post-contrast T1 times. * if p<0.05, † if p<0.001.
Figure S1: Plots showing scatter plots and linear fits for men (red line) and women (blue line) with LV structure and function parameters at year-10 on the x-axis and post-contrast T1 times in ms at 12 minutes at year-10 on the y-axis.
**Figure S2:** Plots showing scatter plots and linear fits for men (red line) and women (blue line) with 10-year change in LV structure and function parameters on the x-axis and post-contrast T1 times in ms at 12 minutes at year-10 on the y-axis.
**Figure S3:** Plots showing scatter plots and linear fits for calibrated baseline and follow-up LV structure and function parameters on the y-axis and y-axis respectively.

LVMI

LV mass index at baseline.

LV mass index at follow-up

$r=0.71, p<0.001$

EDVI

LV volume index at baseline.

LV volume index at follow-up

$r=0.57, p<0.001$

MVR

LV mass to volume ratio at baseline.

LV mass to volume ratio at follow-up

$r=0.45, p<0.001$

LVEF

LV ejection fraction at baseline.

LV ejection fraction at follow-up

$r=0.33, p<0.001$
MESA Criteria for Events

Each potential event is reviewed and classified using standardized criteria. A reviewer’s classification of an event applies only to the specific hospitalization or outpatient situation under review. Unless the review is for death, a reviewer should not be concerned if there is a history of prior incident events identified in the records or in MESA reviews. Each event should be judged separately as “Definite,” “Probable,” or “No/Absent” for a new incident event.

Criteria for Nonfatal Events

Nonfatal events include MI, resuscitated cardiac arrest, angina, congestive heart failure, peripheral vascular disease (PVD), stroke, and TIA. In addition, MESA records revascularization procedures. MESA is purposefully not identifying asymptomatic coronary or ventricular disease as an end point because of concerns about potential bias.

Criteria for Myocardial Infarction

The criteria for myocardial infarction (MI) include information about chest pain, cardiac enzymes, and ECGs. The MESA MI criteria have been adapted from the Atherosclerosis Risk in Communities (ARIC) study. The source for the ARIC criteria is: “ARIC Protocol 3, Surveillance Component Procedures, Version 4.0” (October 1997).

Chest pain: Chest pain is defined as an episode of ischemic pain, tightness, pressure, or discomfort in the chest, arm, or jaw. Other atypical pains identified as due to coronary ischemia may qualify. If there is a clear noncardiac cause, chest pain is considered to be absent. Duration of pain is not considered part of the chest pain criteria.

Enzyme criteria: Table S5 shows the enzyme criteria in the absence of coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA). Equivocal is between "above normal" and "twice the upper limit of normal," and abnormal is greater than "twice the upper limit of normal."

When (non-CABG or non-PTCA) muscle trauma is present, enzymes are downgraded to equivocal. Enzymes collected during the 48 hours following a CABG or PTCA will be classified differently from the scheme described in Table S5. For PTCA, levels of CK or MB above three times the upper limit of normal (ULN) within 48 hours of the procedure will be categorized as abnormal. MB will take precedence over CK if both are available. These abnormal enzymes would not be “downgraded to equivocal” on the basis of the procedure. Similarly for CABG, levels of MB above five times the ULN within 48 hours of the procedure will be categorized as abnormal. Total CK will not be used for post-CABG enzymes. These abnormal enzymes would not be “downgraded to equivocal” on the basis of the surgical procedure.

After 48 hours, the standard enzyme criteria would again apply. Other new measures, such as myoglobin or MB subforms, may need to be added in the future and will be added as necessary with the same criteria for equivocal (between "above normal" and "twice the upper limit of normal") and abnormal (greater than "twice the upper limit of normal").
Supplemental Table S5. MESA Algorithm to Classify Cardiac Enzymes as Abnormal, Equivocal, or Normal

<table>
<thead>
<tr>
<th>Enzyme Value</th>
<th>There is (a) no known muscle trauma/ hemolysis and (b) no PTCA or CABG in past 48 hours*</th>
<th>Muscle trauma/liver/ hemolytic disease exists</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK-MB = present where present or absent</td>
<td>Abnormal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>CK-MB ≥ 2× ULN (upper limit of normal)</td>
<td>Abnormal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>CK-MB** ≥ 10% Total CK, if no ULN is given</td>
<td>Abnormal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Total CK ≥ 2× ULN and LDH ≥ 2× ULN</td>
<td>Abnormal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>LDH 1 : LDH 2 &gt; 1</td>
<td>Abnormal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>LDH 1 ≥ 2× ULN if LDH 2 is missing</td>
<td>Abnormal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Total CK ≥ 2× ULN or LDH ≥ 2× ULN</td>
<td>Equivocal</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal &lt; Total CK &lt; 2× ULN and Normal &lt; LDH &lt; 2× ULN</td>
<td>Equivocal</td>
<td>Normal</td>
</tr>
<tr>
<td>5% Total CK &lt; CK-MB† &lt; 9% Total CK or CK-MB “weakly present”</td>
<td>Equivocal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Normal &lt; CK-MB &lt; 2× ULN</td>
<td>Equivocal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Normal &lt; LDH 1 &lt; 2× ULN</td>
<td>Equivocal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Data present, but insufficient for above criteria</td>
<td>Incomplete</td>
<td>Incomplete</td>
</tr>
<tr>
<td>Normal &lt; Troponins &lt; 2× ULN</td>
<td>Equivocal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Troponins &gt; 2× ULN</td>
<td>Abnormal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Troponins &lt; ULN</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>CK-MB &lt; ULN</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>All other results</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*PTCA–abnormal in first 48 hours requires Troponins or LDH 1 or CK or CK-MB > 3× ULN; equivocal requires 1-3× ULN. CABG–abnormal in first 48 hours requires Troponins or LDH 1 or CK-MB > 5× ULN; equivocal requires 1-5× ULN. † CK and CK-MB must be in same units for this criterion.

**ECG criteria:** The following ECG tracings are identified by the Field Center and scanned:
- The first two codable ECGs after admission;
- The last codable ECG recorded before discharge; and
- The last codable ECG recorded on day 3 (or the first ECG thereafter) following admission or an in-hospital event.

The Coordinating Center provides the scanned ECGs to the Events Review Committee. Committee members (Physician Reviewers) will review the ECGs and classify them into the categories listed below using clinical criteria.

In addition, MESA will do a central reading of ECGs. This will only be done on events reviewed by the committee for MI, to provide a more standardized serial ECG interpretation that includes the baseline exam ECG as well as the hospital ECGs. Criteria for standardized coding at the ECG Reading Center are provided in Appendix A. These criteria are based on the modification of Minnesota rules for serial ECGs.

**MI criteria:** Table S6 shows the diagnostic categories of MI according to the ECG criteria, enzyme categories, and chest-pain history.

**Supplemental Table S6. MESA Diagnostic Criteria for Hospitalized MI**

<table>
<thead>
<tr>
<th><strong>Cardiac Pain Present</strong></th>
<th><strong>Cardiac Enzymes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG Pattern</strong>*</td>
<td><strong>Abnormal</strong></td>
</tr>
<tr>
<td>Evolution of Major Q-Wave</td>
<td>Definite MI</td>
</tr>
<tr>
<td>Evolution of ST Elevation with or without Q-wave Or New LBBB</td>
<td>Definite MI</td>
</tr>
<tr>
<td>Evolution of ST-T Depression/inversion alone Or Evolution of Minor Q-waves alone</td>
<td>Definite MI</td>
</tr>
<tr>
<td>Single ECG with Major Q-Wave Or Single ECG with LBBB, described as new</td>
<td>Definite MI</td>
</tr>
<tr>
<td>Normal, Absent, Uncodable, other</td>
<td>Probable MI</td>
</tr>
</tbody>
</table>

**CRITERIA FOR RESUSCITATED CARDIAC ARREST**

A category of resuscitated cardiac arrest is an additional nonfatal outcome. This diagnosis is reserved for patients who were in full arrest (asystole or ventricular fibrillation and pulseless) and who underwent cardiopulmonary resuscitation (including cardioversion) successfully. Cardiac arrest secondary to noncardiac conditions, such as respiratory arrest, should not be classified as resuscitated cardiac arrest. Because post-arrest enzymes are
difficult to interpret, in general, attempts to classify MI will not be made in patients with resuscitated cardiac arrest. Patients who never awaken and go on to die during a subsequent hospitalization would not qualify for the diagnosis of resuscitated cardiac arrest. Patients who never awaken and go on to die will be classified according to their cause of death (see Section 4.2). To classify an event as a resuscitated cardiac arrest, all of the criteria below must be met:

- The absence of a clear-cut noncardiac cause. Presence of cardiac symptoms (e.g., chest pain) is confirmatory but not necessary.
- The person must have lived at least 24 hours after resuscitation.

**Criteria for Angina**

The MESA criteria for both inpatient and outpatient angina were adapted from the Women’s Health Initiative (WHI). In MESA, angina is a symptomatic event generally involving ischemic chest, left arm, or jaw pain, though the symptoms may be "atypical." Atypical anginal symptoms can include shortness of breath, exertional dyspnea, epigastric discomfort, and back pain, in addition to pain that is isolated to the arm or the jaw. Physician adjudicators categorize angina events as “definite,” “probable,” and “no angina” based on clinical judgment. In addition, reviewers record the criteria met during the hospitalization or outpatient medical visit:

a. Physician diagnosis of angina and receiving medical treatment for angina (e.g., nitrates, beta-blockers, or calcium-channel blockers)
b. CABG surgery or other revascularization procedure
c. 70% or greater obstruction of any coronary artery per angiography
d. Horizontal or down-sloping ST-segment depression or abnormal ST elevation of ≥1 mm on exercise or pharmacological stress testing with pain
e. Scintigraphic or echocardiographic stress test positive for ischemia
f. Resting ECG shows horizontal or down-sloping ST depression or abnormal ST elevation ≥1 mm with pain that is not present on ECG without pain

Reviewers check all criteria that apply. This approach has the advantage of easily permitting a range of analyses based on definitions of angina that include "soft" criteria (#a only) or various types of "hard" criteria (#b–f). In general, the original report of the procedure should be reviewed rather than accepting references in discharge summaries to the results of diagnostic or therapeutic procedures. However, if an original full report is not available, convincing reference to the procedure results in the discharge summary is acceptable.

Given its difficult diagnosis, angina must retain a stringent criteria standard. All of the following guidelines below should be followed:

a. Clear and thorough documentation of symptoms is needed to identify an event as “definite angina.” Even if a test such as an ETT lists “angina” or “chest pain” as its indication, angina should not be ruled unless there is additional, explicit information from the physician regarding symptoms. Likewise, a test showing positive ischemia
or the performance of a further procedure (e.g., catheterization) is not enough to
rule for angina if other MESA criteria are not met.
b. Only code an event as angina if it is distinct from an MI.
c. Reviewers should not angina as part of pain symptoms of an MI.

Angina will require clinical symptoms to be considered a MESA event. If there is only a
physician diagnosis/treatment, then the diagnosis cannot be "definite." If there is more
than just a physician diagnosis, then the reviewer can assign "definite" instead of
"probable."

**Unstable angina:** There is no formal separate classification for unstable angina. The
suggested definition is “nonelective admission (discharge) to the hospital for acute angina
and not codable as definite or probable MI.”

**Revascularization:** Revascularization will be documented on its own, as a category
separate from other events. In cases where revascularization was performed without
clinical symptoms, the reviewers will record the revascularization, but not record angina. A
reviewer’s classification of revascularization applies only to the specific hospitalization or
outpatient situation under review. A reviewer should not be concerned if there is a history
of prior revascularization(s) identified in the records or in MESA reviews.

**Criteria for Congestive Heart Failure (CHF)**
The MESA criteria for CHF were adapted from the WHI. MESA identifies both inpatient and
outpatient diagnoses of heart failure. Physician reviewers categorize CHF events as
"definite," "probable," and "no CHF." A diagnosis of "definite" or "probable" CHF requires
clear and thorough documentation of symptoms, as asymptomatic disease is not a MESA
endpoint. (A ruling of "definite" requires more than a physician diagnosis.) Reviewers
record the adapted MESA criteria for CHF met:

a. CHF diagnosed by physician, and patient receiving medical treatment for CHF (e.g.,
diuretics, digitalis, vasodilators, beta-blockers, or ACE inhibitors)
b. Pulmonary edema/congestion, by CXR
c. Dilated ventricle or poor left ventricular function (e.g., low ejection fraction or wall
motion abnormalities), by echocardiography, radionuclide ventriculogram
(RVG)/multigated acquisition (MUGA), or other contrast ventriculography, or
evidence of left ventricular diastolic dysfunction.

Reviewers will check all criteria that apply. This approach has the advantage of easily
permitting a range of analyses based on definitions of heart failure that include "soft"
criteria (#a only) or various types of "hard" criteria (#b–c).

In general, the reviewer should examine the original report of a procedure rather than
accept references to results of the diagnostic or therapeutic procedures in discharge
summaries. If an original full report is not available, convincing reference to the procedure
results in the discharge summary is acceptable.

**Criteria for Claudication or Peripheral Vascular Disease (PVD)**
The MESA criteria for claudication have been adapted from the WHI. Claudication is a symptomatic event and in MESA refers to only the lower body—typically exertional leg pain relieved by rest. Outpatient records of claudication will not be sought in MESA unless they include a major outpatient diagnostic procedure such as angiography or angioplasty. Physician adjudicators categorize potential MESA PVD events as “definite,” “probable,” and “no PVD” based on clinical judgment. A ruling of “definite PVD” requires more than a physician diagnosis. Good documentation of symptoms is needed. Even if a test such as a Doppler lists “PVD” or “claudication” as its indication, PVD should not be ruled unless there is information documenting symptoms or treatment for PAD.

Physician adjudicators also subclassify PVD as:

a. Lower extremity claudication
b. Atherosclerosis of arteries of the lower extremities
c. Arterial embolism and/or thrombosis of the lower extremities
d. Abdominal aortic aneurysm

Reviewers also record the PVD criteria met:

a. Ultrasonographically- or angiographically-demonstrated obstruction or ulcerated plaque (≥50% of the diameter or ≥75 of the cross-sectional area) demonstrated on ultrasound or angiogram of the iliac arteries or below
b. Absence of pulse by Doppler in any major vessel of the lower extremities
c. Exercise test that is positive for lower extremity claudication
d. Surgery, angioplasty, or thrombolysis for peripheral vascular disease
e. Amputation of one or more toes or part of the lower extremity because of ischemia or gangrene
f. Exertional leg pain relieved by rest and at least one of the following: (1) claudication diagnosed by physician AND (2) ankle-arm blood pressure ratio ≤0.8
g. Surgical or vascular procedure for abdominal aortic aneurysm
h. Doppler, angiogram, CT, or MRI examination positive for abdominal aortic aneurysm

Criteria for Stroke and TIA

All potential cerebrovascular events are classified as “stroke,” “transient ischemic attack” (TIA), or “not a cerebrovascular event.” All events classified as stroke will be further classified by type: subarachnoid hemorrhage, intraparenchymal hemorrhage, other hemorrhage, brain infarction, or unknown. Criteria for TIA, stroke, and type of stroke are provided below. Criteria for infarct subtype are provided in Appendix B. Symptomatic retinal infarction should be classified as "brain infarction" but requires documentation by an ophthalmologist. "Brain Infarct Subtypes" should also be coded for a symptomatic retinal infarction.

TIA
One or more episodes of focal neurologic deficit

AND
Lasting more than 30 seconds
AND
Complete resolution of focal neurologic deficit within 24 hours
AND
No clinically relevant lesion on brain imaging*
OR
Brain imaging not done
AND
None of the following features: clonic jerking, conjugate eye deviation, prolonged focal seizure with spread, scintillating scotoma, headache with nausea and vomiting, or immediately-preceding head trauma

**Stroke**
Rapid onset of neurologic deficit, headache, or meningismus
AND
Neurologic deficits not secondary to brain trauma (closed head injury), tumor, infection (e.g., encephalitis or meningitis), or other nonvascular cause. (But clinical evidence or suspicion of embolic stroke secondary to SBE would be counted as stroke)
AND
Clinically relevant lesion on brain imaging*
OR
Duration greater than 24 hours
OR
Death within 24 hours

**Criteria for Stroke Types**
*Subarachnoid Hemorrhage (SAH)*
Clinical presentation with sudden onset of a headache, meningismus, loss of consciousness, or coma. Focal neurologic deficit may also be present.

*Clinically relevant lesion on brain imaging: Imaging finding judged to be consistent with signs and symptoms regardless of timing of brain imaging (i.e., less or greater than 24 hours), regardless of stroke type (i.e., with or without blood), and regardless of imaging technique (i.e., cranial computed tomography [CT scan] or cranial magnetic resonance imaging [MRI]).*
AND

Consistent imaging findings with blood mainly in the subarachnoid space (basal cistern or convexity) or isolated intraventricular hemorrhage

OR

Cerebral fluid bloody or xanthochromic on direct nontraumatic examination

OR

Surgical or autopsy evidence of subarachnoid hemorrhage

*Intraparenchymal Hemorrhage (IPH)*
Clinical presentation of focal neurologic deficit; coma may be present

AND

Consistent imaging findings with mainly intraparenchymal, dense hemorrhage

OR

If no imaging, cerebral spinal fluid bloody or xanthochromic on direct nontraumatic examination

OR

Surgical or autopsy evidence of intraparenchymal hemorrhage

*Other Hemorrhage (OH)*
Insufficient data to classify subarachnoid or intraparenchymal hemorrhage

AND

Imaging shows blood in the parenchyma, subarachnoid space, or both

OR

Cerebrospinal fluid bloody or xanthochromic on direct nontraumatic examination

OR

Surgical or autopsy evidence of blood in parenchyma, subarachnoid space,

OR

both

*Brain Infarction (INF)*
Not meeting criteria for SAH, IPH, or OH

AND
Clinical presentation of focal neurologic deficit; coma may be present

AND

Consistent imaging findings without clinically relevant lesion or with clinically relevant mainly nonhemorrhagic lesion or hemorrhagic lesion indicating a hemorrhagic infarction

OR

Surgical or autopsy evidence of brain infarction

Other Stroke Type (OS)
Not meeting criteria for SAH, IPH, OH, INF.

[Examples: venous thrombosis with bleed, arterial dissection.]

Unknown Stroke Type
Insufficient data to classify type as SAH, IPH, OH, INF, or OS

[Examples: No work-up was done.]

Criteria for Deaths
Deaths are classified, using criteria provided below, into the following fatal event categories:

a. Atherosclerotic CHD Death, with subclassifications of “definite fatal MI,” “definite fatal CHD,” and “possible fatal CHD”

b. Stroke Death

c. Other Atherosclerotic Disease Death (noncoronary/nonstroke)

d. Other Cardiovascular Disease Death

e. Non-Cardiovascular Disease Death

Those in categories a, c, and d are categorized according to timing from onset of last episode of symptoms to death (<5 min, 5 min to 1 hr, 1 to 24 hr, >24 hr, unknown). They are also classified as to most important mechanism(s) thought to cause death (more than one may apply):

a. Primary arrhythmic death: death <5 minutes without preceding symptoms of ischemia or heart failure

b. Secondary arrhythmic/mechanical death: death with preceding symptoms of ischemia or heart failure, but not directly due to shock or low output state

c. Congestive heart failure – death due to shock or low output state, including pre-renal azotemia

d. Cardiac procedure such as CABG, angioplasty or stent

e. Hemorrhage from thrombolytic therapy

f. Unknown or uncertain

Criteria for Atherosclerotic Coronary Heart Disease Death
Requires the absence of known nonatherosclerotic or noncardiac cause of death.
**Definite Fatal MI**
Any in-hospital death that meets criteria for MI

OR

Out-of-hospital death with a documented MI within previous 28 days

**Definite Fatal CHD**
Does not qualify as a “definite fatal MI”

AND

Chest pain within previous 72 hours

OR

History of CHD

**Possible Fatal CHD**
Does not qualify as “definite fatal MI” or “definite fatal CHD”

AND

Underlying cause of death included in: ICD-10 codes I20–I25, I46, I51.6, R96,

OR

R98–R99

**Criteria for Stroke Death**
a. Stroke occurrence and type determined by stroke event adjudication: subarachnoid hemorrhage, intraparenchymal hemorrhage, other hemorrhage, brain infarction, other stroke type, or unknown stroke type
b. Mechanism of death is recorded as due to critical brain injury or as secondary to complications such as infections (lungs, urine, skin), pulmonary embolism, or arrhythmia. Critical brain injury can be lethal either because of the size of the infarct or bleed with herniation, or because of the location in the brain stem.

**Criteria for Other Atherosclerotic Disease Death**
If not codable, as above, reviewers can assign "Other Atherosclerotic Disease Death" based upon clinical judgment. Such criteria would include: complications of aneurysm, ischemia of any organ or limb leading to death, etc.

**Criteria for Other Cardiovascular Disease Death**
If not codable, as above, reviewers can assign “Other Cardiovascular Disease Death” based upon clinical judgment. Such criteria would include: pulmonary embolism, valvular heart disease, etc.

**Criteria for Other Death**
None of the above causes of death assigned, or a strong history of a likely cause of death that is not CHD.

Use official ICD-10 code (usually indicated on the death certificate).