Visualization and Functional Assessment of Proximal and Middle Left Anterior Descending Coronary Stenoses in Humans With Magnetic Resonance Imaging

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Background—Coronary artery bypass grafting improves survival in patients with >70% luminal diameter narrowing of the 3 major epicardial coronary arteries, particularly if there is involvement of the proximal portion of the left anterior descending (LAD) coronary artery. Measurement of coronary flow reserve can be used to identify functionally important luminal narrowing of the LAD artery. Although magnetic resonance imaging (MRI) has been used to visualize coronary arteries and to measure flow reserve noninvasively, the utility of MRI for detecting significant LAD stenoses is unknown.

Methods and Results—Thirty subjects (23 men, 7 women, age 36 to 77 years) underwent MRI visualization of the left main and LAD coronary arteries as well as measurement of flow in the proximal, middle, or distal LAD both at rest and after intravenous adenosine (140 μg/kg per minute). Immediately thereafter, contrast coronary angiography and when feasible, intracoronary Doppler assessments of coronary flow reserve, were performed. There was a statistically significant correlation between MRI assessments of coronary flow reserve and (a) assessments of coronary arterial stenosis severity by quantitative coronary angiography and (b) invasive measurements of coronary flow reserve (P < 0.0001 for both). In comparison to computer-assisted quantitative coronary angiography, the sensitivity and specificity of MRI for identifying a stenosis >70% in the distal left main or proximal/middle LAD arteries was 100% and 83%, respectively.

Conclusions—Noninvasive MRI measures of coronary flow reserve correlated well with similar measures obtained with the use of intracoronary Doppler flow wires and predicted significant coronary stenoses (>70%) with a high degree of sensitivity and specificity. MRI-based measurement of coronary flow reserve may prove useful for identification of patients likely to obtain a survival benefit from coronary artery bypass grafting. (Circulation. 1999;99:3248-3254.)

Key Words: magnetic resonance imaging ■ coronary disease ■ stenosis ■ blood flow

Since patients with significant narrowing of the left main or proximal left anterior descending (LAD) coronary arteries have improved survival with coronary artery bypass grafting, the reliable identification of these individuals is important. Contrast coronary angiography and coronary flow reserve measurements (obtained invasively) are used to locate and to assess the functional importance of coronary arterial narrowing.

Magnetic resonance imaging (MRI) has been shown to be useful for the noninvasive visualization of coronary arteries, assessment of infarct artery patency, and location of coronary arterial anomalies and stenoses. Recently, we showed that phase-contrast MRI (PC-MRI) provides accurate and reliable measurements of coronary arterial flow reserve. We hypothesized that PC-MRI flow reserve measurements could be used to identify functionally important stenoses in the anterior epicardial arterial circulation. To test this hypothesis, we compared PC-MRI measurements of coronary flow reserve with stenosis severity assessed by computer-assisted quantitative coronary angiography (QCA).

Methods

Study Population
The study was approved by the institutional review boards of The Wake Forest University School of Medicine, Winston-Salem, NC,
and The University of Texas Southwestern Medical Center at Dallas. All participants gave written informed consent. The study population consisted of 33 subjects (26 men and 7 women, age 36 to 77 years) referred for cardiac catheterization because of chest pain. Patients were ineligible for enrollment if they had (a) a contraindication to MRI scanning (a pacemaker, intracranial metal, an unstable medical condition, or claustrophobia); (b) a rhythm disturbance that would interfere with acquisition of adequate images (>20 premature ventricular beats per minute or atrial fibrillation); (c) an underlying condition that could alter coronary flow reserve independent of stenosis severity (dilated or hypertrophic cardiomyopathy, severe poorly controlled hypertension, moderate to severe stenotic or regurgitant valvular disease, prior percutaneous coronary artery intervention within 8 weeks, anterior Q-wave myocardial infarction, or previous coronary artery bypass grafting); or (d) a contraindication to receiving adenosine (atriovenous block or reactive airways disease). In patients who had undergone prior percutaneous intervention, the coronary vessel in which the intervention took place was conveyed to MRI investigators. All substances or medications that might interfere with the action or metabolism of adenosine (eg, caffeine, chocolate, mint, dipyridamole, or theophylline) were withheld 24 hours before study.

**Study Design**

Each subject underwent MRI scanning followed immediately by contrast coronary angiography so that both procedures were separated by <2 hours. During both studies (contrast angiography and 2-dimensional gradient-echo MRI), the left main and LAD coronary arteries were visualized. During MRI, coronary arterial flow was measured at baseline and after intravenous adenosine (140 μg/kg per minute). In a subset of patients in whom the investigators believed that a Doppler velocity wire (Cardiometrics, Inc) could be safely advanced into the LAD, coronary velocity and diameter measurements were made at rest and after adenosine at a similar site to that used during MRI. Heart rate and systemic arterial pressure were monitored and recorded during both studies. All data, including heart rate, systemic arterial pressure, stenosis severity, and coronary flow reserve determinations, were compiled, analyzed, and stored without knowledge of the findings obtained during the other procedure.

**MRI Technique**

MRI was performed in 22 patients (Winston-Salem) with a 1.5-T General Electric Horizon (General Electric Medical Systems) and in 11 patients (Dallas) with a 1.5-T Picker Vista HPQ (Picker International, Inc) whole-body imaging system. A phased-array cardiac surface coil (General Electric) or a standard quadrature 20×26-cm spine coil (Picker) was used as a radiofrequency receiver. Each patient was imaged in the supine position after placement of ECG monitoring leads, a respiratory gating belt (to monitor breath-holds), a pulse oximeter, and the surface coil on the chest. Imaging parameters for coronal and long-axis scout images of the heart were the same as for previously published techniques. These scans incorporated breath-held, fast gradient-echo sequences with first moment compensation, repetition times (TR) of 14 ms (GE) and 19 ms (Picker), and echo times (TE) of 6.7 ms (GE) and 9.4 ms (Picker). Segmented k-space was used to obtain multiple phase-encoding steps for each frame during a cardiac cycle.

After obtaining scout views, we imaged the left main coronary artery in axially positioned planes and the LAD and its proximal diagonal branches in short-axis, tangential, and longitudinal planes. On the Picker system an in-plane presaturation pulse was applied, according to previously published techniques, at the first frame of each cardiac cycle so that in-flowing blood would appear bright relative to stationary tissue. Applying the single presaturating pulse in early systole provided good contrast between the LAD and its surroundings in multiple frames during early and middle diastole when coronary flow is high. On the GE system, fat saturation pulses were used to suppress signal from fatty tissue in the slice so that the LAD appeared bright and of different contrast relative to surrounding tissue. In addition, a cross-sectional view of the LAD was obtained that was perpendicular to the direction of blood flow to ensure that minimal through-plane motion and partial volume effects were present when flow data were analyzed. In arterial segments with a potential stenosis, cross-sectional images of the vessel were obtained along a straight segment of the vessel distal to the most distal area of dropout. As shown previously, this technique allows visualization of the anterior epicardial arterial circulation to within 2.7 cm of the cardiac apex.

To measure flow, cine phase-contrast breath-hold acquisitions were acquired perpendicularly across vessel segments in an optimal slice position as determined from the cine scout images described above. The number of k-space lines acquired per frame in each R-R interval (views per segment [VPS] or phase encoding group [PEG] as defined by General Electric and Picker, respectively) was adjusted for each patient studied to yield 4 to 5 frames per cardiac cycle (temporal resolution ranged from 112 to 168 ms). Other imaging parameters included a 7-mm slice thickness with a 256×256 matrix, a field of view (FOV) of 21 to 24 cm, a flip angle of 40, a TR of 13.8 (with GE) or 19.5 (with Picker) ms, and a TE of 6.7 (GE) or 11 (Picker) ms. A ¼ FOV in the phase-encoding direction was used to keep the duration of the breath-hold at 18 to 28 seconds. Resting coronary arterial flow was measured with the breath-hold technique, after which adenosine (140 μg/kg per minute) was infused intravenously for 6 minutes. During the last 3 minutes of the infusion, coronary flow measurements were repeated during breath holding.

Flow was calculated according to previously published techniques. Velocity maps were generated by pixel-to-pixel subtraction of the phase contrast phase images and the application of a correction algorithm designed to remove background phase error. The paired magnitude images and velocity maps were displayed on an image-processing workstation where flow calculations for each image set (baseline and peak flow with adenosine) were performed. The vessel lumen was traced manually on the magnitude image and then transferred to the velocity map for the determination of mean velocity. Flow was calculated by summing the flow per frame over the cardiac cycle and multiplying by the mean heart rate during the measurement:

\[
\text{Flow (mL/min)} = \text{HR} \times \sum_{i=1}^{n} F_i
\]

where HR is heart rate (cardiac cycles/min); n is the number of frames in the cycle; Fi is flow volume in frame i of the cardiac cycle (cm³/frame)=mean velocity over the vessel area (cm³/s)×vessel area (cm²)×[2×(PEG or VPS) size×TR of the sequence (s/frame)]

\[
\text{Vessel area} = \frac{\text{FOV}_{\text{read-out}} \times \text{FOV}_{\text{phase-encode}}}{\text{phase resolution}_{\text{read-out}} \times \text{phase resolution}_{\text{phase-encode}}}
\]

(No. of pixels within the lumen of the coronary artery on the magnitude image)

Using prospective gating, images were not acquired during the last 30 to 100 ms of diastole. For this terminal portion of the cardiac cycle, we estimated flow to be equivalent to flow in the last imaged diastolic frame. Coronary flow reserve was defined as the ratio of peak flow (measured after adenosine infusion)/baseline flow.

MRI data were stored on optical disks for subsequent recall and analysis. On completion of the MRI scanning procedure, patients were transferred immediately to the catheterization laboratory.

**Cardiac Catheterization**

In each subject, a 7F or 8F sheath was inserted percutaneously into the femoral artery. A 7F diagnostic catheter was positioned in the left coronary ostium, and a single angiogram was performed with nonionic contrast material to exclude disease of the left main coronary artery. In a subset of patients (n=17), a 0.014-in. Doppler velocity wire (FloWire, Cardiometrics Inc) was advanced into the vessel of interest to a similar location as that used for the PC-MRI flow measurements and positioned to obtain a high-quality phasic velocity and a time-averaged instantaneous spectral peak velocity (APV). In those patients with a coronary stenosis, the wire was...
positioned distal to the stenosis at a location derived from the landmarks (on MRI films) supplied by the MRI investigators. After obtaining baseline measurements, a cineangiogram was performed with nonionic contrast material for the determination of coronary arterial diameter. Coronary velocities were allowed to return to baseline, after which the patient was given intravenous adenosine (140 μg/kg per minute) for 6 minutes. Three minutes into the infusion, repeat coronary APV measurements were accomplished, and coronary arterial diameter was reassessed angiographically. Subsequently, multiple standard views of the left main and LAD coronary arteries were obtained. Stenosis severity was determined with computer-assisted QCA according to previously published techniques.21 Time-averaged coronary flow was measured according to previously published techniques, and coronary velocity and flow reserve were defined as the ratio of peak to resting measurements after maximal dilation of the vascular territory with adenosine.22

Data Analysis
All data are expressed as mean ±1 SD. The sensitivity and specificity of a visual interpretation of the gradient-echo images (performed by MRI investigator W.G.H. according to previously published techniques12) and the combination of the gradient-echo and PC-MRI data for determining the presence of coronary luminal narrowing assessed with computer-assisted QCA was determined. For patients with multiple stenoses, the most severe stenosis was used for comparison. The values for stenosis severity calculated from the computer-assisted QCA analyses were compared with the coronary flow reserve measurements made with MRI according to a 2-variable linear regression analysis. To determine if the correlation coefficient was significantly different from 0, a Student’s t test was performed.23 Measurements of coronary reserve obtained with MRI and catheterization were compared with the use of a 2-variable linear regression analysis and an analysis as described by Bland and Altman.24 In addition, a Bland-Altman analysis was used to assess the interobserver variability between the MRI assessments of coronary reserve. For all analyses a value of \( P<0.05 \) was considered significant.

Results
MRI studies were well tolerated in all subjects. Three patients were excluded from further analysis because of poor MRI image quality after adenosine infusion (1 patient had a wrap-around artifact, 1 could not perform the breath-hold, and 1 had improper gating). The remaining 30 subjects formed the study population. Their mean height was 174 cm (range 152 to 198) and mean weight was 79 kg (range 51 to 105). All patients were in sinus rhythm. The mean duration of time for the MRI procedure (actual time spent in the magnet) was 58 minutes (range 44 to 75). The clinical characteristics of the 30 subjects are displayed in the Table. Nine subjects had undergone a previous percutaneous intervention in the left anterior epicardial circulation (6 with an intracoronary stent) at the time of MRI examination. MRI magnitude images and velocity maps from patients with different severity of stenosis are shown in Figure 1.

The heart rate and systolic and diastolic blood pressures of the patients before receiving adenosine were 64 ±10 bpm, 139±30 mm Hg, and 81±13 mm Hg, respectively, and after they received adenosine they were 77±13 bpm, 133±24 mm Hg, and 78±11 mm Hg, respectively. For all subjects the difference between measures of heart rate and systolic and diastolic blood pressures during MRI and catheterization was \( -3±6 \) bpm, \( -4±20 \) mm Hg, and \( 1±13 \) mm Hg, respectively. While patients received adenosine during MRI, 18 had flushing, 9 had chest pain, and 2 had headache. Two patients developed first-degree atrioventricular block (PR interval of 0.22 ms) during the infusion. These symptoms and ECG findings resolved within 3 minutes after termination of the adenosine infusion. No patient had myocardial infarction, hypotension, atrial or ventricular arrhythmia, second- or third-degree atrioventricular block, or congestive heart failure. During adenosine infusion in the catheterization suite (when ST segments could be appreciated), there were no episodes of ST-segment depression.

Coronary arterial diameters as determined by computer-assisted QCA ranged from 2.0 to 4.8 mm. In those patients who received adenosine, the change in arterial diameter as assessed with computer-assisted QCA was 0±0.2 mm. The pixel sizes used to calculate coronary arterial area by MRI ranged from 0.82×0.82 mm² to 0.89×1.0 mm². The most significant luminal narrowing identified in each patient with computer-assisted QCA is displayed in the Table. No patient had a stenosis of >50% of the ostium of the left main coronary artery. In 6 subjects, the length of the left main coronary artery was markedly reduced such that determination of severity was not possible. One patient had an occluded proximal LAD on the gradient echo MRI images. Analysis of the velocity maps on this
patient revealed no net phase shift and a flow value of 0 (assessment was equivalent to the background noise). For the purposes of the analysis, this patient was assigned a coronary reserve measurement of 1.

From the ostium of the left main coronary, the distance along the left main and LAD artery that was visualized with the gradient-echo imaging technique ranged from 2.3 cm (patient with proximal LAD occlusion) to 12.8 cm. MRI investigators properly identified all 6 patients with an intracoronary stent in the left anterior coronary arterial circulation during scanning. In the 24 subjects with a stenosis >40% intraluminal diameter narrowing by QCA who did not have an intracoronary stent, the MRI investigators properly located the most severe stenosis within the LAD. However, interpretation of the gradient-echo images alone without the phase-contrast data rendered a sensitivity of 81% and a specificity of 87% for the identification of a stenosis of ≥50% intraluminal narrowing by QCA. Using the gradient-echo MR images only, investigators were not able to quantify stenosis severity any further.

The number of patients who underwent Doppler wire measurements in Dallas and Winston-Salem was 10 and 7, respectively. The correlation between coronary flow reserve measured by MRI and assessment of stenosis severity determined with quantitative contrast angiography is shown in Figure 2. All patients with a stenosis severity of >70% by computer-assisted QCA were identified as having a coronary flow reserve ≤1.7 by MRI. The sensitivity and specificity of a MRI coronary flow reserve value of ≤1.7 for the identification of a coronary stenosis >70% were 100% and 83%, respectively. The correlation and agreement between MRI and intracoronary Doppler-derived measurements of coronary flow reserve are shown in Figures 3 and 4, respectively. The interobserver variability for the MRI measurement of coronary flow reserve in 17 randomly selected subjects (range of flow reserves measured, 0.7 to 3.95) was 0.0±0.3 (Figure 5).

### Discussion

In patients with symptomatic coronary atherosclerosis, 3 randomized trials showed that coronary artery bypass grafting improves survival in those with (a) >50% luminal diameter narrowing of the left main coronary artery, (b) significant narrowing of all 3 major coronary arteries in conjunction with...
accuracy for assessing stenosis severity. Although Doppler can be used to quantify intracoronary calcification, but it is not accurate, and widely available noninvasive method of identifying these patients would have substantial clinical utility.

To date, noninvasive imaging of the left anterior epicardial arterial circulation has been accomplished with electron beam computerized tomography, transesophageal echocardiography, and MRI. Electron beam computerized tomography can be used to quantify intracoronary calcification, but it is not accurate for assessing stenosis severity. Although Doppler transesophageal echocardiography has been used to estimate stenosis severity in the proximal LAD coronary artery, it is associated with some patient discomfort (because it requires esophageal intubation), and localization of the Doppler sample volume distal to a stenosis or a major side branch is difficult. Two- and 3-dimensional MRI techniques have been used to visualize coronary arteries, but relatively low spatial resolution (particularly when compared with contrast coronary angiography), difficulty with algorithms used in reconstruction (for 3-dimensional techniques), and MRI artifacts have led to imprecise quantitation of stenosis severity. Using the gradient-echo techniques alone in this study, MRI investigators were able to identify stenosis location but not accurately determine stenosis severity. In previously published studies, we demonstrated the accuracy of PC-MRI for assessing coronary flow reserve. In the present study, we have shown the utility of supplementing gradient-echo magnetic resonance coronary angiography with PC-MRI coronary flow reserve measurements to provide a noninvasive method for identifying the most functionally important stenosis in the LAD coronary artery in humans.

Our data allow us to reach several conclusions. First, PC-MRI measurements of coronary blood flow, at rest and during adenosine infusion, can be accomplished safely and efficiently in patients referred for contrast coronary angiography. All of our MRI studies were completed in <75 minutes (baseline imaging plus pharmacological stress). Second, PC-MRI measurements of coronary flow reserve correlate well with (a) stenosis severity assessed with computer-assisted QCA (Figure 2) and (b) coronary flow reserve measured with Doppler guidewire technology (Figure 3). Third, a PC-MRI measurement of flow reserve ≥1.7 distal to a stenosis in the left main or proximal or middle LAD coronary artery reliably identifies a stenosis >70% by computer-assisted QCA (sensitivity of 100%). Importantly, an MRI coronary flow reserve value of 1.7 is similar to the value of 1.6 to 2.0 reported with invasive techniques to differentiate obstructive from nonobstructive stenoses. In addition, the fact that an MRI flow reserve value of 1.7 is 83% specific for detecting a stenosis of >70% luminal diameter narrowing is consistent with studies that use invasive assessments of coronary flow reserve. Previous studies have shown that some stenoses of intermediate severity (45% to 70% luminal diameter narrowing) can be flow limiting during stress. Fourth, although our study was not designed to identify coronary arterial restenosis, our patients had undergone prior percutaneous intervention (6 had intracoronary stents). Our technique allowed the reliable identification of luminal narrowing >70% in these individuals as well.

The use of gradient-echo PC-MRI routinely to exclude functionally important coronary atherosclerosis in the left main and LAD coronary arteries in humans is appealing for several reasons. First, it is safe, does not require the use of ionizing radiation, and is easily performed in an ambulatory setting. Because the procedure is relatively brief and patients do not require subsequent supervision, patients and physicians have minimal time loss from their usual activities. Second, MRI provides useful information, such as location of the stenosis within the LAD artery, an estimate of vessel size, or the relation of adjacent vessel branches, which may
influence the planning of a subsequent revascularization procedure. Third, cardiac MRI is becoming more widely available; as this study illustrates, standardized approaches can be used in multiple centers. Finally, because MRI is versatile, determinations of myocardial mass and ventricular volumes, ejection fraction, and systolic function can be performed during the same procedure.

Our study has limitations. First, all of our patients were in sinus rhythm. None had frequent ventricular ectopy or atrial fibrillation. We are uncertain if this technique provides reliable results in subjects with irregular rhythms. Second, although MRI data are acquired rapidly, processing and analysis is time-consuming when performed manually. However, with automated analysis programs, these times can be reduced substantially (<1 minute for flow measurements). Third, our results are probably not applicable to subjects with conditions associated with marked reductions in coronary flow reserve (dilated or hypertrophic cardiomyopathy, moderate to severe valvular heart disease, previous anterior infarction, or the presence of coronary bypass grafts). In many of the subjects with one of these entities, our MRI procedure may falsely suggest a significant stenosis. Importantly however, our results are applicable to those individuals with hypertension, diabetes, smoking, and hypercholesterolemia that may have mild to moderate reductions (from a normal value of 4 to 5 down to 2 or 3) in coronary flow reserve. Fourth, in our study of consecutively enrolled subjects, none had >50% stenosis of the ostium or proximal portion of the left main coronary artery. Since invasive studies have documented reduced coronary flow reserve in the proximal LAD of these subjects,7,8 our results should be applicable to them as well. Fifth, we did not visualize small vessel segments nor did we visualize nor measure flow reserve in the distal portion of the LAD. Finally, while Doppler-derived assessments of coronary velocity and flow reserve are used widely, they are not a perfect “gold-standard” measurement technique. Doppler wire velocity measurements assume a parabolic velocity profile within the vascular lumen, and coronary area determinations are derived from formulas that assume a circular vessel lumen.

In conclusion, in the LAD coronary artery, cine gradient-echo MRI combined with phase-contrast assessments of coronary arterial flow reserve can be used to identify a stenosis of >70% in the proximal or middle segments with a sensitivity of 100% and a specificity of 83%. These data highlight the fact that these MRI techniques can be used to answer specific questions related to the epicardial coronary arterial circulation, such as discrimination of which patients with left main or proximal LAD coronary artery disease may need referral for contrast coronary angiography and subsequent coronary artery bypass grafting. Further studies are required to determine if this technology can be used to identify functionally important stenoses in the right coronary arterial circulation or restenosis in patients who have undergone percutaneous intervention.

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References
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