Coronary Artery Atherosclerosis Is Related to Reduced Regional Left Ventricular Function in Individuals Without History of Clinical Cardiovascular Disease
The Multiethnic Study of Atherosclerosis

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Objective—We investigated whether regional coronary calcium score by computed tomography is related to regional left ventricular systolic function measured by MRI tagging in participants of the Multiethnic Study of Atherosclerosis.

Methods and Results—The Multiethnic Study of Atherosclerosis is a prospective observational study of men and women without a history of previous heart disease from 4 ethnic groups. Calcium scores were measured separately for the left anterior descendent (LAD), left circumflex (LCX), and right (RCA) coronary arteries. Left ventricular strain and strain rate were determined by tagged MRI in the corresponding vascular territories of the coronary vessels in 509 participants. Greater coronary calcification in the LAD, LCX, and right RCA coronary arteries were related to worse function in their respective perfusion. Anterior wall strain rate was \(-1.37 \pm 0.41\) when LAD calcium was zero versus \(-1.17 \pm 0.24\) \(1/s\) in the highest quartile of calcium score \((P<0.001)\). Similar relationships were evident in the LCX and RCA regions. Participants with 1- and 2-vessel coronary artery calcium had better myocardial function in the remote area compared with the territory supplied by the diseased artery.

Conclusions—High-local calcium score is related to regional dysfunction in the corresponding coronary territory among individuals without a history of previous heart disease. These results indicate a link between atherosclerosis and subclinical regional left ventricular dysfunction. (Arterioscler Thromb Vasc Biol. 2006;26:206-211.)

Key Words: atherosclerosis ■ coronary circulation ■ calcification ■ MRI ■ myocardial function

Left ventricular dilatation and global dysfunction in patients without signs or symptoms of heart failure have been directly linked to the eventual development of symptomatic congestive heart failure in clinical and epidemiologic studies.1,2 These structural and functional alterations of the left ventricle are currently considered as subclinical manifestations of heart failure.3 In the United States and Europe, coronary artery disease is the leading cause of left ventricular dysfunction and heart failure.4 Moreover, because coronary atherosclerosis is the most important primary etiologic factor underlying heart failure, it is expected that myocardial dysfunction would begin as a regional process, later progressing to global ventricular failure and symptomatic congestive disease. However, the relationship between subclinical atherosclerosis and subclinical myocardial dysfunction remains undefined.

MRI offers a unique opportunity to assess regional left ventricular function in a detailed and quantitative manner through myocardial tagging.5,6 MRI tagging is an accurate and objective method for assessing regional myocardial dysfunction.2,4 Similarly, coronary calcification measured by computed tomography (CT) is considered to be a specific and quantifiable subclinical marker of coronary atherosclerosis.9,10 CT also allows for separate assessments of coronary calcification in the 3 main coronary arterial trees supplying the human left ventricle; namely, the left anterior descending (LAD), left circumflex (LCX), and right (RCA) coronary arteries. Therefore, the main hypothesis of this study is that regional coronary calcium scores are related to regional myocardial dysfunction defined by MRI tagging in the corresponding myocardial territories of individuals without any history of clinical cardiac disease. We investigated this hypothesis in the Multiethnic Study of Atherosclerosis (MESA).

Methods
MESA is a prospective, population-based observational cohort study of men and women free of a history or symptoms of clinical...
TABLE 1. Exclusion Criteria for MESA

<table>
<thead>
<tr>
<th>Age &lt;45 or &gt;84 years</th>
<th>Physician-diagnosed heart attack</th>
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<tr>
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<td>Physician-diagnosed angina or taking nitroglycerin</td>
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<td></td>
<td>Physician-diagnosed stroke or TIA</td>
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<td></td>
<td>Physician-diagnosed heart failure</td>
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<td></td>
<td>Current atrial fibrillation</td>
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<td></td>
<td>Having undergone procedures related to cardiovascular disease</td>
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<td></td>
<td>Active treatment for cancer</td>
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<td>Pregnancy</td>
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<td></td>
<td>Any serious medical condition that would prevent long-term participation</td>
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<td>Weight &gt;300 pounds</td>
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<td>Cognitive inability as judged by the interviewer</td>
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<td>Living in a nursing home or on the waiting list for a nursing home</td>
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<td></td>
<td>Plans to leave the community within 5 years</td>
</tr>
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<td></td>
<td>Language barrier (speaks other than English, Spanish, Cantonese, or Mandarin)</td>
</tr>
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<td></td>
<td>Chest CT scan in the past year</td>
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</tbody>
</table>

cardiovascular disease at study enrollment. Study design and population characteristics have been described in greater detail elsewhere. Briefly, 6814 men and women from 4 different ethnic groups (white, African-American, Hispanic, and Chinese), aged 45 to 85 years at baseline, were enrolled in MESA. The exclusion criteria in MESA are listed in Table 1. Participants with known clinical disease were not recruited, and eligibility was determined from self-reported information. Of those, 509 participants underwent both tagged MRI and CT scanning the same day at 6 different centers (Wake Forest University, Winston-Salem, NC; Columbia University, New York, NY; Johns Hopkins University, Baltimore, MD; University of Minnesota, MN; Northwestern University, Chicago, IL, and University of California at Los Angeles, Los Angeles, CA) between July 2000 and September 2002. These individuals were included in the regional function analyses.

All of the MESA participants gave informed consent for the study protocol. The Institutional Review Boards in all of the MESA Field Centers, MRI, and CT Reading Centers approved this protocol.

CT Protocol

All of the MESA participants underwent measurement of coronary artery calcium score using either 4-detector row CT (MDCT) or electron beam CT (EBCT) at the baseline examination. All of the EBCT (University of California Los Angeles, Los Angeles, CA, and Northwestern University) and MDCT scans were prospectively triggered.

EBCT was performed on Imatron C-150 ultrafast scanners with a 100-ms exposure and 35-cm field view. For the sites that used EBCT, parameters were: 130 kVp, 630 mA, scan time of 100 ms, 3-mm collimation, and sharp reconstruction filter. For EBCT scans, prospective cardiac gating was used with scanner triggering at 80% of the electrocardiographic RR interval.

MDCT was performed on either GE Light Speed or Siemens Volume Zoom scanners with 330-ms and 361-ms exposure, respectively, and 35-cm field of view. Participants were scanned twice in succession. At Wake Forest University, a GE Light Speed was used with 120 kVp, 200 mA, 0.8-s scan, 4x2.5-mm collimation, sequential axial scans, segmented reconstruction, and standard filter. Johns Hopkins University and the University of Minnesota used Siemens Volume Zoom at 140 kVp, 139 mA, 0.361-s scan, 4x2.5-mm collimation, sequential axial scans with prospective cardiac gating, and standard filter reconstruction.

The results of the 2 scans were averaged. Calcium scores among scanning centers and between participants were adjusted with a standard calcium phantom scanned simultaneously with the participant. The average calcium score was used in all of the analyses. The presence of calcification was defined as an average calcium score >0 (or >0 on either scan).

MRI Protocol

Images were obtained using 1.5 T magnetic resonance scanners, including Signa LX or CVi (GE Medical Systems) or Symphony or Sonata (Siemens Medical Systems). Images were acquired using a segmented k-space, ECG-gated fast spoiled gradient recalled echo sequence pulse sequence. Torso phase array coils were used for signal reception. One vertical long axis and 6 short axis cine images were prescribed. After completing the standard protocol, 3 tagged short axis slices were obtained. Striped tags were prescribed separately in 2 orthogonal orientations (0° and 90°) using spatial modulation of magnetization. Images were acquired at resting lung volume during ~12-s to 18-s breath holds. Parameters for tagged MRI images included field of view, 40 cm; slice thickness, 8 to 10 mm; repetition time, 3.5 to 7.2 ms; echo time, 2.0 to 4.2 ms; flip angle, 12°; matrix size, 256x96 to 140; 4 to 9 phase encoding views per segment; bandwidth range pf 24.9 to 62.5 kHz; temporal resolution of 36.3±12.0 ms; and tag spacing of 7 mm.

Analysis

For each of the 509 subjects in whom both CT and tagged cardiac MRI data were obtained, stroke volume and ejection fraction were determined using standard commercially available software (MASS, GE, MEDIS). Regional myocardial deformation can be calculated from a tagged MRI study. Peak regional systolic strain in the circumferential direction (Ecc) was used in the 509 consecutive participants who enrolled in the tagged MRI study and were analyzed by Harmonic Phase Imaging at the MRI Reading Center (Johns Hopkins University). Ecc was determined in 6 left ventricular segments (anterior, anterolateral, inferolateral, inferior, anteroseptal, and inferoseptal) from the basal and mid-part of left ventricle and 4 segments (anterior, lateral, inferior, and septal) in the apical part. The midwall layer in each segment was analyzed. The assignment of segments to coronary arterial territories (LAD, LCX, and RCA) was done in accordance with clinical recommendations. The apex was excluded from the analyses because of great variability in myocardial blood supply. Myocardial strain is a measure of regional deformation, whereas strain rate is the rate of deformation or velocity of shortening. Thus, strain and strain rate provide complementary information on segmental myocardial function. Strain rate was determined as the first derivative of strain measurements (Ecc) at 2 consecutive time points. Peak systolic strain rate was derived from the strain trace as shown in Figure 1. By definition, systolic strain and strain rate are negative, because they indicate shortening. Therefore, an increased negativity denotes better function. Individual strain and strain rate reread variability was found to be 4% and 3%, respectively, for all 3 of the arterial systems.

CT scans were evaluated blindly with respect to scan pairs and to all of the clinical data using a computerized interactive scoring system similar to that described by Yaghoubi et al. Calcium scores were measured at the CT Reading Center (University of California Los Angeles) using dedicated analysis software that incorporated adjustment for image attenuation based on the calibration phantom. The computer system used a minimum pixel attenuation of 131 HU and a minimum lesion volume of 5 mm³ to calculate the calcium score. Furthermore, calcium mass and volume were calculated for each participant. Individual calcium scores for LAD, LCX, and RCA were determined. Agreement with regard to the presence of coronary calcification was high (κ-statistic, 0.90 to 0.93 between and within readers), and the intraclass correlation coefficient for the calcium score between readers was 0.99.

Statistical Analysis

Values are presented as mean±SD. Participants were divided into 2 groups: those with positive (greater than 0) calcium scores and those with zero calcium scores. Participants with positive calcium scores were additionally subdivided into quartiles by regional calcium score.
levels to test a possible threshold effect. ANOVA methods with Bonferroni corrections were used to test possible differences among the groups. A paired t test was used to compare left ventricle (LV) function (strain and strain rate) in the calcified and noncalcified regions in patients with 1- and 2-vessel coronary calcium. Proportions were compared with the use of χ² tests. The log normal–transformed calcium scores were used for regression analyses that are based on the assumption of normality. Multiple linear regression was used to study the relationship between global [ejection factor (EF)] and regional LV function (strain and strain rate) and log-transformed total and regional calcium scores (SPSS v. 12.0). Variables that might influence on the regional myocardial function were entered into the regression model including age, gender, race, systolic blood pressure, left ventricular end diastolic mass index, heart rate, and diabetes. All of the reported P values are 2-sided with the α level set at 0.05.

**Results**

The study population consisted of 136 white, 85 African-American, 222 Hispanic, and 66 Chinese subjects. The 509 individuals studied had a mean total coronary calcium score of 529±203 U. The results in this study did not differ significantly when using calcium volume or mass scores. The Hispanic participants were younger than the white and Chinese groups (63.5±9.6 versus 68.6±8.7 years, *P*<0.001, and 69.4±8.0 years, *P*<0.001, respectively).

**Global Measures of Coronary Calcium and Left Ventricular Function**

Demographic data from the subset of MESA participants who had the MRI tagging study are shown in Table 2. Calcium scores greater than zero were found in 284 (56%) participants, were more common in men than in women (61% versus 49%; *P*<0.01), and were associated with greater age (70±8 versus 62±9 years; *P*<0.001) when compared with participants with zero scores.

Participants with positive calcium scores had similar EF and stroke volume as those with zero calcium scores. EF was similar in participants with 1- and 2-vessel coronary calcification (68±7% versus 68±9%; *P* = 0.88).

**Coronary Calcification and Regional Left Ventricular Function**

Positive calcium scores were present in the LAD, LCX, and RCA coronary arteries in 257 (50%), 163 (32%), and 156 (31%), respectively. Eighteen percent of subjects had detectable calcium in 1 artery, 17% in 2 arteries, and 19% in all 3 major coronary arteries. We did not find ethnicity-related differences regarding the distribution of coronary calcium in the separate arterial trees.

The group with calcium score above zero showed reduced regional myocardial function compared with the group with zero calcium score. The differences between the 2 groups at the basal LV level were moderate. Importantly, the most apical levels showed decreased strain and strain rate in each myocardial segment with calcium score above zero. The differences were −1.5±0.4 versus −1.3±0.4 (P<0.01) in the LAD area, −1.5±0.5 versus −1.4±0.4 (P<0.01) in the LCX area, and −1.4±0.5 versus −1.2±0.4 in the RCA area. The regional LV function in the calcified territory was impaired compared with regional LV function in the noncalcified territory in participants with 1-vessel coronary calcium (−1.5±0.4 versus −1.3±0.3 L/s; *P*<0.01). The same pattern was found for strain measurements and in participants with 2-vessel calcification (Table 3).

Moreover, when participants with positive calcium scores are subdivided according to the degree of coronary calcification, those in the higher quartiles have additional reductions

![Figure 1. Representative strain rate (top) and strain (bottom) profiles from 1 MESA participant with positive calcium score in the LAD territory. This example is demonstrating a typical strain rate pattern with E and A waves and is from the anterior midwall segment at mid-left ventricular level.](image-url)
in regional function as compared with those in the lower quartiles (Figure 2). These differences in myocardial function were even more pronounced when comparing participants in the highest coronary calcification quartile with those with zero calcium scores: LAD territory $-1.37 \pm 0.41$ versus $-1.17 \pm 0.24$ L/s ($P<0.001$), LCX $-1.54 \pm 0.53$ versus $-1.09 \pm 0.45$ L/s ($P<0.001$), and RCA $-1.37 \pm 0.44$ versus $-1.09 \pm 0.24$ L/s ($P<0.001$), respectively.

The relationship between regional calcium score and regional myocardial function was also demonstrated by multiple linear regressions. After adjustment for age, gender, race, systolic blood pressure, left ventricular end diastolic mass index, heart rate, and diabetes, the most important variable predictive of regional dysfunction indexed as reduced strain rate in all of the coronary territories was the respective coronary calcium score (Table 4).

### Discussion

To our knowledge, this is the first study showing a direct relationship between local coronary atherosclerosis and regional left ventricular dysfunction in a population of individuals without a history of heart disease. We found that coronary calcium scores were associated with reduced function in the corresponding myocardial perfusion territories of MESA participants. These relationships indicate that subclinical myocardial damage induced by atherosclerosis may occur earlier than previously suspected.

Prior clinical and epidemiologic studies on the natural history of heart failure have focused on global indices of left ventricular dilatation and dysfunction to examine the transition from subclinical to symptomatic disease.1,2 Those studies demonstrated that the progression can be delayed by therapy but is fundamentally irreversible.3,4 The pathophysiology of the processes that precede global enlargement and dysfunction have been investigated mainly in patients who develop congestive heart failure as a consequence of clinically documented myocardial infarction.5,6 In those patients, regional myocardial damage resulting from either a single large infarct or from cumulative damage caused by multiple small infarcts triggers a series of structural alterations and compensatory mechanisms, which ultimately lead to left ventricular dilatation, eccentric hypertrophy, and remodeling.7 However, as many as half of the first coronary events have been reported to be clinically silent.8,9 Additionally, chronic coronary artery disease may lead to congestive heart failure in the absence of discrete episodes of myocardial infarction, through pathways that may or may not be similar to those documented in patients who have a clinical history of myocardial infarction.10 Our findings support the theory that chronic myocardial injury is directly related to the degree of upstream coronary atherosclerosis in individuals free of cardiovascular disease. This mechanism may underlie the dysfunctional process that is often seen in patients with coronary artery disease but no history of discrete previous myocardial infarction.

### Global Left Ventricular Function

Coronary calcium score measured by fast CT has been demonstrated to correlate strongly with histological measurements of calcified plaque, total plaque burden, as well as prevalence of coronary stenoses by coronary angiography.11,12 However, increased calcium score was not associated with declines in ejection fraction or stroke volume in this study. Whereas decreased global left ventricular function may

### Myocardial Function in Regions With and Without Coronary Calcium in Patients With 1 and 2 Vessel Calcification

<table>
<thead>
<tr>
<th>Variable</th>
<th>One Vessel Coronary Calcification</th>
<th>Two Vessel Coronary Calcification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Region With Calcium &gt;0</td>
<td>Regions Without Calcium</td>
</tr>
<tr>
<td>Strain rate, 1/s</td>
<td>$-1.3 \pm 0.3^*$</td>
<td>$-1.5 \pm 0.4$</td>
</tr>
<tr>
<td>Strain, %</td>
<td>$-16.4 \pm 3.7^*$</td>
<td>$-17.7 \pm 3.0$</td>
</tr>
</tbody>
</table>

*P<0.01; †P<0.05.

### Figure 2

Participants with positive calcium score in the LAD, LCX, and RCA arterial trees divided into quartiles by level of calcium score. Participants with a higher regional calcium score demonstrate lower regional myocardial function by strain rates in the different myocardial segments. Values given are mean strain rates, and black bars indicate SD.
or may not lead to symptoms of cardiac failure, entry criteria to MESA precluded a history of symptomatic cardiac disease. This exclusion criterion may have limited our ability to detect a relationship between total calcium score and global left ventricular function in MESA. Alternatively, a compensatory increase of contractility in territories unaffected by atherosclerosis may have contributed to the masking of a relationship between total calcium score and LV ejection fraction in this population.

**Regional Left Ventricular Function**

MRI is well suited for the determination of detailed regional left ventricular function through myocardial tagging.\(^5\) Myocardial systolic deformation can be accurately quantified by measurements of myocardial strain and strain rate.\(^6\) The present study reports that coronary atherosclerosis is associated with depressed regional left ventricular function (Figure 2). Potential mechanisms linking local arterial calcification and atherosclerosis to regional ventricular dysfunction include small vessel microembolization, as well as chronic ischemia caused by stenotic atherosclerotic plaques, endocardial dysfunction, or both.

Coronary atherosclerosis can be detected in its subclinical stages by cardiac CT.\(^10,27,28\) Relationships between the amount of local coronary calcification and the percentage of coronary luminal narrowing have been demonstrated.\(^24,26\) Moreover, a recent study by He et al\(^29\) showed a positive relationship between stress myocardial perfusion tomography and calcium score. The authors concluded that coronary calcium score could identify a high-risk group of asymptomatic subjects who had clinically important ischemia. Our study indicates that calcium score measured by cardiac CT (MDCT and EBCT) may identify individuals at an increased risk of developing local left ventricular dysfunction.

**Methodological Considerations**

The cross-sectional nature of the data reported in this study should be kept in mind when interpreting its results. Moreover, the selection and enrollment of the MESA population was not random, and, therefore, the prevalence of the various risk factors may not exactly reflect the overall population. The history of previous clinical cardiovascular disease was self-reported in MESA. We cannot, therefore, completely exclude that a few number of participants might have experienced overt cardiovascular disease.

Direct comparisons of the 2 different CT methods (MDCT versus EBCT) used in this study have been found satisfactory.\(^12,30\) Only midwall circumferential strain and strain rate measures were assessed. In our opinion, the midwall strains and strain rates would best represent the regional function of the whole segment in an epidemiologic study of this magnitude. Subendocardial and subepicardial measurements result in more noisy data than midwall analysis.

Finally, this is the first study that correlates calcium scores from separate arterial trees with regional function in the corresponding myocardial territory. We recognize that there is great individual anatomic variability in the coronary arterial territories. Therefore, we have assigned the LV segments to coronary arterial territories in accordance with accepted clinical recommendations.\(^15\) The greatest variability in myocardial blood supply is found in the apical segment, and this segment was, thus, excluded from the analyses. Clinical inferences should await confirmation from longitudinal studies.

In summary, coronary artery calcification is related to regional left ventricular dysfunction in the corresponding perfusion territory among individuals with no history of heart disease. These results indicate a link between subclinical atherosclerosis and subclinical regional left ventricular dysfunction that could represent an early step in the continuum of events relating coronary artery disease to congestive heart failure.

**Acknowledgments**

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full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

References
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