Assessment of Coronary Arterial Restenosis With Phase-Contrast Magnetic Resonance Imaging Measurements of Coronary Flow Reserve

W. Gregory Hundley, MD; L. David Hillis, MD; Craig A. Hamilton, PhD; Robert J. Applegate, MD; David M. Herrington, MD, MHS; Geoffrey D. Clarke, PhD; Gregory A. Braden, MD; Mark S. Thomas, RN; Richard A. Lange, MD; Ronald M. Peshock, MD; Kerry M. Link, MD

Background—After successful percutaneous coronary arterial revascularization, 25% to 60% of subjects have restenosis, a recurrent coronary arterial narrowing at the site of the intervention. At present, restenosis is usually detected invasively with contrast coronary angiography. This study was performed to determine if phase-contrast MRI (PC-MRI) could be used to detect restenosis noninvasively in patients with recurrent chest pain after percutaneous revascularization.

Methods and Results—Seventeen patients (15 men, 2 women, age 36 to 77 years) with recurrent chest pain >3 months after successful percutaneous intervention underwent PC-MRI measurements of coronary artery flow reserve followed by assessments of stenosis severity with computer-assisted quantitative coronary angiography. The intervention was performed in the left anterior descending coronary artery in 15 patients, one of its diagonal branches in 2 patients, and the right coronary artery in 1 patient. A PC-MRI coronary flow reserve value ≥2.0 was 100% and 82% sensitive and 89% and 100% specific for detecting a luminal diameter narrowing of ≥70% and ≥50%, respectively.

Conclusions—Assessments of coronary flow reserve with PC-MRI can be used to identify flow-limiting stenoses (luminal diameter narrowings >70%) in patients with recurrent chest pain in the months after a successful percutaneous intervention. (Circulation. 2000;101:2375-2381.)

Key Words: magnetic resonance imaging • coronary disease • restenosis

In 25% to 60% of subjects who have a successful percutaneous coronary arterial revascularization procedure, restenosis, most commonly defined as a recurrent >50% luminal diameter narrowing at the site of intervention, occurs.1–3 The restenotic lesion may impair coronary blood flow, reduce coronary arterial flow reserve (CAFR), limit exercise tolerance, and precipitate chest pain.4,5 Most individuals who have chest pain in the months after a successful percutaneous intervention require contrast coronary angiography for the definitive identification of restenosis.6,7 A noninvasive method for reliably identifying restenosis would have substantial clinical utility.

With MRI, coronary arteries,8,9 arterial stenoses10 and anomalies,11 and intracoronary stents12 can be located, and CAFR can be measured.13 Because flow reserve is reduced in patients with restenosis,3,14 we hypothesized that MRI could be used to identify restenosis in the months after successful percutaneous intervention. To test this hypothesis, we compared MRI measures of CAFR with measures of stenosis severity obtained with computer-assisted quantitative coronary angiography (QCA) in a group of patients with recurrent chest pain after successful percutaneous intervention.

Study Population
The study was approved by the Institutional Review Boards at the Wake Forest University School of Medicine and the University of Texas Southwestern Medical Center, and all participants gave written informed consent. The study population consisted of 20 subjects (16 men and 4 women, age 36 to 77 years) who were referred for coronary angiography with recurrent chest pain ≥6 weeks after successful percutaneous intervention. Data from 7 of these patients were presented in a previously published comparison of MRI and intracoronary Doppler measurements of CAFR.15 Patients were ineligible for enrollment if they (1) had contraindication to MRI (a pacemaker or defibrillator, intracranial metal, or claustrophobia), (2) had contraindication to receiving adenosine (heart block or reactive airways disease), or (3) had an underlying condition that could substantially alter CAFR independent of stenosis severity (previous coronary artery bypass grafting, unstable angina, or prior myocardial infarction in the region subserved by the coronary artery that underwent prior intervention). All substances or medications, such as caffeine, which potentially might interfere with...
the action or metabolism of adenosine, were withheld 24 hours before study.

Study Design
Each subject underwent MRI followed immediately by intravenous adenosine coronary angiography, so that the 2 procedures were separated by 6 hours. During MRI and contrast angiography, the site of previous intervention was visualized. During MRI, coronary flow was measured at baseline and after 140 μg · kg⁻¹ · min⁻¹ IV adenosine (the dose commonly used during studies incorporating radionuclide determinations, were compiled, analyzed, and stored without knowledge of the findings obtained during the other procedure.

MRI Technique
MRI was performed in 12 patients (Winston-Salem) with a 1.5-T GE Horizon, in 6 patients (Winston-Salem) with a 1.5-T GE Cardiovascular (both General Electric Medical Systems), and in 2 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 with ECG monitoring leads, a brachial blood pressure cuff, and a pulse oximeter attached.

The coronary artery in which the previous intervention took place was imaged in tangential and longitudinal planes, according to previously published techniques, through the use of a gradient echo breath-hold acquisition. In patients with an intracoronary stent or a coronary stenosis, a cross-sectional view of the artery 1 to 2 cm distal to the area of signal dropout was obtained (Figure 1). When no signal dropout was appreciated, the cross-sectional image was positioned in the middle segment of the vessel of prior intervention.

To measure flow, cine phase-contrast (PC) breath-hold acquisitions were acquired perpendicularly across vessel segments in the cross-sectional slice position determined from the gradient-echo acquisitions. The number of k-space lines acquired per frame in each R–R interval was adjusted for each patient studied to yield 4 to 5 frames per cardiac cycle (temporal resolution ranging from 112 to 168 ms). Other imaging parameters included a 7-mm slice thickness, a 256 × 256 matrix, a field of view of 21 to 24 cm, a flip angle of 40°, a repetition time of 13.8 (GE) and 19.5 (Picker) ms, and an echo time of 6.7 (GE) and 11 (Picker) ms. A three-quarter–phase field of view was used to keep the duration of the breath-hold between 18 to 28 seconds. After resting coronary arterial flow was measured, 140 μg · kg⁻¹ · min⁻¹ adenosine was infused intravenously for 6 minutes, during the last 3 minutes of which coronary flow measurements were repeated. The segmentation of k-space was reduced (increasing scan time) as the heart rate increased after adenosine administration (decreasing scan time), and thus the duration of the breath-hold remained relatively constant for the baseline and stress acquisitions.

Coronary flow was calculated according to previously published techniques. At the time of analysis of the MRI data, paired magnitude images and velocity maps were displayed on an image-processing workstation. On the baseline and peak flow image sets, a region of interest (ROI) was generated by manually tracing the vessel lumen on the magnitude image. Afterward, the ROI was transferred to the velocity map, and the mean volume flow velocity was determined for each frame of the cine sequence. Mean flow (at baseline and stress) was calculated by averaging the flow per frame over the cardiac cycle.

Using prospective gating, images were not acquired during the last 30 to 100 ms of diastole, when blood flow in the left anterior coronary arterial circulation has been shown with a Doppler guide wire and MRI techniques to be high. For this terminal portion of the cardiac cycle, we estimated flow to be the same as the flow in the last imaged diastolic frame. CAFR was defined as the ratio of peak flow (measured after adenosine infusion) to baseline flow.

Cardiac Catheterization
After MRI, patients were transferred immediately to the catheterization laboratory, and after insertion of a 7F or 8F sheath into the femoral artery, a 7F diagnostic catheter was positioned in the coronary artery ostium of interest. Images of the site of previous intervention were obtained in ≥2 orthogonal views. Stenosis severity was determined with QCA, according to previously published techniques.

Data Analysis
All data are expressed as mean ± 1 SD. The values for stenosis severity calculated with QCA were compared with the CAFR measurements made with MRI with a 2-variable linear regression analysis. To determine if the correlation coefficient was significantly different from 0, a Student’s t test was performed. The interobserver variability in the analysis of PC-MRI flow reserve data was compared by use of the analysis of Bland and Altman.

Results
MRI studies were well tolerated in all subjects. MRI data from 2 patients were excluded from further analysis because of poor image quality after adenosine infusion (1 patient had a wrap-around artifact and 1 could not perform the breath-hold). In a third patient, MRI investigators did not properly identify the site of prior coronary intervention. The remaining 17 subjects formed the study population, and their detailed data are displayed in the Table. Their mean height was 176 cm (range 155 to 193) and mean weight was 89 kg (range 73 to 125). 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), and the image analysis time averaged 1 hour.

The length of artery visualized (from the ostium to the most distal segment) ranged from 6.8 to 12.4 cm in the left anterior descending coronary artery or its diagonal branches and 9.4 cm in the right coronary artery. Coronary arterial diameters distal to the sites of prior intervention as deter-
mined by QCA ranged from 1.8 to 4.8 mm. Representative studies from patients 10 and 9 are displayed in Figures 2 and 3. For patients with a luminal diameter stenosis of 50%, 50% but 70%, and 70%, PC-MRI CAFR values were 3.0 ± 0.6, 2.1 ± 1.2, and 1.1 ± 0.3, respectively (P < 0.0001). The correlation between luminal narrowing determined by QCA and MRI CAFR is shown in Figure 4. The sensitivity and specificity of an MRI CAFR value of #2.0 were 100% and 89%, respectively, for the identification of a coronary arterial stenosis 70%, and 82% and 100%, respectively, for the identification of a stenosis 50%. The interobserver variability for the MRI measurements of CAFR in all subjects (range of flow reserves measured, 0.5 to 4.0) was 20.1 ± 0.4 (Figure 5).

Discussion
Despite innumerable attempts over the past 2 decades to elucidate the mechanism and treatment of restenosis after successful percutaneous coronary intervention, its incidence remains 25% to 60%.1−7 Since noninvasive methods such as stress ECG,21 radionuclide scintigraphy,22 echocardiography,23 and contrast-enhanced electron beam computed tomography24 are less sensitive and specific than contrast coronary angiography for identifying restenosis, most patients with recurrent chest pain after a percutaneous intervention undergo repeat contrast coronary angiography. With MRI, coronary arterial stenoses10 and intracoronary stents can be located, 12 and recently, we showed that PC-MRI measurements of CAFR are accurate for identifying flow-limiting stenoses in the left main and anterior descending coronary arteries.15 In this study, we show that in patients with recurrent chest pain >6 weeks after a successful percutaneous intervention, PC-MRI flow reserve assessments can be used to reliably identify a >70% luminal diameter narrowing at the site of previous intervention (sensitivity 100%; specificity 89%) as compared with QCA.

Restenosis can be characterized by (1) a clinical end point or event (most often recurrent angina or required repeat revascularization),25 (2) an abnormality of coronary flow or fractional flow reserve,26,27 or (3) a diminution of coronary artery luminal dimensions.1−3 Most commonly, it is defined as a recurrent luminal diameter narrowing of >50% at the site of a previously successful intervention.1−7,25 Because we measured CAFR, our data reflect the functional importance of the stenoses within the coronary arterial lumen, not merely the morphology. For this reason, it is not surprising that our technique was only 82% sensitive for detecting a recurrent luminal diameter narrowing of >50%, since this degree of stenosis may or may not be functionally significant. If one uses a 50% luminal narrowing to define restenosis, the sensitivity and specificity of our technique are somewhat higher than other forms of noninvasive functional testing, such as radionuclide scintigraphy22 and stress echocardiography23 (sensitivity 20% to 95% and specificity 59% to 90%) but still not equivalent to contrast coronary angiography. Perhaps the sensitivity and specificity of these other noninvasive modalities for detecting restenosis would be higher if they were compared with a functional rather than a purely angiographic assessment of lumen diameter.

Summary of Patient Data

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Age, y</th>
<th>Site of Prior Intervention</th>
<th>Type of Intervention</th>
<th>Time From Angioplasty to PC-MRI, wk</th>
<th>% Stenosis QCA</th>
<th>CFR PC-MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CAD</td>
<td>M</td>
<td>56</td>
<td>LAD</td>
<td>DCA</td>
<td>8</td>
<td>90</td>
<td>1.2</td>
</tr>
<tr>
<td>2</td>
<td>CAD/LAT MI</td>
<td>M</td>
<td>44</td>
<td>LAD</td>
<td>PTCA/Stent</td>
<td>14</td>
<td>25</td>
<td>3.0</td>
</tr>
<tr>
<td>3</td>
<td>HTN/CAD</td>
<td>M</td>
<td>50</td>
<td>LAD</td>
<td>PTCA</td>
<td>10</td>
<td>38</td>
<td>2.4</td>
</tr>
<tr>
<td>4</td>
<td>CAD</td>
<td>M</td>
<td>68</td>
<td>Diag</td>
<td>PTCA</td>
<td>67</td>
<td>95</td>
<td>1.1</td>
</tr>
<tr>
<td>5</td>
<td>CAD</td>
<td>M</td>
<td>36</td>
<td>LAD</td>
<td>PTCA</td>
<td>6</td>
<td>57</td>
<td>2.9</td>
</tr>
<tr>
<td>6</td>
<td>CAD</td>
<td>M</td>
<td>61</td>
<td>LAD</td>
<td>PTCA/Stent</td>
<td>17</td>
<td>92</td>
<td>0.5</td>
</tr>
<tr>
<td>7</td>
<td>HTN/CAD/IMI</td>
<td>M</td>
<td>50</td>
<td>Diag</td>
<td>PTCA/Stent</td>
<td>69</td>
<td>93</td>
<td>1.5</td>
</tr>
<tr>
<td>8</td>
<td>HTN/CAD/LAT MI</td>
<td>M</td>
<td>42</td>
<td>LAD</td>
<td>PTCA/Stent</td>
<td>17</td>
<td>31</td>
<td>2.6</td>
</tr>
<tr>
<td>9</td>
<td>HTN/CAD</td>
<td>M</td>
<td>59</td>
<td>LAD</td>
<td>PTCA/Stent</td>
<td>86</td>
<td>57</td>
<td>0.8</td>
</tr>
<tr>
<td>10</td>
<td>CAD/LAT MI/CHF</td>
<td>F</td>
<td>77</td>
<td>LAD</td>
<td>PTCA/Stent</td>
<td>11</td>
<td>35</td>
<td>3.1</td>
</tr>
<tr>
<td>11</td>
<td>CAD</td>
<td>M</td>
<td>43</td>
<td>LAD</td>
<td>PTCA/Stent</td>
<td>8</td>
<td>77</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>HTN/CAD</td>
<td>M</td>
<td>59</td>
<td>LAD</td>
<td>PTCA</td>
<td>126</td>
<td>43</td>
<td>2.9</td>
</tr>
<tr>
<td>13</td>
<td>CAD/IMI</td>
<td>M</td>
<td>59</td>
<td>LAD</td>
<td>PTCA</td>
<td>23</td>
<td>80</td>
<td>0.9</td>
</tr>
<tr>
<td>14</td>
<td>HTN/CAD</td>
<td>M</td>
<td>62</td>
<td>LAD</td>
<td>PTCA/Stent</td>
<td>46</td>
<td>88</td>
<td>1.4</td>
</tr>
<tr>
<td>15</td>
<td>CAD/HTN</td>
<td>F</td>
<td>74</td>
<td>LAD</td>
<td>PTCA</td>
<td>14</td>
<td>72</td>
<td>1.4</td>
</tr>
<tr>
<td>16</td>
<td>CAD/HTN</td>
<td>M</td>
<td>61</td>
<td>RCA</td>
<td>PTCA/Stent</td>
<td>&gt;200</td>
<td>0</td>
<td>4.0</td>
</tr>
<tr>
<td>17</td>
<td>CAD/IMI</td>
<td>M</td>
<td>54</td>
<td>LAD</td>
<td>PTCA/Stent</td>
<td>8</td>
<td>55</td>
<td>2.7</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; CFR, coronary flow reserve; CHF, congestive heart failure; Diag, diagonal branch; DCA, directional coronary atherectomy; HTN, hypertension; IMI, inferior myocardial infarction; LAD, left anterior descending coronary artery; LAT MI, lateral myocardial infarction; PC-MRI, phase-contrast MRI; PTCA, percutaneous rotational atherectomy; QCA, quantitative coronary arteriography; and RCA, right coronary artery.
There is disagreement as to whether clinical end points or functional/physiological assessments such as CAFR should be used to define restenosis rather than a dichotomous variable based on 50% encroachment of the coronary arterial lumen.28 Because the angiographic analysis of the coronary lumen may underestimate the severity of narrowing in patients with diffuse coronary artery disease,29 particularly if lesion geometry is complicated,28,29 several investigators have reported on the utility of intracoronary Doppler-derived measurements of CAFR for identifying restenosis.27,30,31 Our results with PC-MRI are similar to those obtained invasively in 3 respects. First, our CAFR value of 1.6 to 2.0 is similar to the invasive value of 1.5 ± 0.4 for identifying restenosis.27,30,31 Second, the interobserver variability of invasive measures of CAFR is 0.1 ± 0.5, whereas with PC-MRI it is −0.1 ± 0.4.27,30,31 And third, our data are consistent with previously published invasive assessments of CAFR, which indicate that some stenoses of intermediate severity (45% to 70% luminal diameter narrowing) are flow limiting during stress, whereas others are not.32

The use of PC-MRI to measure CAFR is advantageous for several reasons. First, it is safe and easily performed in an outpatient setting without the need for ionizing radiation or intravenous contrast material. This allows for serial quantitative assessments to be performed, a helpful feature when monitoring patients long term after a therapeutic intervention. Second, it provides a method of visualizing coronary anatomy directly, including the location of stenoses and previously deployed stents. This information is not provided with ECG, echocardiography, or radionuclide scintigraphy, and it may be useful in preparation for a repeat revascularization procedure. Third, it can be used to detect functional restenosis regardless of the type of percutaneous intervention (balloon angioplasty, directional or rotational atherectomy, or intracoronary stenting). The use of PC-MRI to measure flow reserve distal to the site of prior intervention is particularly useful in patients with intracardiac stents (<50% of our cases) because the metal in an intracoronary stent causes a signal void (Figures 1 and 3) that prohibits an assessment of stenosis severity with the use of conventional gradient echocardiographic techniques.12

Our study has limitations. First, our results are not applicable to patients with abnormal CAFR at rest, including (1) those who have chest pain within 6 weeks of their...
percutaneous intervention, since the vasoreactivity of the microcirculation returns slowly to normal after the intervention.\textsuperscript{4,30,31} (2) Those with disease processes that impair microcirculatory vasoreactivity, such as previous myocardial infarction, dilated or hypertrophic cardiomyopathy, moderate to severe valvular heart disease, severe hypertension, or (3) the presence of coronary bypass grafts that attach to the coronary artery distal to the slice position where CAFR was measured.\textsuperscript{18} In these patient groups, the measurement of fractional flow reserve may be useful for assessing the severity of epicardial coronary arterial stenoses.\textsuperscript{18} Second, our total scan time (range 44 to 75 minutes) and analysis time (average 1 hour) were lengthy.

**Figure 3.** Tangential (top left) and cross-sectional (top right) MRI angiograms of left anterior descending coronary artery (LAD) in patient 9. Right, Selected image from patient’s contrast coronary angiogram is displayed. In tangential MRI and contrast coronary angiogram, location of intracoronary stent is shown. On right velocity map, persistent gray pixels after adenosine in patient indicate impaired coronary flow reserve (value = 0.8) that corresponded to presence of 57% stenosis by QCA. LM indicates left main; Cx, circumflex.

**Figure 4.** Relation between stenosis severity with computer-assisted QCA (horizontal axis) and PC-MRI measurements of CFR (vertical axis) for 17 patients. Each symbol represents data from 1 patient. Regression line (solid line) and equation are shown.

**Figure 5.** Mean PC-MRI coronary flow reserve by 2 separate readers (horizontal axis) and difference between 2 readers’ measurements (vertical axis) for 17 patients. Each symbol represents data from 1 patient. Mean difference (solid line) and ±2 SD from this difference (dashed lines) are shown. There is excellent agreement (thus low interobserver variability) in determination of PC-MRI measurements of CFR.
Strategies that incorporate real-time imaging and automated analysis could substantially reduce these times. Third, MRI investigators were notified of the site of prior intervention before scanning. We are uncertain of our results if the site of prior intervention was unknown. Although MRI investigators misidentified the site of intervention in 1 patient, the review of the catheterization images from the initial percutaneous intervention could be used to identify the underlying anatomy and avoid this type of error. Fourth, we measured CAFR in anterior coronary artery segments >2 mm in diameter. We did not measure absolute coronary flow in the left anterior circulation, nor did we measure CAFR in vessel segments that undergo marked in-plane motion such as the middle right or circumflex coronary arteries. Precise measurements of absolute coronary flow may require strategies that use higher spatial resolution or through-plane motion correction. In addition, pulse sequences that incorporate higher temporal resolution (which reduce the blurring of vessel regions caused by marked lateral in-plane motion) may increase the accuracy of coronary flow and flow reserve measurements further.

In conclusion, in patients who have chest pain >6 weeks after percutaneous intervention, PC-MRI measures of coronary arterial flow reserve can be used to identify functionally important narrowings at the site of prior intervention in the proximal and middle segments of anterior coronary arterial segments. The utility of this technique for detecting 50% luminal narrowings by angiography (the most commonly used definition of restenosis) is similar to other noninvasive imaging modalities.

Acknowledgments
This research was supported in part by the North Carolina Baptist Medical Center Technology Development Fund (BG96-302), the American Heart Association North Carolina Affiliate (S98692N), and the National Institutes of Health (3-M01-RR07122). Adenosine used for this project was kindly supplied by Fujisawa, Inc. The authors appreciate the assistance of Belinda Youngdahl in preparing the manuscript.

References

280 Circulation May 23, 2000

Downloaded from http://circ.ahajournals.org/ by guest on April 13, 2017
Assessment of Coronary Arterial Restenosis With Phase-Contrast Magnetic Resonance Imaging Measurements of Coronary Flow Reserve

W. Gregory Hundley, L. David Hillis, Craig A. Hamilton, Robert J. Applegate, David M. Herrington, Geoffrey D. Clarke, Gregory A. Braden, Mark S. Thomas, Richard A. Lange, Ronald M. Peshock and Kerry M. Link

Circulation. 2000;101:2375-2381
doi: 10.1161/01.CIR.101.20.2375

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/101/20/2375

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation 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 is online at:
http://circ.ahajournals.org//subscriptions/