Elevated Homocysteine Is Associated With Reduced Regional Left Ventricular Function
The Multi-Ethnic Study of Atherosclerosis

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Background—An elevated homocysteine (Hcy) level has been reported to be a risk factor for the development of congestive heart failure in individuals free of myocardial infarction. In this study, we aim to investigate the relationship between Hcy levels and regional left ventricular function in an asymptomatic population.

Method and Results—Regional peak systolic midwall circumferential strains were calculated from 1178 tagged magnetic resonance imaging studies in participants in the Multi-Ethnic Study of Atherosclerosis (MESA). Left ventricular regions were defined by coronary territories (left anterior descending, left circumflex, right coronary artery). For the 1178 study participants (66±10 years of age, 58% males), the median (interquartile range) of Hcy was 9.1 (9.0 to 9.3). After adjustment for traditional risk factors, race, height, weight, left ventricular end-diastolic mass/volume, serum creatinine, and measures of atherosclerosis, reduced regional myocardial circumferential shortening across sex-specific quartiles of plasma Hcy in the left anterior descending (P=0.038) and left circumflex (P=0.009) regions persisted, which indicated an important association of reduced function with elevated Hcy. Multiple linear regression analyses confirmed that circumferential systolic dysfunction was associated with log transformed Hcy levels in the left anterior descending (P=0.004) and left circumflex (P=0.0002) regions. In the fully adjusted model, the odds ratio for left ventricular strains below the 10th percentile with 1 SD increases in log-transformed Hcy was 1.33 (95% confidence interval, 1.04 to 1.70; P=0.022) for the left anterior descending, 1.28 (95% confidence interval, 1.00 to 1.64; P=0.046) for the left circumflex, and 1.32 (95% confidence interval, 1.03 to 1.69; P=0.025) for the right coronary artery region.

Conclusion—in this asymptomatic population, an elevated Hcy level is associated with reduced regional left ventricular systolic function detected by tagged magnetic resonance imaging. (Circulation. 2007;115:180-187.)

Key Words: contractility ■ heart failure ■ homocysteine ■ imaging ■ magnetic resonance imaging

In the past decade, plasma total homocysteine (Hcy) has been extensively explored and proposed as an independent cardiovascular disease (CVD) risk factor. Elevated total Hcy levels have been related to greater risk of CVD outcomes, which include myocardial infarction, stroke, and cardiovascular mortality, in many but not all studies. However, recent clinical trials have not been able to demonstrate a reduction of clinical CVD end points with a decrease of Hcy levels. However, plasma Hcy was reported to be a risk factor for the development of congestive heart failure (CHF) in the Framingham Heart Study. Although experimental evidence strongly suggests that the myocardium may be uniquely susceptible to Hcy-induced injury, it is unclear whether hyperhomocysteinemia (Hhe) is independently associated with a reduced intrinsic left ventricular (LV) myocardial function in asymptomatic individuals free of CVD.

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This study hypothesized that individuals with Hhe would exhibit alterations in regional LV function. We used magnetic resonance imaging (MRI) to test this hypothesis because, apart from precise measurement of global LV volumes, LV mass, and LV ejection fraction (LVEF), MRI permits assessment of regional LV function in a detailed and quantitative manner through myocardial tagging. Detection of subclinical reduction in LV function potentially identifies asymptomatic individuals at high risk for the development of clinical heart failure. A detailed characterization of regional ventricular function with Hhe may also help elucidate the mechanisms that underlie the increased risk of CHF associated with Hhe.
Methods

Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective study designed to evaluate mechanisms that underlie the development and progression of subclinical CVD in asymptomatic individuals. The details of MESA have been previously described. In short, 6814 men and women, 45 to 85 years of age, from 4 ethnicities (non-Hispanic white, black, Hispanic, and Chinese) were enrolled by 6 participating centers (Wake Forest University, Winston Salem, NC; Columbia University, New York, NY; Johns Hopkins Hospital, Baltimore, Md; University of Minnesota, Minneapolis, Minn; Northwestern University, Chicago, Ill; and University of California, Los Angeles). On entry, all participants underwent extensive evaluation that included clinical questionnaires, physical examination, and laboratory tests, which included fasting plasma glucose, triglycerides, and total, high-density lipoprotein, and low-density lipoprotein cholesterol levels. Individuals with symptomatic CVD were excluded. Total plasma Hcy was measured with high-performance liquid chromatography with fluorometric detection. The coefficient of variation for this assay was 3.8%.

The carotid arteries were evaluated with high-resolution B-mode ultrasonography. One real-time transverse (short-axis) scanning sequence and 1 longitudinal image of the common carotid artery were acquired. The maximal intimal medial thickness (IMT) of the common carotid artery was defined as the mean of the maximal IMT of the near and far wall on both the left and right sides, and it was measured at 10 mm proximal to the common carotid bulb. The values were expressed as mean ± SE in millimeters. Computed tomography scanning of the chest was performed either with an ECG-triggered (at 80% of the RR interval) electron beam computed tomography scanner (Chicago, Los Angeles, and New York field centers: Imatron C-150, GE/Imatron, South San Francisco, Calif) or with prospectively ECG-triggered scan acquisition at 50% of the RR interval with a multidetector computed tomography system at 4 simultaneously acquired 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode (Baltimore, Md, Forsyth County, NC, and St. Paul, Minn field centers: Lightspeed [General Electric Health Care, Chalfont St. Giles, United Kingdom] or Volume Zoom [Siemens, Munich, Germany]). The coronary artery calcification measurements among scanning centers and between participants were adjusted with a standard calcium phantom scanned simultaneously with each participant. The mean Agatston score was used in measurements among scanning centers and between participants.

MRI Protocol for Tagged Images

Images were acquired by 1.5T MR scanners (SIGNA [LX and CV1], General Electric Medical Systems, Waukesha, Wisc, and Siemens Medical Solutions [Vision and Sonata], Erlangen, Germany). All images were obtained by ECG-triggered segmented k-space fast spoiled gradient-echo (SPGR or FLASH) pulse sequence during breath-holding (12 to 18 seconds). Dedicated phase array coils were used for signal reception. After completion of the standard protocol, 4 tagged short-axis slices were obtained. Parallel stripe tags were prescribed in 2 orthogonal orientations (0° and 90°) with an identical pulse sequence with additional spatial modulation of magnetization-encoding gradients.

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; 4 to 9 phase encoding views per segment, and tag spacing of 7 mm. With these parameters, 19 to 27 phases per cycle were acquired, which yielded a temporal resolution of 40 ms (range 20 to 41 ms).

Harmonic Phase Analysis

Tagged short-axis slices were analyzed by harmonic phase imaging (HARP, version 2.0, Diagnosoft Inc, Palo Alto, Calif). HARP is a new method that enables a fast determination of myocardial strain and remodeling. It has been demonstrated that strain measures obtained by HARP have a good overall agreement when compared with Findtags (open source software), a well-established method of strain analysis. To assess the interobserver and intraobserver agreement for myocardial MR-tagging images with the HARP technique, 3 independent observers performed 2 separate and blinded quantitative strain analyses of myocardial cine MR tagging images in 24 MESA trial participants. Intraclass correlation coefficients R for interobserver and intraobserver agreement for peak systolic midwall ECC were 0.81 and 0.84, respectively.

To evaluate regional myocardial function, we used peak midwall systolic/diastolic strain. An in-house tool was developed to evaluate regional strains according to the coronary artery perfusion areas (left anterior descending [LAD], left circumflex [LCX] and right coronary artery perfusion territories). Assignment of the different regions to coronary territories was done according to recent publications. By convention, regional strains have been defined as negative because they indicate systolic circumferential shortening. Therefore, an increased negativity denotes enhanced function.
TABLE 1. Characteristics of the Study Population According to Homocysteine Quartiles

<table>
<thead>
<tr>
<th>Homocysteine Quartiles*</th>
<th>First Quartile</th>
<th>Second Quartile</th>
<th>Third Quartile</th>
<th>Fourth Quartile</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62 ± 10</td>
<td>65 ± 9</td>
<td>68 ± 9</td>
<td>70 ± 9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Men, %</td>
<td>52</td>
<td>54</td>
<td>53</td>
<td>54</td>
<td>0.96</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>124 ± 20</td>
<td>127 ± 19</td>
<td>129 ± 20</td>
<td>135 ± 23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension, † %</td>
<td>35</td>
<td>44</td>
<td>47</td>
<td>61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio</td>
<td>4.1 ± 1.2</td>
<td>4.1 ± 1.3</td>
<td>4.0 ± 1.1</td>
<td>4.1 ± 1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.88 ± 0.16</td>
<td>0.93 ± 0.17</td>
<td>0.98 ± 0.18</td>
<td>1.12 ± 0.44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, ‡ %</td>
<td>15</td>
<td>18</td>
<td>15</td>
<td>23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>10</td>
<td>13</td>
<td>9</td>
<td>12</td>
<td>0.41</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166 ± 10</td>
<td>166 ± 10</td>
<td>165 ± 9</td>
<td>165 ± 10</td>
<td>0.55</td>
</tr>
<tr>
<td>Weight, lb</td>
<td>169 ± 34</td>
<td>166 ± 31</td>
<td>167 ± 30</td>
<td>167 ± 35</td>
<td>0.89</td>
</tr>
<tr>
<td>Coronary artery calcification §</td>
<td>0 (0-79)</td>
<td>6 (0-139)</td>
<td>19 (0-167)</td>
<td>44 (0-296)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid intima media thickness, mm</td>
<td>0.99 ± 0.55</td>
<td>1.06 ± 0.65</td>
<td>1.12 ± 0.60</td>
<td>1.27 ± 0.78</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or %.

HDL indicates high-density lipoprotein.

*Homocysteine (μmol/L) quartiles for women: first, 4.3–7.2; second, 7.3–8.3; third, 8.4–10.1; fourth, 10.2–20.3. Homocysteine (μmol/L) quartiles for men: first, 3.8–8.3; second, 8.4–9.8; third, 9.9–11.6; fourth, 11.7–41.1.

†Hypertension defined as diastolic blood pressure ≥ 90 mm Hg, systolic blood pressure ≥ 140 mm Hg, or receiving treatment for hypertension.

‡Diabetes mellitus defined as fasting plasma glucose ≥ 126 mg/dL or receiving treatment for diabetes.

§Data presented as median (interquartile range).

**Statistical Analysis**

The associations of Hcy with demographic characteristics and cardiovascular risk factors were determined by categorization of the cohort into Hcy quartiles. For comparison of variables with normal distribution, ANOVA was used, whereas the Kruskal-Wallis test was used for variables with skewed distribution. In case of categorical variables, χ² testing was used.

Multiple linear regression models were used to examine relations of systolic circumferential strains in the LAD, LCX, and right coronary artery regions as the dependent variables to plasma Hcy. Three sets of multivariable models were examined in a hierarchical fashion: (1) adjusted for age, gender, and race; (2) adjusted for age, gender, race, height, weight, systolic blood pressure, antihypertensive treatment, cigarette smoking status, diabetes, and total cholesterol/high-density lipoprotein ratio; (3) adjusted for age, gender, race, height, weight, systolic blood pressure, antihypertensive treatment, cigarette smoking status, diabetes status, total cholesterol/high-density lipoprotein ratio, LV mass/volume ratio, serum creatinine, coronary artery calcification, and carotid IMT.

In all of these models, we summarized the means of the LV measurements across quartiles of plasma Hcy. The trend across the quartiles was tested for statistical significance by scoring each quartile by its median value and entering the score as a continuous variable with natural logarithmic transformation as measures of effect, in accordance with the above models. Additionally, logistic regression was used to assess the odds of strains below the 10th percentile for increasing levels of Hcy. The 10th percentile cutoff was also used to categorize values of peak systolic strains as clinically meaningful. We selected this cutoff because the resultant values are in the range shown by Kraitchman et al14 to be dysfunctional. In secondary analyses, we incorporated interaction terms individually in multivariate model 3 (log transformed plasma Hcy × covariate) to test for the presence of effect modification by age, gender, race, systolic blood pressure, and creatinine.

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**

The median (interquartile range [IQR]) and geometric mean (95% confidence interval) of Hcy for the 1178 study participants (mean age ± SD 66 ± 10 years, 58% males) were 9.1 (9.0 to 9.3) and 9.3 (9.1 to 9.5) μmol/L, respectively. The median (IQR) of Hcy levels among females was 8.3 (7.1 to 10.1) μmol/L compared with 9.8 (8.2 to 11.6) μmol/L in males (P < 0.001). As a result, the population was categorized by sex-specific Hcy quartiles. The respective ranges for Hcy (μmol/L) quartiles for women were: first, 4.3 to 7.2; second, 7.3 to 8.3; third, 8.4 to 10.1; and fourth, 10.2 to 20.3; and for men were: first, 3.8 to 8.3; second, 8.4 to 9.8; third, 9.9 to 11.6; and fourth, 11.7 to 41.1. Baseline characteristics of the study population by Hcy quartiles are listed in Table 1. Higher Hcy levels were associated with greater age, systolic blood pressure, serum creatinine, coronary artery calcification, and carotid IMT (all P < 0.0001). Those with higher Hcy levels were also more likely to be hypertensive and have diabetes.

The least-squares mean values of adjusted regional myocardial circumferential shortening across sex-specific quartiles of plasma Hcy are shown in Table 2. In models adjusted for age, gender, and race (model 1), regional systolic function was lower across increasing sex-specific quartiles of plasma Hcy in the LAD and LCX regions (LAD P = 0.047; LCX P = 0.023; right coronary artery P = 0.075 for trend). The relationship of regional myocardial circumferential strains to plasma Hcy quartiles was robust after adjustment for clinical covariates (model 2). The association was unaltered with further adjustment for creatinine levels, left ventricle end-diastolic mass/volume ratio, coronary artery calcification, and carotid IMT (model 3).
When considered as a continuous variable, greater plasma Hcy levels (1 SD increase in log transformed Hcy) were significantly associated with regional circumferential systolic strains in the LAD (P=0.02 to 0.004) and LCX (0.02 to 0.015) for the right coronary artery. Logistic regression analyses demonstrated that in the fully adjusted model (model 3), the odds ratio for LV strains below the 10th percentile with a 1-SD increase in log-transformed Hcy levels was 1.33 (95% confidence interval, 1.07 to 1.68; P=0.002) for the LAD, 1.28 (95% confidence interval, 1.00 to 1.60; P=0.049) for the LCX, and 1.32 (95% confidence interval, 1.03 to 1.69; P=0.003) for the right coronary artery.

As far as global LV indices (LVEF, LV end-diastolic mass, LV end-diastolic volume, LV mass/volume ratio) are concerned, no differences were observed across increasing sex-specific quartiles of Hcy (Table 4). Overall, the associations of Hcy levels with LV indices (regional and global) did not vary by age, gender, race, systolic blood pressure, or creatinine (P for all interactions >0.10) (data not shown).

### Discussion

The present study cross-sectionally examined the relationship of plasma Hcy to regional LV function in a large community-based sample of asymptomatic individuals. Evidence exists in the literature that Hhe is associated with diverse parameters of subclinical CVD such as endothelial dysfunction, vascular stiffness, and atherosclerosis. Our findings extend these observations by demonstrating that greater Hcy

### Tables

**Table 2. Adjusted Mean Left Ventricular Regional Circumferential Strains Across Homocysteine Quartiles**

<table>
<thead>
<tr>
<th>Homocysteine Quartiles</th>
<th>First Quartile</th>
<th>Second Quartile</th>
<th>Third Quartile</th>
<th>Fourth Quartile</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left anterior descending</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Model 1†</td>
<td>−15.7±0.25</td>
<td>−15.8±0.25</td>
<td>−15.6±0.25</td>
<td>−15.0±0.25</td>
<td>0.047</td>
</tr>
<tr>
<td>Model 2‡</td>
<td>−15.8±0.25</td>
<td>−15.8±0.25</td>
<td>−15.5±0.26</td>
<td>−15.0±0.27</td>
<td>0.044</td>
</tr>
<tr>
<td>Model 3§</td>
<td>−15.9±0.25</td>
<td>−15.7±0.26</td>
<td>−15.5±0.25</td>
<td>−15.0±0.26</td>
<td>0.038</td>
</tr>
<tr>
<td>Left circumflex</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Model 1†</td>
<td>−17.5±0.29</td>
<td>−17.1±0.30</td>
<td>−16.9±0.30</td>
<td>−16.6±0.30</td>
<td>0.023</td>
</tr>
<tr>
<td>Model 2‡</td>
<td>−17.6±0.30</td>
<td>−17.2±0.30</td>
<td>−16.9±0.30</td>
<td>−16.5±0.32</td>
<td>0.011</td>
</tr>
<tr>
<td>Model 3§</td>
<td>−17.7±0.29</td>
<td>−17.1±0.30</td>
<td>−16.8±0.30</td>
<td>−16.4±0.31</td>
<td>0.009</td>
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<tr>
<td>Right coronary artery</td>
<td></td>
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<tr>
<td>Model 1†</td>
<td>−12.4±0.24</td>
<td>−12.2±0.26</td>
<td>−12.0±0.25</td>
<td>−11.8±0.26</td>
<td>0.075</td>
</tr>
<tr>
<td>Model 2‡</td>
<td>−12.4±0.25</td>
<td>−12.1±0.25</td>
<td>−12.1±0.26</td>
<td>−11.8±0.27</td>
<td>0.080</td>
</tr>
<tr>
<td>Model 3§</td>
<td>−12.5±0.25</td>
<td>−12.1±0.26</td>
<td>−12.0±0.26</td>
<td>−11.8±0.27</td>
<td>0.070</td>
</tr>
</tbody>
</table>

*Homocysteine (μmol/L) quartiles for women: first, 4.3–7.2; second, 7.3–8.3; third, 8.4–10.1; and fourth, 10.2–20.3. Homocysteine (μmol/L) quartiles for men: first, 3.8–8.3; second, 8.4–9.8; third, 9.9–11.6; and fourth, 11.7–41.1. Quartiles data are adjusted least square means (mean±SEM).

†Model 1: adjusted for age, sex, and race.
‡Model 2: adjusted for age, sex, race, height, weight, cigarette smoking status, diabetes status, systolic blood pressure, antihypertensive medications, and cholesterol/high-density lipoprotein ratio.
§Model 3: adjusted for age, sex, race, height, weight, cigarette smoking status, diabetes status, systolic blood pressure, antihypertensive medications, cholesterol/high-density lipoprotein ratio, left ventricular end-diastolic mass/volume ratio, creatinine, carotid IMT, and coronary artery calcification.

**Table 3. Relations of Plasma Homocysteine to Regional Left Ventricular Circumferential Strains**

<table>
<thead>
<tr>
<th></th>
<th>Regression Coefficients* (95% CI)</th>
<th>P</th>
<th>Regression Coefficients* (95% CI)</th>
<th>P</th>
<th>Regression Coefficients* (95% CI)</th>
<th>P</th>
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<td></td>
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<tr>
<td>Left Anterior Descending</td>
<td></td>
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</tr>
<tr>
<td>Model 1†</td>
<td>0.29 (0.04 to 0.55)</td>
<td>0.02</td>
<td>0.34 (0.04 to 0.63)</td>
<td>0.02</td>
<td>0.31 (0.11 to 0.38)</td>
<td>0.30</td>
</tr>
<tr>
<td>Model 2‡</td>
<td>0.31 (0.05 to 0.56)</td>
<td>0.02</td>
<td>0.41 (0.11 to 0.71)</td>
<td>0.007</td>
<td>0.16 (0.02 to 0.41)</td>
<td>0.21</td>
</tr>
<tr>
<td>Model 3§</td>
<td>0.43 (0.14 to 0.72)</td>
<td>0.004</td>
<td>0.54 (0.20 to 0.89)</td>
<td>0.002</td>
<td>0.25 (0.04 to 0.54)</td>
<td>0.086</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

*Linear regression coefficients represent difference in systolic strains (%) for 1-SD increment in log-transformed homocysteine.
†Model 1: adjusted for age, sex, and race.
‡Model 2: adjusted for age, sex, race, height, weight, cigarette smoking status, diabetes status, systolic blood pressure, antihypertensive medications, and cholesterol/high-density lipoprotein ratio.
§Model 3: adjusted for age, sex, race, height, weight, cigarette smoking status, diabetes status, systolic blood pressure, antihypertensive medications, cholesterol/high-density lipoprotein ratio, left ventricular end-diastolic mass/volume ratio, creatinine, carotid IMT, and coronary artery calcification.
levels are associated with a lower regional LV systolic function independent of potential confounders among individuals free of coronary heart disease.

The association of Hcy with CVD outcomes in the literature is inconsistent. In the Physicians’ Health Study, a modest increase in plasma Hcy level conferred a 3-fold increase in relative risk for myocardial infarction and mortality from cardiovascular disease. However, after further follow-up, the association was not statistically significant. An elevated Hcy level was independently associated with incident stroke in a middle-aged male population free of prior heart disease. A number of other prospective epidemiological studies of subjects initially free of coronary heart disease have shared similar findings. A recent meta-analysis indicated that Hcy level is only weakly related to CVD risk in healthy populations. More recently, evidence for an association of Hcy with prevalent and incident CHF has been postulated. Among patients with CHF, elevated plasma Hcy levels have been previously reported. In a prospective study of 2491 adults, Vasan et al demonstrated that baseline Hcy concentration was associated positively with risk of CHF during a follow-up of 8 years. Our study indirectly supports this concept by demonstrating a cross-sectional association between elevated serum Hcy and reduced myocardial strain in asymptomatic participants of the MESA study, most of whom (95%) had LVEF >55%.

### Plausible Mechanisms

The mechanisms by which Hhe affects cardiac function remain an active area of research, with a number of studies elucidating the basic pathomechanisms that link Hcy to myocardial dysfunction with appropriate animal models. Increased Hcy levels can promote endothelial dysfunction of coronary resistance vessels. Investigators have also emphasized the critical role of Hcy as a source of increased oxidative stress, a factor known to promote myocardial damage. In addition to indirect effects on myocardial performance, Hcy may have direct effects on the myocardium. Short-term exposure of isolated papillary muscle to Hcy decreases the rate of rise and duration of action potentials, without detectable changes in the resting membrane potential. In Hhe rats, a depression in the ST segment as well as an increased duration of the QRS complex (cardiac depolarization) has been observed. Elevated Hcy has also been implicated in induction of cardiac fibrosis, probably by activation of transforming growth

### TABLE 4. Adjusted Global Left Ventricular Indices Across Homocysteine Quartiles

<table>
<thead>
<tr>
<th>Homocysteine Sex-Specific Quartiles (µmol/L)*</th>
<th>First Quartile</th>
<th>Second Quartile</th>
<th>Third Quartile</th>
<th>Fourth Quartile</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Model 1†</td>
<td>69.5±0.43</td>
<td>68.9±0.44</td>
<td>68.0±0.44</td>
<td>68.9±0.45</td>
<td>0.10</td>
</tr>
<tr>
<td>Model 2‡</td>
<td>69.8±0.43</td>
<td>69.0±0.44</td>
<td>68.1±0.44</td>
<td>68.8±0.45</td>
<td>0.09</td>
</tr>
<tr>
<td>Model 3§</td>
<td>69.7±0.43</td>
<td>68.9±0.44</td>
<td>68.2±0.44</td>
<td>68.9±0.046</td>
<td>0.10</td>
</tr>
<tr>
<td>Left ventricular end-diastolic mass, g</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Model 1†</td>
<td>143.7±1.98</td>
<td>141.5±2.07</td>
<td>148.6±2.04</td>
<td>146.1±2.08</td>
<td>0.21</td>
</tr>
<tr>
<td>Model 2‡</td>
<td>145.7±1.67</td>
<td>142.6±1.73</td>
<td>147.8±1.72</td>
<td>143.0±1.75</td>
<td>0.72</td>
</tr>
<tr>
<td>Model 3§</td>
<td>145.5±1.59</td>
<td>142.9±1.61</td>
<td>147.9±1.59</td>
<td>142.8±1.68</td>
<td>0.73</td>
</tr>
<tr>
<td>Left ventricular end-diastolic volume, mL</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Model 1†</td>
<td>121.9±1.69</td>
<td>121.4±1.76</td>
<td>127.2±1.74</td>
<td>122.5±1.77</td>
<td>0.38</td>
</tr>
<tr>
<td>Model 2‡</td>
<td>123.1±1.54</td>
<td>122.0±1.58</td>
<td>126.2±1.58</td>
<td>121.1±1.61</td>
<td>0.96</td>
</tr>
<tr>
<td>Model 3§</td>
<td>123.2±1.33</td>
<td>121.7±1.36</td>
<td>126.1±1.34</td>
<td>121.5±1.42</td>
<td>0.96</td>
</tr>
<tr>
<td>Left ventricular end-diastolic mass/volume ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1†</td>
<td>1.19±0.01</td>
<td>1.18±0.01</td>
<td>1.19±0.01</td>
<td>1.21±0.01</td>
<td>0.43</td>
</tr>
<tr>
<td>Model 2‡</td>
<td>1.20±0.01</td>
<td>1.19±0.01</td>
<td>1.19±0.01</td>
<td>1.20±0.01</td>
<td>0.92</td>
</tr>
<tr>
<td>Model 3§</td>
<td>1.20±0.01</td>
<td>1.18±0.01</td>
<td>1.19±0.01</td>
<td>1.19±0.01</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM unless otherwise indicated.  
*Homocysteine (µmol/L) quartiles for women: first, 4.3–7.2; second, 7.3–8.3; third, 8.4–10.1; and fourth, 10.2–20.3. Homocysteine (µmol/L) quartiles for men: first, 3.8–8.3; second, 8.4–9.8; third, 9.9–11.6; and fourth, 11.7–41.1.  
†Model 1: adjusted for age, sex, and race.  
‡Model 2: adjusted for age, sex, race, height, weight, cigarette smoking status, diabetes status, systolic blood pressure, antihypertensive medications, and cholesterol/high-density lipoprotein ratio.  
§Model 3: adjusted for age, sex, race, height, weight, cigarette smoking status, diabetes status, systolic blood pressure, antihypertensive medications, cholesterol/high-density lipoprotein ratio, left ventricular end-diastolic mass/volume ratio, creatinine, carotid IMT, and coronary artery calcification.  
||Not adjusted for left ventricular end-diastolic mass/volume ratio in model 3.
factor-β. Also, because of its limited ability to metabolize Hcy, the myocardium may be particularly sensitive to elevated Hcy levels.

Methodologic Considerations
Our study includes 1178 subjects, which makes it one of the largest MRI series of quantitative regional myocardial function that we are aware of. HARP is a new tool that is capable of a fast and reliable determination of global and regional LV function. Although the limitations of MRI tagging and regional function assessment by HARP are well known, this tool permits analysis of a large amount of MRI data within a reasonable time period. More importantly, however, the cross-sectional character of our study does not allow any conclusion on the temporality of the described relationships.

Previous data on the relationship of Hcy with global LV indices are limited and conflicting. Nørgard et al demonstrated an inverse association between LVEF and Hcy in patients with coronary artery disease, whereas no correlation was observed by Retterstol et al. In a recent study, Cesari et al reported Hhe to be strongly associated with the presence of a low ejection fraction (<40%) in individuals with arterial hypertension but not among normotensives. We did not find any association between LVEF and Hcy, even when stratified by hypertension status (data not shown). Cesari et al studied high-risk individuals referred for coronary artery angiography, whereas we studied a low- to intermediate-risk cohort without known clinical CVD.

When one considers Hcy-induced endothelial dysfunction of coronary resistance vessels, increased oxidative stress, myocardial fibrosis, and direct myocardial effects (which include negative inotropy) as potential mechanisms that may lead to myocardial dysfunction, one might expect that these mechanisms should affect global LV function. However, the fact that we observed a relationship of increasing Hcy with regional myocardial dysfunction in the absence of global dysfunction can be explained on the following basis: It is widely accepted that individuals may progress through an asymptomatic phase of LV dysfunction before the development of clinical heart failure. Although abnormalities of global LV structure and function represent an advanced stage in the development of CHF, they likely evolved from more localized alterations, particularly when one considers that the most common etiologies of myocardial damage are regional in nature. Regional alterations of myocardial perfusion, metabolism, and inflammation, as well as segmental function, are well documented in patients with global processes such as cardiomyopathies and LV hypertrophic disease. We also believe that regional function is potentially more sensitive than global function for detection of early changes in LV function. Finally, because the MESA study precluded the inclusion of patients with symptomatic CVD, those with global LV dysfunction were likely excluded from the study. In our study, only 3 individuals had LVEF <40% and 5% had LVEF <55%. In order to describe a more direct relationship of Hcy with LV dysfunction, follow-up studies are required in these patients to assess whether Hcy correlates with further reduction in regional LV function and especially with development of global LV impairment.

Assignment of LV myocardial regions to major coronary territories in our study was performed in accordance with established criteria. The importance of this analysis stems from the fact that it is routinely used in other imaging modalities, which include stress echo and nuclear studies. Importantly, our study highlights the relationship between myocardial perfusion in the major coronary territories and regional LV function.

Conclusion
In summary, our study provides evidence that reduced regional systolic function is observed in asymptomatic individuals with elevated Hcy levels. If Hhe is a causal factor in progression from segmental to global LV dysfunction, then an association of elevated Hcy with worsening of myocardial function and development of CHF should be demonstrable in prospective studies.

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

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Disclosures
None.

References


Increased homocysteine has been shown to be associated with incident congestive heart failure in the Framingham Heart Study. Although experimental evidence strongly suggests that the left ventricle is susceptible to homocysteine-induced injury, the relationship between elevated homocysteine levels and regional function has not been studied in individuals without a history of coronary artery disease. In our study, 1078 participants of the Multi-Ethnic Study of Atherosclerosis (MESA), without a known history of cardiovascular disease, underwent myocardial strain with magnetic resonance imaging. Higher levels of homocysteine were associated with reduced regional peak systolic circumferential strain. The relationship persisted after adjustment for traditional risk factors, left ventricle size, renal function, and measures of atherosclerosis. On the other hand, no such relationship existed with global left ventricular functions. Future studies are required to assess the relationship of elevated homocysteine levels with reduction in left ventricular function to establish causality.
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