Regional Coronary Endothelial Function Is Closely Related to Local Early Coronary Atherosclerosis in Patients With Mild Coronary Artery Disease
Pilot Study

Allison G. Hays, MD; Sebastian Kelle, MD; Glenn A. Hirsch, MD, MHS; Sahar Soleimanifard, MSE; Jing Yu, PhD; Harsh K. Agarwal, PhD; Gary Gerstenblith, MD; Michael Schär, PhD; Matthias Stuber, PhD; Robert G. Weiss, MD

Background—Coronary endothelial function is abnormal in patients with established coronary artery disease and was recently shown by MRI to relate to the severity of luminal stenosis. Recent advances in MRI now allow the noninvasive assessment of both anatomic and functional (endothelial function) changes that previously required invasive studies. We tested the hypothesis that abnormal coronary endothelial function is related to measures of early atherosclerosis such as increased coronary wall thickness.

Methods and Results—Seventeen arteries in 14 healthy adults and 17 arteries in 14 patients with nonobstructive coronary artery disease were studied. To measure endothelial function, coronary MRI was performed before and during isometric handgrip exercise, an endothelial-dependent stressor, and changes in coronary cross-sectional area and flow were measured. Black blood imaging was performed to quantify coronary wall thickness and indices of arterial remodeling. The mean stress-induced change in cross-sectional area was significantly higher in healthy adults (13.5%±12.8%, mean±SD, n=17) than in those with mildly diseased arteries (−2.2%±6.8%, P<0.0001, n=17). Mean coronary wall thickness was lower in healthy subjects (0.9±0.2 mm) than in patients with coronary artery disease (1.4±0.3 mm, P<0.0001). In contrast to healthy subjects, stress-induced changes in cross-sectional area, a measure of coronary endothelial function, correlated inversely with coronary wall thickness in patients with coronary artery disease (r=−0.73, P=0.0008).

Conclusions—There is an inverse relationship between coronary endothelial function and local coronary wall thickness in patients with coronary artery disease but not in healthy adults. These findings demonstrate that local endothelial-dependent functional changes are related to the extent of early anatomic atherosclerosis in mildly diseased arteries. This combined MRI approach enables the anatomic and functional investigation of early coronary disease. (Circ Cardiovasc Imaging, 2012;5:341-348.)

Key Words: coronary disease ■ endothelium ■ MRI

Coronary atherosclerosis results in anatomic changes involving increases in coronary wall thickness (CWT) and later luminal stenosis as well as functional changes such as reduced endothelial-dependent coronary vasoreactivity. Although both anatomic and functional changes are important indices of coronary atherosclerosis, their assessment has traditionally required invasive techniques and thus any relationship has not been delineated noninvasively in patients with early coronary atherosclerotic disease nor studied in healthy and low-risk populations.1,3

Clinical Perspective on p 348

Both anatomic and functional changes of the coronaries can now be measured noninvasively using MRI. Early anatomic changes in the development of atherosclerosis include outward arterial remodeling with relative preservation of the lumen.4 Because thickening of the vessel wall precedes luminal narrowing, the degree of coronary artery disease (CAD) may be underestimated with conventional, x-ray angiographic imaging of the coronary lumen.5 Using black blood MRI techniques, early increases in the coronary vessel wall thickness can be visualized6,7 and both vessel wall thickness and area quantified,8 enabling the noninvasive detection of subclinical coronary atherosclerosis.

Abnormal coronary endothelial vasoreactivity is a functional vascular change, which predicts late cardiovascular events.9–14 Our current understanding of coronary endothelial biology and
its relationship to atherosclerotic development and progression in humans is limited, primarily because invasive imaging techniques were previously required. However, we recently developed high-field MRI methods capable of quantifying coronary endothelial vasoreactivity noninvasively with good reproducibility. This technique demonstrated abnormal coronary endothelial function in patients with coronary disease that, in a given patient, is heterogeneous and related to the extent of local stenotic disease. Luminal stenosis develops late in the atherosclerotic process and although abnormalities in endothelial function have been observed invasively in patients with mild stenotic disease, the extent to which both anatomic and functional changes of the coronary arteries are related in early atherosclerosis is unknown. Therefore, by means of previously described noninvasive MRI methods to assess endothelial-dependent coronary vasoreactivity and CWT, as one of the earliest indices of anatomic coronary atherosclerosis, we sought to test the hypothesis that local coronary endothelial vasoreactivity is inversely related to local CWT and other indices of positive arterial remodeling in early, mildly diseased coronary arteries.

Methods

Participants

Subjects were outpatients with no contraindications to MRI. Healthy subjects were those aged <50 years without a history of CAD and traditional CAD risk factors and for those aged >50 years with an Agatston coronary artery calcium score<10. CAD subjects were individuals with no unstable coronary syndromes and no history of myocardial infarction who had mild coronary artery disease (≤30% maximum stenosis) in the vessel imaged (and ≤50% maximum stenosis in other coronaries) documented on coronary x-ray angiography performed within 8 months of the MRI examination. The subjects in the study were recruited consecutively de novo and were not a subset of subjects reported in prior published studies. The protocol was approved by the Institutional Review Board at Johns Hopkins University School of Medicine and complies with the Declaration of Helsinki. All participants provided written informed consent.

Study Protocol

A commercial human 3-T MRI scanner (Achieva; Philips, Best, The Netherlands) with a 32-element cardiac coil for signal reception was used. MRI was performed in the morning after an overnight fast and before administration of prescribed vasoactive medications. Images were taken perpendicular to a proximal, linear segment of the coronary artery best identified on survey scans and without stenosis by invasive coronary angiography (Figure 1A). When the image quality on the survey scan was equivalent for the right coronary artery and left anterior descending artery, both arteries were imaged and analyzed. To ensure slice orientation perpendicular to the coronary artery, double oblique scout scanning was performed as previously reported. The imaging plane for both endothelial function and wall thickness measurements was localized in a proximal or midarterial segment that was straight over a distance of approximately 2 cm. All acquisitions were performed during a prespecified period of least cardiac motion.

Cross-sectional anatomic and flow velocity-encoded spiral MRI were performed using single breath-hold cine sequences. Black blood coronary vessel wall imaging was performed at rest. For endothelial function imaging, alternating anatomic and velocity-encoded images were collected at baseline and during 4½ minutes of continuous isometric handgrip exercise as previously described. Each subject performed sustained isometric handgrip exercise using an MRI-compatible handgrip dynamometer (Stoelting, Wood Dale, IL) at 30% of their maximum grip strength under direct supervision. Heart rate and blood pressure were measured throughout using a noninvasive and MRI-compatible electrocardiogram and blood pressure monitor (In vivo; Precess, Orlando, FL). The rate pressure product was calculated as systolic blood pressure×heart rate.

MRI Parameters

For the assessment of endothelial function, the temporal/spatial resolution for the anatomic images was 15 ms/0.89×0.89×8.0 mm³ and 34 ms/0.8×0.8×8 mm³ for the flow velocity images with velocity encoding of 35 cm per second. Approximately 15 to 22 cardiac phases were acquired for the coronary flow scan, depending on heart rate. The radiofrequency excitation angle was 20°, 17 spiral interleaves were acquired, and all scans were prospectively triggered. For coronary vessel wall imaging, black blood dual-inversion spiral imaging was used with a heart rate-dependent inversion time. MRI parameters were: echo time=0.84 ms, spectrally selective fat suppression, breath-hold duration approximately 15 to 23 seconds, acquisition window=21 ms, spatial resolution (acquired/reconstructed)=0.6×0.6×8.00 mm³/0.49×0.49×
8.00 mm$^3$, and a radiofrequency excitation angle=45°. A 45° spectral spatial radiofrequency excitation angle was used because it led to the highest visual vessel conspicuity when compared with higher flip angles and is preferred at higher heart rates. The total duration of the MRI was 35 to 40 minutes.

**Image Analysis**

Images were analyzed for cross-sectional area changes and CWT using a semiautomated software tool (Cine version 3.15.17; General Electric, Milwaukee, WI) after being magnified 4-fold. A circular region of interest was manually traced around the coronary artery in diastole during the period of least coronary motion. The coronary cross-sectional area was then automatically calculated using a full-width half-maximum computer algorithm, which was shown to be highly reproducible with good inter- and intraobserver variability on blinded analysis.\textsuperscript{15,25} For the black blood coronary cross-sectional images, semiautomated measurements were made of the inner and outer vessel borders (Cine, Version 3.15.17) to determine total vessel wall area and mean vessel wall thickness using the full-width half-maximum algorithm. The normalized wall index, a measure of arterial remodeling that accounts for differences in vessel size, was calculated by dividing the wall area by the total vessel area.\textsuperscript{26}

For flow measurements, images were analyzed using semiautomated commercial software (FLOW Version 3.0, Medis, The Netherlands). Peak diastolic coronary flow velocity was used for the velocity measurement to avoid adverse effects of motion blurring and because through-plane motion of the coronaries is minimized during diastole. Coronary artery blood flow (in mL/min) was calculated using the adapted equation (to convert units to mL/min) as coronary artery cross-sectional area \times coronary artery peak diastolic velocity \times 0.3.\textsuperscript{27}

**Statistical Analysis**

Data are expressed as mean values \pm 1 SD. Paired Student $t$ tests were used to compare baseline and stress coronary artery cross-sectional area (CSA), diastolic coronary flow velocity, and blood flow measurements. Student unpaired $t$ tests were used to compare the changes from rest to stress in coronary cross-sectional area, peak diastolic coronary flow velocity, blood flow measurements, and hemodynamic variables between the healthy and CAD subjects as well as to compare CWTs between the 2 groups. Linear regression analysis was performed to assess the relationship between continuous variables of coronary vasoreactivity, age, body mass index, and the anatomic atherosclerosis indices of CWT and normalized wall index. We performed separate univariate regression analysis to assess the relationships of the independent variables CWT and normalized wall index with the outcome variable, coronary vasoreactivity (percent change in CSA with stress) in the 2 groups. We also performed separate, univariate linear regression models to assess the relationship between the independent variable of age with the outcome variable, CWT, in the healthy population. The data were tested for normality using the Shapiro-Wilk test and the results indicated that parametric testing was appropriate. Statistical Package for the Social Sciences 12.0 for Windows was used for statistical analyses. Statistical significance was defined as a 2-tailed probability value $<0.05$.

**Results**

All subjects completed the study without complication and no subject was excluded before the MRI examination. One patient with CAD and 1 healthy volunteer were excluded from the analysis of coronary flow velocity because of poor image quality related to patient motion. A total of 17 arterial segments in 14 patients with CAD and 17 segments in 14 healthy volunteers were analyzed. Baseline characteristics of the study population are shown in the Table.

**Hemodynamic Effect of Isometric Handgrip Stress**

Isometric handgrip exercise induced significant hemodynamic effects in both healthy subjects and those with CAD. In the

<table>
<thead>
<tr>
<th>Table. Characteristics of the Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Healthy Subjects (N=14)</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Mean \pm 1 SD</td>
</tr>
<tr>
<td>Male, no. (%)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
</tr>
<tr>
<td>Ratio</td>
</tr>
<tr>
<td>Coronary artery imaged</td>
</tr>
<tr>
<td>RCA alone, no. (%)</td>
</tr>
<tr>
<td>LAD alone, no. (%)</td>
</tr>
<tr>
<td>Both RCA and LAD, no. (%)</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Family history of premature CAD</td>
</tr>
<tr>
<td>Body mass index</td>
</tr>
<tr>
<td>ACE inhibitor use, no. (%)</td>
</tr>
<tr>
<td>Beta-blocker use, no. (%)</td>
</tr>
<tr>
<td>Statin use, no. (%)</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; RCA, right coronary artery; LAD, left anterior descending artery; ACE, angiotensin converting enzyme; N/A, not available; NS, nonsignificant.

*CAD risk factors excluding age and sex. One point is assigned for each risk factor: hypertension, high cholesterol, diabetes, family history of premature CAD, and smoking.

In the healthy group, we observed a 9.6% increase in mean systolic blood pressure ($P<0.0001$ versus baseline, $N=14$ subjects) and a 15.7% increase in mean heart rate with stress ($P=0.001$), whereas in patients with CAD ($N=14$), the increases were 9.2% and 17.0%, respectively (both $P<0.0001$ versus baseline). The rate pressure product increased by 28% with handgrip stress ($P=0.001$) in healthy subjects to $10784 \pm 2358$ mm Hg*beats/min and by 28% ($P<0.0001$) in patients with CAD to $11335 \pm 1046$ mm Hg*beats/min. Absolute rate pressure product during stress and the percent increase in rate pressure product from baseline did not significantly differ between healthy subjects and patients with CAD.

**Coronary Vasoreactivity**

In the healthy group, coronary arteries dilated significantly with stress (baseline coronary CSA $11.1 \pm 3.4$ mm$^2$ versus stress, $12.6 \pm 4.2$ mm$^2$; $P=0.002$, $N=17$ arteries in 14 subjects), whereas in the CAD group, the coronary CSA did not significantly change with stress (baseline area, $13.8 \pm 3.5$ mm$^2$ versus $13.5 \pm 3.7$ mm$^2$; $P=0.80$, $N=17$ arteries in 14 subjects). The percent change in stress-induced CSA was significantly higher in healthy subjects (13.5% \pm 12.8%) than in those with CAD ($-2.2% \pm 6.8%$, $P<0.0001$; Figure 2A). The baseline coronary CSA was higher (although not significantly) in patients with CAD (13.8 \pm 3.5 mm$^2$) than in healthy subjects (11.1 \pm 3.4 mm$^2$, $P=0.07$). Coronary area measurements (percent CSA change
with stress) showed excellent intraobserver agreement \((r=0.99, P<0.001)\) and interobserver agreement \((r=0.98, P<0.001)\), similar to prior published observations.\(^{15}\)

**Coronary Flow Velocity and Blood Flow Measures**

Peak diastolic coronary flow velocity increased in healthy subjects with stress (baseline velocity, 20.9±5.2 cm/s versus stress 25.8±7.3 cm/s; \(P=0.0009, N=17\)), whereas there was no significant change in peak diastolic velocity in CAD subjects (baseline velocity 21.7±5.0 cm/s versus stress 21.3±6.1 cm/s; \(P=0.87, N=17\)). The relative exercise-induced change in peak diastolic coronary flow velocity was also greater in healthy subjects \((+23.4\%\pm23.0\%)\) than in patients with CAD \((-1.8\%\pm11.0\%;\ P<0.001)\).

In healthy subjects, coronary blood flow increased significantly with isometric handgrip (71.5±3.4 mL/min versus 88.5±4.1 mL/min; \(P=0.0002, N=17\)), whereas blood flow was not significantly changed with stress in patients with CAD (91.5±38.1 mL/min versus 88.5±41.5 mL/min; \(P=0.83, N=17\)). The percentage change in coronary blood flow changes with stress was significantly greater in the healthy group \((+37.6\%\pm31.7\%)\) than in the CAD group \((-4.3\%\pm13.0\%, P<0.0001;\ Figure 2A)\).

**Coronary Wall Thickness**

Mean CWT was significantly greater \((1.4\pm0.3\ mm)\) in patients with mild CAD than in healthy subjects \((0.9\pm0.2\ mm, P<0.0001\) healthy versus CAD; Figure 2B; \(N=17\) each group) as was the mean coronary vessel wall area \((19.8\pm5.6\ mm^2\) versus 11.5\±3.0 mm\(^2\); \(P<0.0001)\). The normalized wall index, a marker of positive arterial remodeling, was also significantly higher in patients with CAD \((0.72\pm0.08, N=17)\) than in the healthy group \((0.59\pm0.08; P=0.0009, N=17)\). Consistent with prior observations,\(^{28,29}\) wall thickness measurements showed excellent intraobserver \((r=0.99, P<0.001)\) and interobserver agreement \((r=0.98, P<0.001)\).

**Relationship Between Arterial Remodeling and Endothelial-Dependent Coronary Vasoreactivity**

In the entire population of healthy adults and patients with CAD combined \((N=34\ arterial segments)\), there was a significant relationship between CWT and percent coronary artery area change with stress \((r=-0.64, P<0.0001;\ Figure 3)\). However, in the healthy group alone, we observed no significant relationship between CWT and percent CSA with handgrip stress \((r=-0.19, P=0.47;\ Figure 4A)\). In contrast, in the CAD patient group, there was a strong inverse relationship between CWT and percent area change with stress \((r=-0.73, P=0.0008;\ Figure 4B)\). The significant relationship between the 2 parameters persisted even after excluding those patients with CAD whose endothelial function was in the top and bottom 10\% of the group \((r=-0.67, P=0.001)\). Similarly, there was no significant relationship between normalized wall index and stress-induced percent CSA change in healthy subjects \((r=-0.11, P=0.67)\), whereas we observed a strong inverse relationship between normalized wall index and percent CSA change in the patients with CAD \((r=-0.67, P=0.003;\ Figure 5)\).

There was no significant relationship between CWT and percent coronary velocity change with stress in either healthy adults \((r=-0.10, P=0.66)\) or patients with CAD \((r=-0.23, P=0.37;\ Figure 4)\). Although there was a significant inverse relationship between CWT and percent coronary flow change with stress in patients with CAD \((r=-0.58 P=0.01)\), this was not observed in healthy subjects \((r=-0.19, P=0.46)\).

Because of the small sample size, multivariate analysis with respect to coronary risk factors and age could not be performed, although univariate linear regression analysis of the healthy subjects indicated a significant correlation be-
between age and CWT (r = 0.66, P = 0.009). A comparison of a subset of the 7 oldest healthy subjects (mean age, 54.9 ± 10.9 years) with patients with CAD (mean age, 59.7 ± 7.0 years, P = 0.75) still showed significant differences in both CWT and percent CSA change with stress between the mild CAD and healthy age-matched group (mean CWT = 1.06 ± 0.2 mm healthy, P = 0.01 versus mild CAD CWT; percent CSA change with stress = 9.0% ± 9.7%, P = 0.03 versus mild CAD percent CSA change with stress).

**Discussion**

This study demonstrated that abnormal coronary endothelial function and increased coronary wall thickness can be detected during a single, noninvasive 3-T MRI examination and, importantly, that abnormal coronary endothelial-dependent vasoreactivity is present locally in mildly diseased coronaries and, related to the earliest noninvasive in vivo measure of local coronary atherosclerosis, an increase in coronary artery wall thickness. We previously reported that coronary endothelial function was closely related to the degree of luminal stenosis. Our current pilot study in patients with nonobstructive CAD demonstrates that local functional and anatomic changes of the coronary arteries are closely related in early atherosclerosis, before the development of significant luminal stenoses, a late occurrence in the progression of atherosclerotic disease.

The present study detected significantly higher mean CWT, wall area, and normalized wall index in patients with mild CAD compared with those of healthy subjects. This increase in wall thickness in patients with CAD relative to healthy subjects and preservation of luminal area is indicative of positive arterial remodeling.

The values for coronary wall area, wall thickness, and coronary endothelial function reported here are similar to those previously reported using MRI and invasive techniques in separate studies, although the endothelial-dependent stressors varied across studies. The observation that mild structural and/or functional coronary disease may contribute to reduced endothelial-dependent coronary flow supports earlier positron emission tomography vasomotor flow studies. However, the ability to measure both vessel wall remodeling and endothelial-dependent coronary vasoreactivity in a single noninvasive examination, demonstrated here for the first time, enables a more complete measure of early atherosclerotic disease than previously possible. Finally, the length of the coronary protocol makes it feasible to combine the imaging sequence with an MR evaluation of left ventricular structure or function, leading to a more comprehensive cardiac examination.

**Figure 4.** MRI measures of coronary wall thickness (CWT) versus percent coronary cross-sectional area changes and percent velocity changes with isometric handgrip stress. Individual data points shown for healthy subjects (blue diamonds) and for patients with coronary artery disease (red diamonds). CWT (mm) versus percent coronary area change with stress is shown for (A) healthy subjects (standard error of the estimate [SEE] = 0.18), and (B) patients with CAD (SEE = 0.22). Coronary wall thickness versus percent coronary velocity change with stress is shown (C) for healthy subjects (SEE = 0.18) and (D) for patients with CAD (SEE = 0.21). CAD indicates coronary artery disease.

**Figure 5.** MRI measure of normalized wall index (NWI) versus percent coronary cross-sectional area change with isometric handgrip stress in (A) healthy subjects (standard error of the estimate [SEE] = 0.08) and (B) patients with coronary artery disease (SEE = 0.06).
In a recent report, abnormal coronary endothelial function varied among arteries in a given patient with CAD and was related to the severity of luminal stenosis.\textsuperscript{15} The observation here that CWT and local endothelial function are associated in patients with mild, nonstenotic CAD is novel and demonstrates that anatomic and functional early atherosclerosis not only coexist in coronary arteries, but are also closely related. Although structural alterations in the arterial wall may impair flow-mediated epicardial vasodilation, we previously showed that the administration of nitroglycerin to patients with significant CAD dilated the same arteries that constricted with isometric handgrip exercise.\textsuperscript{15} That demonstration that endothelial-independent mechanisms are intact shows that the likely mechanism for impaired epicardial vasodilation during isometric handgrip exercise is likely endothelial dysfunction rather than a mechanical disturbance such as may occur with heavy coronary calcification, especially in these patients with very mild atherosclerosis.

In contrast to the findings in patients with CAD, there was no relationship between coronary endothelial function and CWT in healthy subjects. Although prior work demonstrated that stimuli like tobacco abuse or high circulating lipids\textsuperscript{35,36} can induce transitory abnormal endothelial function in healthy subjects, all such stimuli were avoided here by protocol design.

Although our study detected a relationship between endothelial-dependent coronary vasodilation (area change) and wall thickness in arteries with mild atherosclerosis, we found no apparent relationship between coronary velocity change with stress and early anatomic atherosclerosis in either group. These findings suggest that early local anatomic atherosclerotic changes are more closely related to measures of and, therefore, local coronary endothelial function (eg, area change within the same epicardial coronary segment) than to endothelial function measures, which incorporate nonlocal parameters (eg, coronary flow velocity).

The extent of early anatomic atherosclerosis and endothelial function has been well characterized in peripheral arterial beds.\textsuperscript{37,38} Several previous studies evaluated the relationship between brachial endothelial function (flow-mediated dilation) and carotid intimal thickness using B-mode ultrasound and reported varying results.\textsuperscript{37-39} Although earlier studies found a positive relationship between carotid intimal medial thickness and peripheral endothelial function,\textsuperscript{37} more recent studies found no significant correlation between the 2 parameters.\textsuperscript{38,39} The latter findings may be explained by the fact that different vascular beds were evaluated for anatomic and functional measurements of atherosclerotic disease.

Although atherosclerosis is a systemic process, studies of different vascular territories have shown that vasoreactivity may not be uniform across vascular regions within the same individual. One study using MRI compared changes in flow and vessel radius before and during postocclusion hyperemia in the upper (brachial) versus lower (femoral) extremities and found that femoral but not brachial reactivity was impaired in patients with increased cardiovascular risk.\textsuperscript{40} Other data suggest that peripheral and coronary endothelial function measures may not be strongly related\textsuperscript{41,42} possibly due to differences in vascular properties.\textsuperscript{43} Moreover, acute brachial arterial plaque rupture rarely occurs in contrast to acute coronary plaque rupture. Although peripheral and coronary endothelial vasoreactivity have not been directly compared using the same stressor and imaging modality, our previous data show significant heterogeneity of coronary endothelial function within the coronary tree.\textsuperscript{15} Thus, the noninvasive measurement of coronary endothelial function is likely more relevant for defining factors related to local coronary artery atherosclerosis and plaque progression.

In vivo human studies evaluating coronary endothelial function and its relationship to early local vessel remodeling have not been performed before, likely because invasive techniques were required. The most commonly used technique to identify positive coronary arterial remodeling has been intravascular ultrasound.\textsuperscript{44,45} Traditionally, studies of coronary endothelial function have been performed during x-ray coronary angiography with acetylcholine or cold pressor testing as the endothelial-dependent stressor.\textsuperscript{2,9} Those techniques, however, are not suitable for screening low-risk and asymptomatic populations because of their invasive nature and associated risk. Although multidetector computed tomography has been used to assess positive remodeling and plaque progression in patients with CAD,\textsuperscript{46} the exposure to ionizing radiation and contrast media limits repeated studies and its use in low-risk populations. It is also unable to measure coronary velocity or flow for the assessment of endothelial function. Black blood coronary wall MRI can detect coronary arterial wall changes indicative of positive arterial remodeling,\textsuperscript{7} with good reproducibility.\textsuperscript{28,29} Moreover, MRI studies of the coronaries may be safely applied to low-risk populations to noninvasively quantify coronary vessel wall dimensions and to measure endothelial-dependent vasoreactivity. There were no noteworthy variations in image quality with respect to body mass index, heart rate, or other clinical parameters and the sequences performed equally well with the right coronary artery and left anterior descending artery in most cases. Lastly, in our study, the use of an MRI contrast agent (gadolinium) was not necessary, which offers the ability to safely study patients with renal insufficiency.

One limitation to the current study is that the spatial resolution of MRI of the coronaries is not able to distinguish separate layers of the vessel wall or plaque components. Therefore, radiofrequency intravascular ultrasonography determination of early anatomic changes in the coronary arterial wall may be more sensitive at detecting and characterizing early disease than MRI; however, we were not able to ethically justify the risk associated with invasive coronary procedures in healthy and low-risk subjects studied here as an alternative validation approach. In addition, we are currently limited in the choice of the coronary segment that can be imaged. Although we primarily focused on proximal and midcoronary segments of the right coronary artery or left anterior descending artery to evaluate stress-induced area changes, the ability to also measure coronary velocity and flow permits a more global assessment of downstream endothelial function that complements the measurement of local epicardial vasoreactivity. Therefore, technical developments designed to improve spatial resolution and volumetric coverage will likely advance endothelial function studies and permit greater flexibility in the choice of the imaging plane and local characterization of plaque morphology. Another limitation to this pilot study is the relatively small sample size. However, with only 34 coronary arteries investigated, we observed significant differences in both
positive arterial remodeling and vasomotor responses to a known endothelial-dependent stressor between healthy and CAD subjects. Lastly, the 2 groups were not age-matched. However, on further statistical analysis of a subset of healthy subjects age-matched to the patients with CAD, significant differences in CWT and exercise-induced change in CSA were still observed between patients with mild CAD and healthy age-matched control subjects. Because of the small sample size, multivariate analysis with respect to coronary risk factors and age could not be performed.

In summary, the present findings demonstrate that local coronary endothelial function is inversely related to local positive arterial remodeling in patients with nonobstructive CAD. These findings indicate that early nonstenotic atherosclerosis is associated with abnormal local endothelial function and therefore that anatomic and physiological indicators of coronary vascular pathology are related in patients at the earliest stages of coronary atherosclerosis that can be detected noninvasively in humans. This may contribute to improved detection and monitoring of atherosclerotic disease and its response to therapy at an early, preclinical stage as well as the ability to noninvasively investigate anatomic and functional predictors of disease progression.

Acknowledgments

We thank Angela Steinberg, RN, and Rob van der Geest, PhD, for their assistance and the patients and healthy volunteers for their participation in this study.

Sources of Funding

This work was supported by National Institutes of Health (R01-HL084186, ARRA 3R01-HL084186-04S1, R01-HL61912) and by the Donald W. Reynolds Foundation and the Clarence Doodeman HL084186, ARRA 3R01-Hl084186-04S1, R01-HL61912) and by their assistance and the patients and healthy volunteers for their cooperation.

Disclosures

None.

References


**CLINICAL PERSPECTIVE**

This study demonstrates, for the first time, (1) that abnormal coronary endothelial function and increased coronary wall thickness can be detected during a single, noninvasive 3-T MRI examination; and (2) that abnormal coronary endothelial-dependent vasoreactivity is present locally in mildly diseased coronaries and related to the earliest noninvasive in vivo measure of local coronary atherosclerosis, an increase in coronary artery wall thickness. Thus, in a given coronary artery segment, early anatomic markers of coronary atherosclerosis are closely linked to functional markers in that segment that may occur long before the development of severe stenotic disease. The ability to noninvasively and without contrast evaluate both structural subclinical atherosclerosis and coronary endothelial function provides an opportunity to evaluate both aspects of the coronary response to therapeutic intervention. This may also contribute to improved detection and monitoring of atherosclerotic subclinical disease and its response to therapy at an early, preclinical stage as well as the ability to noninvasively investigate anatomic and functional predictors of disease progression.
Regional Coronary Endothelial Function Is Closely Related to Local Early Coronary Atherosclerosis in Patients With Mild Coronary Artery Disease: Pilot Study
Allison G. Hays, Sebastian Kelle, Glenn A. Hirsch, Sahar Soleimanifard, Jing Yu, Harsh K. Agarwal, Gary Gerstenblith, Michael Schä"{a}r, Matthias Stuber and Robert G. Weiss

_Circ Cardiovasc Imaging_. 2012;5:341-348; originally published online April 5, 2012; doi: 10.1161/CIRCIMAGING.111.969691
_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/5/3/341

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Imaging_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Imaging_ is online at:
http://circimaging.ahajournals.org//subscriptions/