Assessment of Myocardial Perfusion in Coronary Artery Disease by Magnetic Resonance
A Comparison With Positron Emission Tomography and Coronary Angiography

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Background—Monitoring contrast medium wash-in kinetics in hyperemic myocardium by magnetic resonance (MR) allows for the detection of stenosed coronary arteries. In this prospective study, the quality of a multislice MR approach with respect to the detection and sizing of compromised myocardium was determined and compared with positron emission tomography (PET) and quantitative coronary angiography.

Methods and Results—A total of 48 patients and 18 healthy subjects were studied by MR using a multislice hybrid echo-planar pulse sequence for monitoring the myocardial first pass kinetics of gadolinium-diethylenetriamine pentaacetic acid bismethylamide (Omniscan; 0.1 mmol/kg injected at 3 mL/s IV) during hyperemia (dipyridamole 0.56 mg/kg). Signal intensity upslope as a measure of myocardial perfusion was calculated in 32 sectors per heart from pixelwise parametric maps in the subendocardial layer and for full wall thickness. Before coronary angiography, coronary flow reserve (hyperemia induced by dipyridamole 0.56 mg/kg) was determined in corresponding sectors by $^{13}$N-ammonia PET. Receiver-operator characteristic analysis of subendocardial upslope data revealed a sensitivity and specificity of 91% and 94%, respectively, for the detection of coronary artery disease as defined by PET (mean coronary flow reserve minus 2SD of controls) and a sensitivity and specificity of 87% and 85%, respectively, in comparison with quantitative coronary angiography (diameter stenosis $\geq$50%). The number of pathological sectors per patient on PET and MR studies correlated linearly (slope, 0.94; $r$=0.76; $P$<0.0001).

Conclusions—The presented MR approach reliably identifies patients with coronary artery stenoses and provides information on the amount of compromised myocardium, even when perfusion abnormalities are confined to the subendocardial layer. This modality may qualify for its clinical application in the management of coronary artery disease. (Circulation. 2001;103:2230-2235.)

Key Words: imaging ■ perfusion ■ heart diseases

In patients with coronary artery disease (CAD), clinical decisions regarding the need for angioplasty or bypass surgery are based on the evaluation of coronary anatomy and are ideally combined with an assessment of the hemodynamic significance of the disease. Therefore, perfusion assessment by single photon emission computed tomography (SPECT) plays a key role in patient management. However, the method suffers from attenuation artifacts¹ and exposes patients to radiation. Positron emission tomography (PET) imaging corrects for attenuation and allows for the quantification of perfusion,² but it is not widely available.

In the early 1990s, myocardial first-pass magnetic resonance (MR) perfusion imaging was shown to detect CAD in patients.³ Because the extent of disease relates to the patient’s prognosis, multislice approaches were developed. The application of multislice techniques to highly selected patient populations with documented single-vessel disease yielded sensitivities of 100%.⁴ However, the application of a multislice mode to a mixed unselected study population either yielded low sensitivity (44% in 10 patients)⁵ or low specificity (44% in 45 patients).⁶ In a recent prospective study using a single-slice approach, sensitivity and specificity were 90% and 83%, respectively, for the detection of stenosis $\geq$75%.⁷ In that study, a high sampling rate of one image per heartbeat allowed calculation of contrast medium (CM) first-pass kinetics but precluded a multislice acquisition. In MR perfu-

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sion studies evaluated thus far in patients with coronary artery stenoses, data acquisition windows (including inversion recovery preparation) amounted to 650 to 750 ms. In the present study, a hybrid echo-planar readout was used and combined with a saturation recovery approach, which reduced the data acquisition window to 239 ms. We hypothesized that such an approach would yield highly reliable perfusion data, even in a multislice mode, and moreover, it would allow evaluation of perfusion indexes quantitatively within distinct myocardial layers.

Methods

Study Population
We prospectively studied 48 patients with suspected CAD who were referred for coronary angiography. Exclusion criteria were unstable angina, atrial fibrillation, valvular heart disease, a history of revascularization, or previous myocardial infarction as indicated by history, (2) Q waves in the resting 12-lead ECG, or (3) wall motion abnormalities at rest (by echocardiography or MR). Within 2 weeks before coronary angiography, patients underwent MR and PET perfusion studies in random order. Antianginal medication was withdrawn ≥24 hours before the tests, as were caffeinated beverages or food. The volunteers (n = 18, aged 29 ± 3 years) were at low risk for CAD because of their medical history, normal physical examination, and normal resting and stress ECGs. The study protocol was approved by the local Ethics Committee, and all subjects gave written informed consent. MR, PET, and angiographic data were analyzed and stored without knowledge of the findings obtained during the other procedures.

MR Examination
All subjects were examined in the supine position with a 1.5T system (CV/i, GE Medical Systems), and a 4-element phased-array radiofrequency coil was used for signal reception. After the assessment of resting cardiac function, vasodilatation was induced by dipyridamole (0.56 mg/kg IV over 4 minutes). During a breath-hold, the extravasated CM, gadolinium-diethylenetriamine pentaacetic acid bismethylamide (Omniscan, gadodiamide injection; Nycomed Imaging AS, Oslo, Norway), was injected into a cubital vein (0.1 mmol/kg over 4 minutes). The first pass was monitored using a hybrid echo-planar pulse sequence (repetition time/echo time, 6.6/2.0 ms; echo train length, 4; preparation pulse, 90°; delay time, 120 ms; slice thickness per gap, 8.5 mm; rectangular field of view, 34 to 40 cm by 26 to 30 cm; matrix, 128 × 96, with a pixel size of 2.7 × 3.5 mm interpolated to 1.3 to 1.6 mm for further analysis) that acquires a complete image within 119 ms and yields 4 slices every 2 R-R intervals up to a heart rate of 125 beats/min. During the study, blood
pressure and heart rate were acquired at 2-minute intervals, and ECG was monitored continuously (MR Equipment, Model 9500).

After manual correction of images for gross cardiac motion, endocardial and epicardial contours were drawn and 8 equiangular sectors per slice were generated automatically (rotating clockwise using the anterior septal insertion of the right ventricle as a reference point; Figure 1); these sectors were further subdivided into an inner and outer half (ie, into a subendocardial and subepicardial layer, respectively), which resulted in 64 regions per heart. For each slice, an algorithm then extracted the maximal slope in each pixel of the myocardium and the left ventricular blood pool (5-point and 3-point linear fit, respectively) using a sliding window. Relative upslope was obtained by dividing the upslope data by the precontrast signal intensity. Finally, mean slopes were calculated in all sectors (subendocardial layer and full wall thickness) and divided by the upslope of the signal in the left ventricular cavity, which was regarded as a measure of the input function.7,9

PET Examination

Dynamic PET measurements were performed using a whole-body PET scanner (Advance, GE Medical Systems). Images were reconstructed using filtered backprojection (Hanning filter; cutoff, 5 mm transaxial and 8.5 mm axial) and a 128x128 pixel output matrix. Beginning with the intravenous bolus administration of 700 to 800 MBq of 13N-ammonia, serial images were acquired for 15 minutes. After a delay time of at least 50 minutes to allow for 13N decay (physical half-life, 9.9 minutes), hyperemia was induced by dipyridamole (same regimen as for MR study), and flow measurement was repeated followed by a transmission scan for attenuation correction. On reformatted short-axis views, 8 regions of interest per slice were placed using the anterior septal insertion of the right ventricle as a reference point (Figure 1). From the resulting 32 regions of interest per heart, regional myocardial tissue time-activity curves were obtained. The arterial input function was derived from a region of interest in the left ventricular blood pool. As a direct estimator of myocardial blood flow, 13N-ammonia uptake (K1) (in mL·min⁻¹·g⁻¹) was calculated from the time-activity curves using a previously validated 2-compartment model (K1, 13N-ammonia washout rate (k1), spill-over correction). In each myocardial region of interest, coronary flow reserve (CFR) was calculated as hyperemic/resting myocardial blood flow.

Receiver-Operator Characteristics of MR Perfusion Imaging Versus PET and X-Ray Coronary Angiography

The studies were also performed in healthy volunteers, who were randomly divided into 3 groups. Group 1 (n=8) was used to generate reference values (slopeendo.norm and slopetrans.norm for the subendocardial layer and full-wall thickness, respectively; values are mean±SD). Group 2 (n=10) was added to the patient cohort to simulate the relatively high proportion of normal subjects that are typically referred for noninvasive testing to achieve a more reliable calculation of specificity. For the comparison of PET versus quantitative coronary angiography (QCA), the study cohort of 41 patients (33 with documented CAD, 8 without CAD) was supplemented by an additional 8 low-likelihood subjects (collected randomly from our normal database) for the same reasons. Receiver-operator characteristic (ROC) analyses14 were employed to determine the diagnostic performance of MR upslope data for the detection of CAD. CAD was defined either anatomically as ≥1 stenosis ≥50% in diameter in any of the 3 coronary arteries (and their side branches with a diameter ≥2 mm) or hemodynamically as ≥1 sector with a CFR <1.65 (mean minus 2SD of the normal database at our institution), which is in agreement with CFR threshold values of 1.2 to 1.7.15,16 Further, ROC analyses were performed separately for 1-, 2-, and 3-vessel disease. To test the performance of MR perfusion imaging for each coronary artery, sectors 1 and/or 8, 3, and 5 and/or 6 from all slices were assigned to the left anterior descending, the circumflex, and the right coronary artery, respectively, assuming these sectors as centers of corresponding perfusion territories (sectors 2, 4, and 7 were not used for this analysis). The coronary angiograms were analyzed by an automated geometric-densitometric edge-detection algorithm.17

Statistical Analysis

Values are given as mean±SD. Using the reference values derived from the normal group 1 subjects (slopeendo.norm and slopetrans.norm), the threshold values [given as slopeendo minus (x±SD)] were determined by ROC analyses in the patient cohort that best discriminated patients with CAD (defined either hemodynamically or anatomically) from those without CAD.14 To compare disease extent by MR and PET, a repeated measures ANOVA was performed followed by paired t tests and Bonferroni correction. Sensitivities and specificities of the MR approach in different vascular territories and in patients with 1-, 2-, and 3-vessel disease were compared using χ²

Figure 2. ROC of MR upslope data are shown for the detection of coronary artery disease defined either hemodynamically by PET (A; ≥1 sector with a CFR <1.65; n=51) or anatomically by QCA (B; ≥1 artery with ≥50% diameter stenosis; n=57). MR upslope data, particularly from the subendocardial layer, are highly reliable in the detection of hemodynamically significant disease (A). In the detection of ≥50% diameter stenoses, the diagnostic performance of MR and PET are comparable (B). Numbers in parentheses represent sensitivity, specificity, and area under the ROC curve, respectively.
tests. Intraobserver and interobserver variabilities of MR slope data are reported as mean ± 2SD of differences of paired analyses. A P < 0.05 was considered statistically significant.

**Results**

A total of 48 patients were studied by MR, PET, and coronary angiography, and an additional 18 healthy volunteers were examined by MR. All examinations were well tolerated without complications. One MR and 2 PET studies were excluded from analysis for technical reasons. One PET study was cancelled for logistic reasons, and 4 were lost due to a storage media failure, resulting in 41 PET examinations available for comparison with MR. Demographics of patients and healthy subjects (normal group 2) included in the ROC analyses are given in Table 1, and hemodynamic data for patients and volunteers are given in Table 2.

**Diagnostic Performance of MR Perfusion Imaging**

**Detection of CAD**

In Figure 1, MR images demonstrate wash-in of CM is delayed transmurally in territories supplied by stenosed coronary arteries. In corresponding sectors, hyperemic flow on PET is impaired (Figure 1H). The ROC analysis in Figure 2A revealed a high diagnostic reliability of subendocardial MR upslope data for detection of hemodynamically significant CAD; corresponding results for the detection of anatomically defined CAD are given in Figure 2B.

**Assessment of Extent of CAD**

For a direct visualization of MR perfusion data, polar map representations of the signal intensity upslope in the subendocardial layer were generated (Figure 3). In Figure 4, the number of myocardial sectors with impaired subendocardial flow on MR (slope_endo.norm minus 1.75SD) and reduced CFR on PET (<1.65) are compared (8.1 ± 6.5 sectors versus 9.0 ± 5.7 sectors, respectively; overall P = 0.22). The number of pathologic sectors measured by MR and PET correlated linearly (slope, 0.94; r = 0.76; P < 0.0001). Sectors with transmurally reduced flow underestimated the extent of disease (4.9 ± 5.34 sectors versus 9.0 ± 5.7 sectors with PET; P < 0.005). In Figures 5 and 6, the influence of the number and type of coronary artery involvement, as determined by QCA, on the sensitivity and specificity of MR data is shown, respectively.

For the intraobserver variability of slope_endo and slope_trans (evaluated in 320 sectors of 10 randomly chosen patients), the mean differences (with the 95% confidence intervals in parentheses) were -0.3% (-18.3% to 17.7%) and -2.5% (-14.3% to +9.4%), respectively. For interobserver variability, the results were 5.6% (-15.3% to 26.5%) and 4.7% (-14.7% to 24.1%), respectively.

**Figure 3.** In this patient with a stenosis in the right coronary artery (arrow in G), the transit of CM through the left ventricular myocardium during hyperemia (time resolution, 4 slices every 1.2 s) demonstrates delayed wash-in in the subendocardium of sectors 4 through 6 (arrowheads in D through F). In the corresponding pixel-wise parametric slope map (I), the perfusion deficit is demonstrated in blue (color-coding as in Figure 1G). In K, a polar map represents perfusion in the subendocardium (with the apex located in the center of the map and the anterior, lateral, inferior, and septal wall represented by sectors 1, 3, 5, and 6 through 8, respectively). The subendocardial perfusion deficit in the territory of the right coronary artery extends from base to apex, whereas the perfusion deficit in the anterior and septal wall (sectors 1, 7, and 8) extends from the midventricular level to the apex (slices 3 and 4), in concordance with the stenosis in the midportion of the left anterior descending coronary artery (arrow in H).

**Figure 4.** Comparison of pathological sectors, as defined by MR and PET, in patients with 1-, 2-, and 3-vessel disease (VD) and no disease (for details, see Results). There was a trend toward underestimation of the extent of disease by MR (P = 0.22 vs PET), P < 0.05 vs no disease, †P < 0.01 vs no disease (2-way ANOVA for repeated measures, Bonferroni-corrected; error bars represent SEM).
Figure 5. Sensitivities and specificities to detect CAD, as defined by QCA, was not different for 1-, 2-, or 3- vessel disease (VD). For calculation of sensitivity and specificity in the 1-, 2-, and 3-vessel disease population, patients with 1-, 2-, or 3-vessel disease were considered, respectively, and combined with subjects without disease (ie, patients with normal coronary angiography and normal group 2 subjects). The portion of patients with CAD is indicated in parentheses below the bars.

Discussion

There are 3 major findings in this study: (1) the presented MR first-pass perfusion approach reliably detects and quantifies perfusion deficits in patients with CAD; (2) the presented MR technique resolves transmural differences in perfusion and generates polar maps of perfusion deficits in the subendocardium; and (3) the robustness of this MR approach is demonstrated even when combined with a peripheral CM injection.

Diagnostic Performance of MR Perfusion Imaging

The diagnostic performance of MR perfusion imaging was evaluated with respect to anatomically and functionally defined CAD. $^{13}$N-ammonia PET is well established for quantifying blood flow, and it was used as a reference for myocardial perfusion. The best results for the detection of CAD by MR perfusion imaging were obtained when CM wash-in was assessed in the subendocardial layer, which is most sensitive to an ischemic challenge. The presented MR perfusion approach yielded a sensitivity and specificity of 91% and 94%, respectively, for the detection of patients with reduced CFR as defined by PET. Moreover, the amount of compromised myocardium, as assessed by MR, closely agreed with PET measurements. Thus, the presented MR approach provides an estimate of disease extent that includes important prognostic information and is therefore essential for patient management.

Recently, similar sensitivities and specificities were reported for an MR perfusion approach that detected angiographically defined CAD; however, the technique was limited to perfusion assessment in a single slice. In this and most other MR perfusion studies published so far, a fast low-angle shot readout lasting 360 to 450 ms was used and was combined with an inversion pulse involving preparation times of 300 to 400 ms. In the present study, a hybrid echo-planar readout of 119 ms duration was combined with a saturation recovery approach, reducing the preparation time to 120 ms. The short acquisition window allows a high sampling rate of perfusion data, even in multislice mode, and reduces motion-induced blurring, whereas the preparation time of 120 ms places data collection into phases of minimal cardiac motion. As a result, the MR data were of adequate quality to perform a linear fit of the signal increase on a pixel by pixel basis, and reproducibility of the mean upslope/sector was high for both full-wall thickness and the subendocardial layer. To our knowledge, this is the first time that polar maps of subendocardial zones of hypoperfusion were derived observer-independently from linear fits of MR first-pass data by applying threshold values to patient data.

In highly selected patients with documented severe proximal left anterior descending coronary artery stenosis, 100% agreement between a multislice MR approach and SPECT data were reported. In unselected patient populations, however, multislice approaches performed worse, with a sensitivity of 50% and specificity $<50\%$. In the present study, which was performed prospectively in unselected patients, the sensitivity and specificity for detecting anatomically defined CAD were 87% and 85%, respectively, which compared favorably with the values obtained with PET. With the MR approach, similar sensitivities and specificities were observed for all 3 vascular territories, indicating that all myocardial segments were visualized with similar image quality.

Limitations

Patients with previous myocardial infarctions were excluded from this study, and the performance of the MR technique in these patients remains to be determined. Specifically, the influence of altered hemodynamics on CM first-pass kinetics, and hence on the applicability of thresholds to myocardial upslope data, warrants further investigation. To identify necrotic/scar tissue, a so-called late-enhancement MR technique could be employed. Similarly, conventional scintigraphy typically includes a resting study to allow redistribution of tracer to identify viability. For detection of ischemia, however, PET studies provide evidence that hyperemic flow is as accurate a predictor for the presence of significant coronary stenoses as flow reserve. We therefore refrained from performing an additional resting MR study for ischemia detection.

Conclusions and Implications

This novel MR approach reliably identifies and quantifies perfusion deficits in an unselected patient population, and it specifically allows assessment of perfusion in distinct myo-
cardiac layers. In comparison with PET and QCA, the ROC analyses indicate a high diagnostic performance of this MR technique. With the short examination time of $\approx 1$ hour and a time-efficient analysis ($\approx 15$ minutes on average), this MR perfusion approach emerges as an easy and fast method for the noninvasive assessment of CAD, even when perfusion deficits are restricted to the subendocardial layer. The robustness of this technique may qualify it for clinical application in the management of patients with known or suspected CAD.

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