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

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MRI is a valuable tool for assessing regional myocardial perfusion in epidemiological studies by virtue of its high spatial resolution and its lack of radiation risk, compared with other imaging modalities. First-pass contrast enhancement (CE) studies with MRI were found to be highly accurate for the detection of coronary artery disease. Myocardial perfusion reserve can be determined with MRI by measuring perfusion, both at rest and during vasodilatation by adenosine. A high correlation was observed when CE MRI with adenosine was compared with MBF measured with radioactive labeled microspheres to define areas at risk for myocardial ischemia and infarction.
Similarly, myocardial tagging enables precise tracking of myocardial motion and deformation in normal and ischemic myocardium.\(^\text{16-18}\) 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.\(^\text{19}\) 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 substudy 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 (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, Diagnosoft, 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).\(^\text{20}\) 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\(_\text{1}\)-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). Gadopentetate dimeglumine (Gd-DTPA) 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).\(^\text{15}\)

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 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. In addition, no gender interaction was evident, and data are presented for both genders together.

Important, there was no relation between MBF and regional perfusion during adenosine hyperemia ($P=0.89$), end-systolic ($P=0.24$), end-diastolic volume ($P=0.39$), and ejection fraction ($P=0.12$).

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 pressure3 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

![Figure 1](http://circ.ahajournals.org/)

A, Relation between peak systolic Ecc in the RCA region and MBF in the inferior wall. The study sample was divided into quartiles of hyperemic MBF in the inferior wall. Mean±SE bars are presented. Trend was tested by using unadjusted linear regression. As the dependent variables, dummy variables obtained from means of regional Ecc for each of the perfusion quartiles were used (test for trend, \(P=0.01\)). B, Relation between peak systolic Ecc in the LCX territory region and MBF during hyperemia in the posterior wall (test for trend, \(P=0.05\)). C, Relation between peak systolic Ecc in the LAD territory region and MBF during hyperemia in the anterior wall (test for trend, \(P=0.21\)).

![Figure 2](http://circ.ahajournals.org/)

A, Relation between peak global systolic Ecc (endocardium) and quartiles for global averages of hyperemic MBF. Mean±SE bars are presented (test for trend, \(P=0.06\)). B, Relation between peak global systolic Ecc (mid-wall) and quartiles for global averages of hyperemic MBF (test for trend, \(P=0.03\)). C, Relation between peak global systolic Ecc (epicardium) and quartiles for global averages of hyperemic MBF (test for trend, \(P=0.004\)).
perfusion ratio (hyperemia/index variations and history of hypertension markedly reduced the scatter in the relation of Ecc and hyperemic MBF, as can be seen in Figure 3.

The range of MBF at rest (1.0±0.2 mL/min per gram) is similar to the results described in previous studies. However, average MBF during hyperemia was lower.26 This difference is explained by older age (45 to 85 versus 20 to 47 years old) and higher prevalence of risk factors for coronary artery disease in the present cohort.27 Perfusion ratio (hyperemia/rest) values below 1.1 have been shown to be related to hemodynamically significant coronary stenoses in patients with suspected coronary artery disease or those undergoing coronary interventions.11 In the present cohort, only 6 participants had perfusion reserve below 1.1, precluding a subanalysis in individuals with critical reduction of 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 and 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-
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. 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. 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. It is well established that the sympathetic and parasympathetic nerves travel with the blood vessels even to the capillary level; in the heart, a sympathetic neuron parallels each blood vessel. It is therefore conceivable that lower sympathetic innervation and lesser activation of $\beta_1$ and $\beta_2$ 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 by PET scan. 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, 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. 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...
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) and related 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 measurements with implanted sonomicrometer crystals. Nevertheless, there is still residual uncertainty about the exact matching of the segments acquired during contrast enhanced and tagged magnetic resonance studies because of slice prescription 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 myocardial blood flow.

In conclusion, lower myocardial perfusion reserve is directly 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.

Acknowledgments

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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 indicated by absolute hyperemic flow, may, in the future, significantly enhance the ability to identify early subclinical coronary atherosclerosis in patients at risk.
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