Lower Myocardial Perfusion Reserve Is Associated With Decreased Regional Left Ventricular Function in Asymptomatic Participants of the Multi-Ethnic Study of Atherosclerosis

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Background—Myocardial ischemia is an important determinant of regional left ventricular systolic function. Myocardial blood flow reserve may be impaired by cardiovascular disease before alterations of myocardial perfusion at rest become manifest. Nevertheless, the relation between flow reserve and regional myocardial function has not been studied in individuals without a history of clinical heart disease.

Methods and Results—Seventy-four participants (66±9 years, mean±SD) of the Multi-Ethnic Study of Atherosclerosis (MESA) underwent myocardial magnetic resonance tagging and contrast-enhanced perfusion studies. Regional myocardial function was evaluated as peak systolic circumferential strain (Ecc) in the three main coronary territories (left anterior descending [LAD], left circumflex, and right coronary artery [RCA]). Myocardial blood flow at rest and during adenosine-induced hyperemia was quantified by contrast-enhanced magnetic resonance imaging, to study the relation between regional flow and function after multivariable adjustment for age, gender, body mass index, left ventricular mass, and traditional risk factors. Lower regional myocardial blood flow during hyperemia was associated with reduced regional left ventricular function expressed as lower Ecc in the RCA (P<0.01) and left circumflex regions (P=0.05) measured in the subendocardium, mid-wall, and subepicardium. In contrast, no significant association was seen in the LAD territory (P=0.16). In addition, segmental function in LAD and RCA regions was reduced when individuals in the lowest 10th percentile for regional myocardial flow reserve were compared with the other participants. Absolute decreases in mid-wall Ecc LAD and RCA and global Ecc were 3.0%, 3.4%, and 2.8%, respectively (P<0.05 for all regions).

Conclusions—Lower myocardial flow reserve is related to reduced regional function in asymptomatic individuals. (Circulation. 2006;114:289-297.)

Key Words: contractility ■ epidemiology ■ magnetic resonance imaging ■ myocardium ■ regional blood flow ■ risk factors ■ systole

Adequate myocardial perfusion is vital for normal left ventricular (LV) function. Acute coronary artery occlusion causes a rapid and substantial reduction in regional systolic function. Moreover, reversible wall motion abnormalities secondary to a 30% to 35% decrease in myocardial blood flow at rest or a 50% reduction in perfusion pressure have been observed in experimental models of coronary artery stenosis. Close relations between reduced myocardial blood flow (MBF) and regional wall motion abnormalities have been demonstrated in patients with coronary artery disease by contrast ventriculography, nuclear imaging, echocardiography, and magnetic resonance imaging (MRI), at rest and during stress induced by exercise and pharmacological stimulation.
Similarly, myocardial tagging enables precise tracking of myocardial motion and deformation in normal and ischemic myocardium.\textsuperscript{16--18} Hence, a detailed quantitative description of global and regional cardiac function and perfusion can be obtained noninvasively by MRI as part of prospective observational studies.

Accordingly, both methodologies of tagged and perfusion MRI were combined to examine the hypothesis that subclinical reduction of myocardial flow reserve may be associated with decreased regional function in asymptomatic individuals with no history of clinical cardiovascular disease.

**Methods**

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective observational study, designed to investigate mechanisms underlying the development and progression of subclinical cardiovascular disease in asymptomatic individuals.\textsuperscript{19} Enrolled in the study were 6814 men and women, 45 to 85 years of age, from 4 different ethnic origins (white, black, Hispanic, and Chinese). Individuals with symptomatic cardiovascular disease were excluded; 1066 cohort members were enrolled at the St Paul, Minn, field center; 255 randomly selected members of the St Paul, Minn, cohort underwent tagged MRI.

All participants from the original cohort were invited to participate in the subcohort of contrast-enhanced perfusion imaging. Individuals with known sensitivity to gadolinium or adenosine, bradycardia, asthma, or chronic obstructive pulmonary disease were excluded; 234 participants underwent myocardial perfusion studies; 82 individuals underwent both myocardial MRI tagging and contrast-enhanced perfusion studies. The mean time lag between tagged MR and perfusion studies was 177 days. The results of those who underwent both studies are described in the current work.

The institutional review board of the study center approved the protocols for the tagged MRI and contrast studies. Informed consent was obtained from all the cohort members.

**Protocol for Tagged Magnetic Resonance Studies**

MRI studies were performed at the University of Minnesota hospital, using a 1.5-T magnetic resonance scanner (Siemens Medical Solutions, Iselin, NJ) with a dedicated 4-element, receive-only, phased-array coil. Tagged cine images were acquired for three short-axis slices, using an ECG-triggered, fast low-angle shot pulse sequence during an approximately 14-second breath-hold (see online Data Supplement). Parallel stripe tags were prescribed in 2 orthogonal orientations, using identical pulse sequence.

**Harmonic Phase Analysis**

Tagged short-axis slices were analyzed by harmonic phase (HARP, version 2.0, Diagnosticom, Inc, Palo Alto, Calif). Peak systolic circumferential strain (Ecc) was determined in 12 segments for 3 slices and in 3 myocardial layers in each study. Peak mid-wall systolic Ecc (expressed as percentage) was used to evaluate regional function. Systolic Ecc values are normally negative because they reflect circumferential shortening. Hence, a smaller absolute value of Ecc indicates reduced regional function. Regional Ecc was analyzed in the three coronary perfusion territories according to standard criteria, that is, left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA).\textsuperscript{20} Peak “global” systolic strain was defined as the peak Ecc averaged across all segments.

**MRI Perfusion Study**

Participants were asked to refrain from caffeine intake for 12 hours before their MRI examination. T\textsubscript{1}-weighted gradient echo imaging with magnetization saturation preparation was used to cover 2 to 3 slices in the short-axis orientation during the first pass of the contrast agent bolus through the LV cavity and myocardium with temporal resolution equal to the R-to-R duration (see online Data Supplement). Gd-DPTA contrast agent at a dosage of 0.04 mmol/kg of body weight (Magnevist, Berlex, Wayne, NJ) was administered intravenously at a rate of 7 mL/s. First-pass scan was performed at rest, followed by a second scan, 15 minutes later, during hyperemia induced by adenosine infusion (0.14 mg/kg per minute for 3 minutes, before the onset of scanning). Adenosine infusion was discontinued after observing the first pass of contrast in the LV, 10 to 15 seconds after starting the perfusion scan.

**MRI Perfusion Image Analysis**

Region of interest intensity curves were generated with MASS software (Laboratory for Clinical and Experimental Image Processing, Leiden University, Leiden, The Netherlands). The myocardium was divided into eight equal transmural sectors. Myocardial blood flow at rest and during hyperemia were determined independently (in units of mL/min per gram) (see online Data Supplement).\textsuperscript{15}

**Data Analysis**

Data are presented as mean±standard deviation. Relations between MBF in the anterior, posterior, and inferior walls and regional LV function indexed as peak systolic Ecc in the myocardial regions supplied by the LAD, LCX, and RCA were studied at rest and during hyperemia. Sectors that straddled 2 coronary perfusion territories were excluded. Linear regression was used to analyze Ecc-MBF relations. MBF, age, gender, body mass index, LV mass, and traditional risk factors (history of hypertension, treatment for hypertension, diabetes defined as fasting glucose ≥126 mg/dL [7 mmol/L] or receiving treatment, total cholesterol, and cigarette smoking were included in the regression model. Of the independent variables, MBF, body mass index, LV mass, history, and treatment for hypertension have been forced into the model. Probability value criterion for retention in the regression model during backward model selection was P<0.2.

Study participants were grouped into quartiles of MBF. Trend was tested by using linear regression. Dummy variables obtained from means of regional Ecc for each of the perfusion quartiles were used as dependent variables. Regional MBF at rest and during hyperemia were compared across coronary territories by using linear mixed effects (LME) models to account for repeated measurements within individuals. Similarly, the relation between regional Ecc and function was also studied by using an LME model. As a post hoc analysis, the group with low levels of MBF (lowest 10th percentile of MBF) during hyperemia was compared with the rest of the study sample. STATA Statistical Software, Release 8.0 (Stata Corporation, Inc, College Station, Tex) and R (R version 2.2.1, Vienna, Austria: R Foundation for Statistical Computing; 2006) were used. A probability value of <0.05 was considered significant.

The reproducibility of HARP and perfusion analysis was assessed by repeated analysis and repeated measurements, respectively (see online Data Supplement).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Results**

Eighty-two participants underwent both tagged and perfusion MRI studies. Eight individuals were excluded from analysis because of adenosine infusion intolerance (n=3), inadequate perfusion or tagging MRI study (n=2), transient complete A-V block (n=2), and caffeine consumption shortly before the study (n=1). Thus, 74 participants are included in the final analysis. Their demographic characteristics and risk factor profile are shown in Table 1.

Compared with the original cohort enrolled in the St Paul Minnesota field center, participants in the current study were older (P=0.002), included a higher proportion of Hispanics (P=0.013) and men (P=0.005). The subcohort had a similar risk factor profile except for higher baseline systolic and...
diastolic blood pressures. One third of the study participants had a history of hypertension, and 11% had diabetes mellitus.

### Regional MBF at Rest and During Hyperemia

MBF after adenosine infusion was 2.8 times higher than MBF at rest ($P<0.0001$ for all regions) (Table 2). No significant differences were noted between mean blood flows in the different sectors at rest. In contrast, during hyperemia, there was a reduced MBF in the posterior and inferior walls compared with the anterior wall ($P=0.0011$ and 0.0029, respectively). When regional perfusion during hyperemia was classified by quartiles, 12%, 8%, and 16% of study participants had reduced regional perfusion (were in the lowest quartile) in 1, 2, and 3 regions, respectively.

### TABLE 1. Demographic Characteristics and Risk Factor Profile of the Study Participants

<table>
<thead>
<tr>
<th>Demographic Data</th>
<th>Original Cohort</th>
<th>Perfusion and Tagging Substudy</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>525 (49)</td>
<td>49 (67)</td>
<td>0.005</td>
</tr>
<tr>
<td>Women</td>
<td>541 (51)</td>
<td>25 (33)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>604 (57)</td>
<td>31 (41)</td>
<td>0.013</td>
</tr>
<tr>
<td>Hispanic</td>
<td>462 (43)</td>
<td>43 (59)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>61±11</td>
<td>65±9</td>
<td>0.002</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29±5</td>
<td>29±4</td>
<td>1.0</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>122±20</td>
<td>127±18</td>
<td>0.04</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70±10</td>
<td>73±11</td>
<td>0.01</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>366 (34)</td>
<td>22 (30)</td>
<td>0.5</td>
</tr>
<tr>
<td>Treatment for hypertension</td>
<td>252 (24)</td>
<td>13 (18)</td>
<td>0.3</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol ≥200 mg/dL (5.2 mmol/L)</td>
<td>505 (47)</td>
<td>32 (57)</td>
<td>0.5</td>
</tr>
<tr>
<td>LDL cholesterol ≥130 mg/dL (3.4 mmol/L)</td>
<td>389 (36)</td>
<td>48 (65)</td>
<td>0.8</td>
</tr>
<tr>
<td>HDL cholesterol ≤40 g/dL (1.0 mmol/L)</td>
<td>332 (31)</td>
<td>25 (34)</td>
<td>0.6</td>
</tr>
<tr>
<td>Triglycerides ≥150 mg/dL (1.7 mmol/L)</td>
<td>446 (42)</td>
<td>29 (39)</td>
<td>0.7</td>
</tr>
<tr>
<td>Treatment for hyperlipidemia</td>
<td>135 (13)</td>
<td>9 (12)</td>
<td>0.9</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>472 (44)</td>
<td>34 (47)</td>
<td></td>
</tr>
<tr>
<td>Former smokers</td>
<td>418 (39)</td>
<td>31 (43)</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>172 (16)</td>
<td>7 (10)</td>
<td>0.3</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma glucose, mg/dL (mmol/L)</td>
<td>102±27 (5.7±1.5)</td>
<td>105±23 (5.8±1.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>98 (9)</td>
<td>7 (9)</td>
<td>0.9</td>
</tr>
<tr>
<td>Major Q-wave abnormalities by ECG</td>
<td>22 (2)</td>
<td>2 (3)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean±SD; categorical variables are displayed as number (percentage). *Characteristics of individuals enrolled in the perfusion-tagging substudy were compared with participants of the original cohort. For continuous variables, $t$ test was performed, $\chi^2$ test was used to study differences in frequencies.

### TABLE 2. Regional MBF at Rest, During Hyperemia, and Flow Ratio

<table>
<thead>
<tr>
<th>Region</th>
<th>Rest MBF (mL/min per gram)±SE</th>
<th>MBF During Hyperemia (mL/min per gram)±SE</th>
<th>Flow Ratio±SE</th>
<th>$P$ (Hyperemia vs Rest)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior wall</td>
<td>1.02±0.03</td>
<td>2.86±0.11</td>
<td>2.86±0.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Posterior wall</td>
<td>1.00±0.03</td>
<td>2.65±0.11</td>
<td>2.77±0.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inferior wall</td>
<td>0.98±0.03</td>
<td>2.63±0.11</td>
<td>2.80±0.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Septum</td>
<td>1.07±0.03</td>
<td>2.78±0.11</td>
<td>2.65±0.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average flow</td>
<td>1.02±0.03</td>
<td>2.79±0.10</td>
<td>2.78±0.08</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Standard errors for means in each region represent the standard error for the region category in a linear mixed-effects model. Standard errors for the average over all regions are calculated from the variance of the values for all regions.
Peak Systolic Regional Strain
Peak systolic Ecc (circumferential shortening, percent) was greater in the LCX than in the LAD and lowest in the RCA territory: $-19.1 \pm 3.6$ (mean$\pm$SD), $-16.6 \pm 3.1$, and $-14.0 \pm 3.3$, respectively ($P<0.005$ for all comparisons). Peak global Ecc (%) for all segments was $-16.1 \pm 3.4$. When regional Ecc was classified by quartiles, 23%, 7%, and 12% of study participants had reduced Ecc (lowest quartile) in 1, 2, and 3 regions, respectively.

Relation Between Peak Systolic Ecc and MBF at Rest and During Adenosine Hyperemia
Quadratic or cubic powers of MBF did not contribute significantly in regression models for Ecc (Table 3 and Figures 1 and 2). Therefore, Ecc was modeled as a linear function of MBF. In addition, no gender interaction was evident, and data are presented for both genders together. There was a direct relation between regional function and MBF during hyperemia. The strongest relation between Ecc and hyperemic blood flow was seen in the RCA territory: $-1.0 \pm 0.1$ (0.030) for all comparisons. Peak global Ecc (%) for all segments was $-1.6 \pm 0.7$ (0.001). Also, in the LCX territory, reduced MBF was accompanied by lower strain measures (regression coefficient, $-1.0$ change in Ecc [%] per 1 mL/min per gram increase in MBF during hyperemia; 95% CI: $-2.5$, $-0.7$; $P=0.001$) (Table 3 and Figure 1A). Also, in the LCX territory, reduced MBF was accompanied by lower strain measures (regression coefficient, $-1.0$ change in Ecc [%] per 1 mL/min per gram increase in MBF during hyperemia; 95% CI: $-1.9$, $-0.1$, $P=0.030$, Figure 1B). In contrast, no significant association was seen in the LAD territory ($P=0.16$, Figure 1C). Importantly, no association between coronary calcium scores and regional perfusion or Ecc was observed in any of the regions (data not shown). Moreover, no significant changes in the strength of the relation between MBF and regional strain were observed after including coronary artery calcium scores in the regression model.

Significant direct relations were seen between mean MBF during hyperemia and peak systolic Ecc when all segments were averaged for subendocardial, mid-wall, and subepicardial Ecc (Figure 2, A through C, respectively).

The LME models for Ecc (Figure 3) confirmed the previous findings that there was a significant association between regional function and perfusion during hyperemia ($P<0.003$, with or without adjustment for coronary territory) but no association with rest perfusion ($P=0.59$). Similar relations were obtained for subendocardial and subepicardial peak systolic Ecc. In contrast, there was no significant relation between peak regional systolic Ecc and MBF at rest in any of the coronary territories.

Regional function was reduced in MESA participants with hyperemic MBF in the lowest 10th percentile for the entire study sample. As shown in Table 4, reduced systolic Ecc was seen in the LAD and the RCA regions ($P<0.05$ for both regions) in the lowest hyperemic MBF percentile group when compared with the remaining participants. Similar relations were observed for mean hyperemic flow and subendocardial, mid-wall, and subepicardial Ecc’s. There were no significant changes in gender distribution between the group with the lowest hyperemic MBF and those with higher blood flow ($P=0.2$). Also, there were no significant differences in the percentages of those who had a history of hypercholesterolemia ($P=0.25$) or diabetes mellitus ($P=0.33$).

Myocardial Perfusion and Global LV Function
After multivariable adjustment, there were no significant associations between mean perfusion during hyperemia and global parameters of LV function, including stroke volume ($P=0.89$), end-systolic ($P=0.24$), end-diastolic volume ($P=0.39$), and ejection fraction ($P=0.12$).

Discussion
This study demonstrates a direct association between decreased regional LV function and reduced regional myocardial perfusion reserve in individuals with coronary artery disease risk factors but who are asymptomatic and have no history of heart disease. This relation was most pronounced in the inferior and posterior walls of the left ventricle. The association between perfusion and regional function was presumably weakened by confounding factors that could not be controlled in this population-based study, yet the observed relation was significant. The ability to detect such a subtle relation is attributed to the accuracy of MRI in quantifying both regional LV function and perfusion reserve.

Importantly, there was no relation between MBF and function at rest among MESA participants, whereas a significant association between regional function at rest with perfusion during adenosine induced hyperemia is docu-
mented. Therefore, our findings cannot be explained by local physiological mechanisms controlling function/perfusion matching.

It is well known that an acute reduction in perfusion leads to myocardial ischemia and to regional myocardial dysfunction.7,21 Wall motion abnormalities have been observed with moderate reductions of perfusion pressure1 and myocardial blood flow.2,4 Quantitative evaluation of myocardial perfusion can be performed by PET,22 echocardiography,23 and MRI. The main advantages of MRI are high spatial resolution and an ability to assess diverse features of myocardial and coronary artery structure and function.9,24 MRI enables assessment of transmural perfusion gradient (subepicardium versus subendocardium) in healthy volunteers as well as patients with coronary artery disease, transplant arteriopathy, and syndrome X.10,25,26

This study documents an association between blunted myocardial blood flow during hyperemia and reduced resting regional LV function, quantified by contrast-enhanced and tagged MRI, respectively. This relation has been reported previously in acute models of coronary ischemia or infarction.2–4,9,21,24 Our study extends this relation to individuals asymptomatic for coronary artery disease.

The observed correlations were for several reasons not strong, with a relatively wide scatter. First, only asymptomatic individuals were studied. The exclusion of symptomatic persons with low perfusion/reduced function may have attenuated the observed relation. Second, there are technical
perfusion ratio (hyperemia/rest) values below 1.1 have been shown to be related to myocardial perfusion and underscoring the preexclusion of individuals with coronary artery disease from the MESA cohort. A strong relation between regional LV function and MBF during adenosine-induced hyperemia could in theory also be secondary to epicardial stenoses that do not limit flow at rest but curtail flow augmentation during stress-induced demand.12,28 Local atherosclerosis expressed by coronary calcium scores is associated with regional myocardial function, evaluated by strain and strain rate,29 and also with regional perfusion.30 The fact that reduced myocardial function was detected at rest and that no significant changes in the strength of the relation between myocardial strain and MBF was observed after adjustment for coronary artery calcium, however, argues against the sole effect of flow-limiting stenoses. We have previously shown that risk factors, including high diastolic blood pressure as well as smoking, are related to reduced regional function.31 It was hypothesized that this relation might be due to subclinical atherosclerosis. It is premature to delineate these associations in a cause-and-effect sequence because of the cross-sectional design of the studies. In our study participants, we did not observe a significant association between regional calcium scores and regional perfusion (or regional function). This lack of significant association may be related to small sample size (n=74), yet it may also suggest that local atherosclerosis may not provide the sole explanation for a perfusion reserve impairment and that other processes involving microvascular dys-

Figure 3. A, Top row shows scatterplots of adjusted Ecc versus hyperemic myocardial blood flow (MBF) by coronary territory. Ecc averages in each coronary territory were adjusted for body mass index and history of hypertension and by the best linear unbiased predictor for the random effects in a linear mixed effects (LME) model. The fixed effects included, besides hyperemic MBF (P<0.002), also the body mass index (P=0.03), history of hypertension (P<0.02), and coronary territory (P<0.0001). Random effects, grouped by subject, consisted of an intercept term. Solid line shows the Ecc predicted by the LME model; dotted line represents a local smoothing regression line. A, Ecc-LAD and anterior wall hyperemic MBF (unadjusted correlation coefficient (r)=−0.16, P=0.17). B, Ecc-LCX and posterior wall hyperemic MBF (r=−0.22, P=0.05). C, Ecc- RCA and inferior wall hyperemic MBF (r=−0.38, P=0.001). B, Bottom row: Adjusted Ecc values are shown by myocardial layer against the global average of hyperemic MBF in each participant (P<0.005), with adjustment in the LME model as fixed effects, for body mass index (P<0.03), history of hypertension (P<0.03), and myocardial layer location (P<0.0001). D, Peak global endocardial Ecc and average hyperemic MBF (r=−0.22, P=0.06). E, Peak mid-wall global Ecc and average hyperemic MBF (r=−0.28, P=0.02). F, Peak global epicardial Ecc and average hyperemic MBF (r=−0.33, P=0.0045).
innervation and lesser activation of vessel. It is therefore conceivable that lower sympathetic level; in the heart, a sympathetic neuron parallels each blood nerves travel with the blood vessels even to the precapillary well established that the sympathetic and parasympathetic

oxidation and myocardial dysfunction.32,33 Finally, it is possible oxygen species with consequent reduction of local nitric by PET scan.35 An alternative explanation for the documented regional disparities is a survival bias, for example, individuals with reduction in anterior wall perfusion and dysfunction might have become more readily symptomatic and thus were excluded from the MESA study.

Finally, in contrast to the association between regional function and hyperemic perfusion, no significant relation was observed between mean myocardial perfusion at rest or during hyperemia and global parameters of LV function, indicating that changes in regional perfusion reserve are related to changes in regional LV function, as opposed to altered global LV function.

**Methodological Considerations**

In contrast to several previous studies,10–12 absolute hyperemic MBF was used here as an indicator of myocardial flow reserve, because it is less dependent on baseline perfusion than a hyperemia/rest flow ratio and is less susceptible to measurement errors. Regional LV function and myocardial perfusion were analyzed in separate laboratories, at Minnesota and Johns Hopkins universities, respectively, with investigators assessing 1 test blinded to the results of the other. Measurement errors. Regional LV function and myocardial perfusion were analyzed in separate laboratories, at Minnesota and Johns Hopkins universities, respectively, with investigators assessing 1 test blinded to the results of the other. This is a cross-sectional study; therefore, cause-and-effect relations between MBF and function cannot be ascertained. The number of study participants was relatively small (n = 74), and only 25 women were included. This small subgroup does not completely reflect the subcohort enrolled at St Paul, Minn, or the entire MESA cohort. Such a small number of participants reduced our power to detect gender interaction and significantly limited our ability to study potentially important subgroup differences, including patients with hypertension or dyslipidemia.

Both tagged magnetic resonance and CE studies were analyzed quantitatively, yielding a detailed map of regional function in terms of circumferential shortening and regional

### Table 4. Peak Systolic Ecc (Mean±SD) in Individuals With Low Myocardial Blood Flows During Hyperemia Compared With Persons With Higher Blood Flows

<table>
<thead>
<tr>
<th>Region and Percentile Group for MBF</th>
<th>Flow During Hyperemia, mL/min per gram*</th>
<th>Mean±SD Systolic Ecc (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>&lt;10% (n=7) 1.0–1.8</td>
<td>−14.1</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>≥10% (n=67) 1.8–5.9</td>
<td>−16.8</td>
<td>0.02</td>
</tr>
<tr>
<td>RCA</td>
<td>&lt;10% (n=7) 1.0–1.6</td>
<td>−10.5</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>≥10% (n=67) 1.7–5.0</td>
<td>−14.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LCX</td>
<td>&lt;10% (n=7) 1.1–1.5</td>
<td>−17.2</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>≥10% (n=67) 1.5–4.9</td>
<td>−19.2</td>
<td>0.15</td>
</tr>
<tr>
<td>Mean</td>
<td>&lt;10% (n=7) 1.3–1.8</td>
<td>−13.9</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>≥10% (n=67) 1.9–5.6</td>
<td>−16.7</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

P values indicate significance levels when individuals with MBFs below the 10th percentile are compared with the rest of the study group (for each region separately); n indicates number of individuals in each group.

*Ranges of MBF during hyperemia.

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function, impaired vasomotion, or other unknown mechanisms are involved.

A blunted perfusion reserve could be due to microvascular dysfunction mediated or not by impaired nitric oxide release. In support of the latter mechanism, close relations between microvascular dysfunction and regional ischemia have been well documented after adenosine- or dipyridamole-induced hyperemia in coronary artery disease, transplant arteriopathy, and in patients with syndrome X.10,11,13,25 Reduced myocardial perfusion reserve in the absence of flow-limiting coronary stenoses may be related to the local accumulation of oxygen species with consequent reduction of local nitric oxide and myocardial dysfunction.32,33 Finally, it is possible that decreased regional contractility and deformation at rest also lowers the requirements for the myocardial perfusion reserve for maintaining an adequate supply of oxygen and nutrients. The observed regional function/perfusion relation may in fact reflect a conditioning of perfusion reserve by resting function.

Decreases of regional myocardial function in proportion to coronary perfusion reserve reductions were noted in the inferior and the posterior regions corresponding to the RCA and LCX perfusion territories, whereas no significant association was seen in the anterior wall. It has been shown that LV inferior and posterior walls have less sympathetic innervation than the anterior wall, with decreased responses to sympathetic stimulation due to reduction in local blood flow.34 It is well established that the sympathetic and parasympathetic nerves travel with the blood vessels even to the precapillary level; in the heart, a sympathetic neuron parallels each blood vessel. It is therefore conceivable that lower sympathetic innervation and lesser activation of β1 and β2 receptors would be mirrored by a lower stimulatory response and reduced vasodilator capacity. In this regard, an altered MBF has been demonstrated in patients with diabetic autonomic neuropathy
perfusion. Perfusion and tagged studies were performed in
different examinations. The methods of segmentation for
perfusion and for regional strain analysis were different. To
reduce signal-to-noise ratio and facilitate perfusion/regional
function matching, we used peak systolic strain in relatively
large segments (LAD/RCA/LCX coronary areas)36 and re-
lated them to perfusion in corresponding segments (anterior/
inferior and posterior segments, respectively). This approach
is similar to the one used in numerous experimental animal
studies when blood flow measurements with radioisotope
labeled microspheres were compared with strain measure-
ments with implanted sonomicrometer crystals.37 Never-
theless, there is still residual uncertainty about the exact match-
ing of the segments acquired during contrast enhanced and
tagged magnetic resonance studies because of slice prescrip-
tion and through plane motion.

The 10th lowest percentile of MBF during hyperemia was
chosen post hoc as an arbitrary cutoff to define a group with
a marked reduction of MBF reserve, because lower cutoffs
(for example, 5th lowest percentile or 2 SD below mean)
yielded too small groups. This relatively high cutoff might
have “diluted” the group with the lowest MBF reserve. A
value of $P<0.05$ was used as a significance criterion. This
increases the possibility of type I error, considering multiple
tests in a relatively small sample size.

Finally, because the MESA study precluded the inclusion
of patients with symptomatic cardiovascular disease, none of
the study participants had symptoms of coronary artery
disease consistent with flow-limiting coronary stenosis. This
limited our ability to compare participants with perfusion
reserve reduction with those having deficits of resting myo-
cardial blood flow.

In conclusion, lower myocardial perfusion reserve is di-
rectly related to decreasing local contractile function in
asymptomatic individuals without a history of heart disease.
This association between perfusion reserve and regional
function is presumably weakened by various confounding
factors. This suggests that additional factors may be involved
in this relation as well.

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

Myocardial ischemia is known to affect regional left ventricular function. Coronary occlusion causes rapid reduction of myocardial function in the area supplied by this artery. Nevertheless, the relation between perfusion and regional function has not been studied in individuals without history of coronary artery disease. Seventy-four participants of MESA underwent myocardial strain and contrast-enhanced perfusion studies (at rest and during adenosine-induced hyperemia) with magnetic resonance imaging. Lower regional myocardial perfusion reserve, expressed as absolute flow during hyperemia, was associated with reduced regional peak systolic circumferential strain. Both reductions in function and perfusion reserve were previously shown to be independently associated with risk factors. Moderate impairments in regional function and perfusion reserve rather than perfusion at rest, in the absence of symptoms of ischemia, and in a population with low probability of flow-limiting coronary lesions, suggest that microvascular dysfunction could have a significant role in subclinical atherosclerosis. Although structural markers of atherosclerosis such as coronary calcification have attracted great attention for their potential role in risk stratification, new functional markers of subclinical disease, such as reduced regional myocardial strains and blunted perfusion reserve indicate by absolute hyperemic flow, may, in the future, significantly enhance the ability to identify early subclinical coronary atherosclerosis in patients at risk.
Lower Myocardial Perfusion Reserve Is Associated With Decreased Regional Left Ventricular Function in Asymptomatic Participants of the Multi-Ethnic Study of Atherosclerosis

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