Magnetic Resonance Perfusion Measurements for the Noninvasive Detection of Coronary Artery Disease

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Background—With MRI, an index of myocardial perfusion reserve (MPRI) can be determined. We assessed the value of this technique for the noninvasive detection of coronary artery disease (CAD) in patients with suspected CAD.

Methods and Results—Eighty-four patients referred for a primary diagnostic coronary angiography were examined with a 1.5 T MRI tomograph (Philips-ACS). For each heartbeat, 5 slices were acquired during the first pass of 0.025 mmol gadolinium-diethylenetriamine pentaacetic acid/kg body weight before and during adenosine vasodilation by using a turbo-gradient echo/echo-planar imaging–hybrid sequence. MPRI was determined from the alteration of the upslope of the myocardial signal intensity curves for 6 equiangular segments per slice. Receiver operating characteristics were performed for different criteria to differentiate ischemic and nonischemic segments. Prevalence of CAD was 51%. Best results were achieved when only the 3 inner slices were assessed and a threshold value of 1.1 was used for the second smallest value as a marker for significant CAD. This approach yielded a sensitivity of 88%, specificity of 90%, and accuracy of 89%.

Conclusion—The determination of MPRI with MRI yields a high diagnostic accuracy in patients with suspected CAD. (***Circulation***. 2003;108:432-437.)

Key Words: magnetic resonance imaging ■ perfusion ■ coronary disease

Alterations of myocardial perfusion are highly sensitive for the detection of myocardial ischemia. In clinical practice, perfusion is usually assessed with single-photon emission tomography (SPECT) or PET, which reaches sensitivities and specificities from 83% to 95% and 53% to 95%.[1–4] SPECT is limited by the occurrence of attenuation artifacts, which can be found mainly in obese patients and women.[4] In addition, the application of radioactive tracers prohibits follow-up examinations. Although myocardial perfusion can be quantitatively assessed with PET, the technique is limited by its reduced availability.

Myocardial perfusion can be assessed with cardiovascular MRI at rest and during pharmacological vasodilation, and results from animal experiments have shown a correlation ($r^2=0.87$) with microspheres for the assessment of blood flow.[5] Flow differences of a factor ≥ 2 can be detected,[5] which occur in patients with $\geq 70\%$ coronary artery stenosis during vasodilation. Preliminary studies with small patient populations have shown promising results.[6–12] Parameters for the assessment of myocardial perfusion are usually gained by analyzing the first pass of a contrast agent bolus through the myocardium.[6,9,13,14] With extensive modeling, quantitative determination of myocardial perfusion is possible; however,

this approach relies on several assumptions that may not be fulfilled in patients.[13,15–17] We have recently shown that a linear fit of the upslope is easy to perform, is highly reproducible, and shows promising accuracy in a selected patient population.[18] Visual assessment may allow for a rapid diagnosis without the need for quantification.

We aimed to optimize the approach for evaluating MR perfusion measurements and to determine their value for the detection of significant stenoses in patients with suspected coronary artery disease (CAD).

Methods

Patients

All patients gave written informed consent. Ninety consecutive patients (73 male; age, 63 ± 8 years; body weight, 75 ± 11 kg; 21% smokers) with suspected CAD who were scheduled for a primary diagnostic invasive coronary angiography were included, 84 of which form the analysis population (see Results).

Patients with myocardial infarction <7 days, unstable angina pectoris, arterial hypertension (>160/140 mm Hg), diabetes mellitus, ejection fraction <50%, atrial flutter or fibrillation, sick sinus rhythm, SA- or AV-block >I, ventricular premature beats ($\geq$Lown-III), relevant obstructive pulmonary disease or valvular disease $\geq$II, or contraindications to the MR examination (incompatible metallic implants, claustrophobia) were excluded. To ensure minimal basal

Figure 1. Examples of 5 short-axis views of a patient with RCA disease at rest (top) and stress (middle). The stress images are magnified (bottom), and ischemic areas marked by arrows.

blood flow and a maximal vasodilatory response to adenosine, patients were instructed to refrain from smoking, tea, or coffee, as well as β-blockers and antianginal medication, for 24 hours before the examination. Patients were excluded from the study if they had not followed these instructions.

Magnetic Resonance Imaging

All patients were examined in the supine position (1.5 T ACS-NT, Philips) using a 5-element phased-array cardiac coil. After determination of the axis and length of the left ventricular (LV) cavity, 5 short-axis planes were imaged. The distance between each plane was individually set as one sixth of the end-systolic length of the LV cavity. A single shot segmented k-space turbo-gradient-echo/echo-planar-imaging (EPI)–hybrid technique (echo time [TE], repetition time [TR], and flip: 3.3, 12.5, and 30, respectively; 4 α-pulses followed by 11 EPI readouts each; spatial resolution, 1.7 to 2.2 mm×1.9 to 2.4 mm; slice thickness, 8 mm; 5 images per heart beat; 1 saturation prepulse for all slices; prepulse delay, 200, 300, 400, 500, and 600 ms for slices 1, 3, 5, 2, and 4, respectively) was used (Figure 1). Images were acquired during breath-holding for 10 heartbeats before and 60 heartbeats during the first pass of 0.025 mmol gadolinium-diethylenetriamine pentaacetic acid (DTPA)/km body weight (Schering) flushed with 10 mL 0.9%NaCl (flow rate, 8 mL/s; Medrad, Spectris).

After 15 minutes to allow for the clearance of the first contrast agent injection, 0.14 mg adenosine · kg body weight^{-1} · min^{-1} were infused for 4 minutes under continuous ECG and blood pressure monitoring. During the last minute of the infusion, the perfusion scan was repeated.

Coronary Angiography

After the MR examination, all patients underwent biplane coronary angiography in Judkins' technique. Two experienced blinded observers visually assessed the coronary angiographies. When needed, quantitative assessment was performed by a third blinded observer (ARRI, Munich, Germany). Hemodynamically relevant CAD was defined as ≥75% area reduction with respect to prestenotic segment area in at least 1 major epicardial coronary artery or major branch (>2.5-mm diameter). Patients were classified as having 1-, 2-, or 3-vessel disease. Coronary artery territories were defined from the angiogram in patients with 1-vessel disease by using the American Heart Association/American College of Cardiology guidelines.[19]

Image Analysis

The endocardial and epicardial contours were traced by an examiner blinded to angiography (MASS, Medical Imaging Solutions, Leiden, the Netherlands) and corrected manually for displacements (eg, breathing). The inner 10% and outer 30% of the myocardium were excluded to get stronger weighting of the subendocardium and reduce influences from the LV. The myocardium was divided into 6 equiangular segments per slice. LV signal intensity (SI) of the basal slice and myocardial SI were determined for all time points (Figure 2). Mean SI before contrast agent injection was subtracted from all postcontrast data, and the upslope of the resulting SI time curves was determined by using a linear fit of 4 consecutive images in myocardial curves (2 in the LV curves to account for the shorter bolus duration in the LV versus the myocardium). The results of the myocardial segments were corrected for differences of the speed and compactness of the contrast agent bolus by division of the myocardial upslope through the LV upslope. An index for myocardial perfusion reserve (MPRI) was calculated by dividing the results at maximal vasodilation through the results at rest.[18]

A patient was classified as having significant CAD if the minimum MPRI (one segment) was below the cutoff in any slice or the 3 inner slices only, or the second smallest MPRI (any 2 segments) was below the cutoff in any slice or the 3 inner slices only.

Visual Assessment

Rest and stress images were visually compared. If a segment showed a reduced peak SI or delayed wash-in at stress but not at rest, it was regarded as pathological.

Statistical Analysis

Continuous variables are expressed as mean±1 SD. Group differences were tested by using Student's *t* test for continuous variables. Significance was defined as $P<0.05$. Receiver operating characteristic (ROC) analyses were performed to evaluate the diagnostic
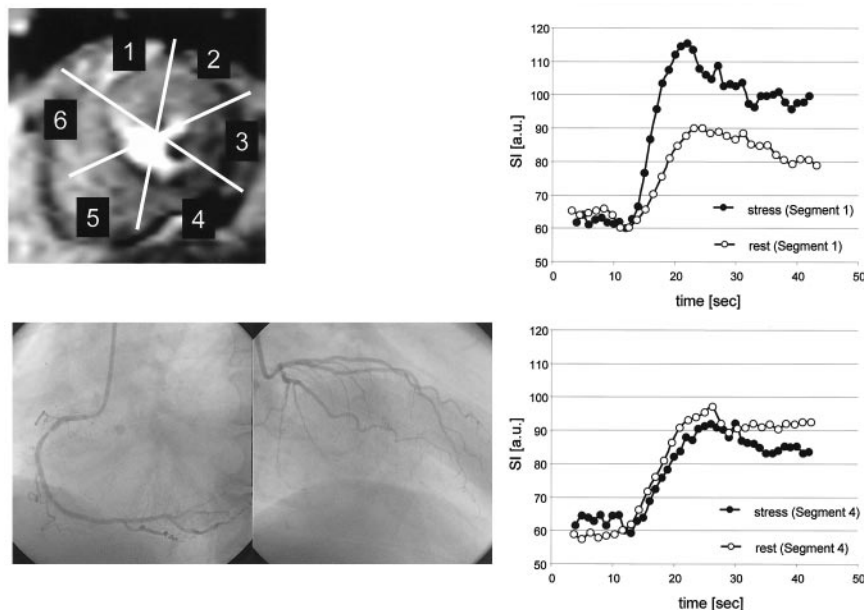
Figure 2. A, Segmentation of the myocardium into 6 equiangular segments per slice, starting clockwise from the anterior septal insertion point of the right ventricle. B, Coronary angiogram of the patient (same as Figure 1). C, In the normally perfused anterior segment, there is a clear increase of the upslope after adenosine (●) when compared with rest (○), whereas in the inferior segment of the same slice there is no change of the upslope after vasodilation with adenosine.

potential of each of the indicators used for semiquantitative assessment. Areas under the curve (AUCs) were determined and cutoff values chosen that maximized the Youden-criterion for each indicator. Sensitivities, specificities, and diagnostic accuracies were determined with regard to each cutoff. In patients with 1-vessel disease, location was determined by using the segment with the smallest perfusion index, as well as the segment with the second smallest perfusion index, and compared with invasive angiography.

Results

Patient Population
In 6 patients (7%), MRI could not be successfully completed. This was owing to claustrophobia (n=3), obesity (>150 kg body weight, n=1), severe anginal symptoms (n=1), or AV block III (n=1). In 5% of patients, examination conditions were difficult owing to strong breathing artifacts during adenosine infusion (n=1), delayed delivery of the contrast agent (n=2), or MRI artifacts (susceptibility artifacts) in the anterior segments (n=1). However, these patients were kept in the final analysis.

Table 1 lists the hemodynamic results. Most patients had minimal side effects (flush, warmth, headache), 6 had angina, and one had AV-block II that resolved within 30 seconds after stopping the infusion.

SI Time Curves
Analysis time to extract the relevant parameters was ≈30 minutes per patient. The upslopes for different myocardial

segments showed a systematic difference both at rest and stress, with higher values of the anterior in comparison to the inferior segments. However, these differences were corrected for by the calculation of the MPRI (Figure 3).

Individual patients showed large variations of LV upslopes between rest and stress, with only a mild correlation (upslope at stress=0.65×upslope at rest+40; $r=0.59$). Correction of the MPRI on the individual LV upslopes led to a smaller variation of data, resulting in a better differentiation between patients with and without significant CAD (Figure 4).

Diagnostic Accuracy
Prevalence of hemodynamically relevant CAD was 51% (43 patients). Nineteen patients had 1-vessel disease, 9 patients had 2-vessel disease, and 15 patients had 3-vessel disease.

The comparison of MR perfusion with angiography is shown in Table 2. AUC was largest when only the 3 inner slices were evaluated and the second smallest value was used to determine the cutoff value, which reached a maximum at 1.1 (Figure 5), yielding 88% sensitivity with 90% specificity. In patients with 1-vessel disease, sensitivity was 84%, in 2-vessel disease sensitivity was 90%, and in 3-vessel disease sensitivity was 93%.

Determination of Disease Location
In 18 of 19 patients (94.7%) with 1-vessel disease, the segment with the lowest MPRI of 5 or 3 slices correctly identified the location of the stenotic coronary artery.

Determination of Disease Severity
The number of diseased vessels correlated with the number of ischemic segments ($r=0.71$), without a clear cutoff value to determine disease severity owing to overlap between the groups.

Visual Assessment
Visual analysis required ≈10 minutes per patient. Fifty-six patients were correctly diagnosed for the presence or absence

TABLE 1. Hemodynamic Data

	Rest	Adenosine
Frequency, per min	66±10	81±16*
Systolic blood pressure, mm Hg	124±21	123±20
Diastolic blood pressure, mm Hg	81±9	79±10
Pulse pressure product, mm Hg×bpm	8180±2423	9979±2924*

Values are mean±SD.
*Significant differences to rest values ($P<0.05$).
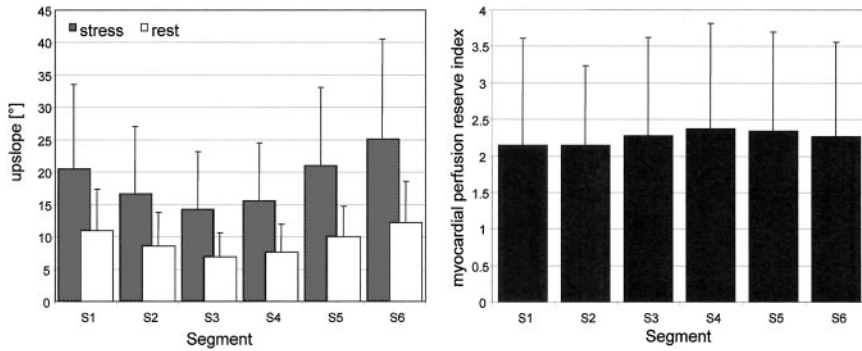
Figure 3. Left, Mean±SD for the upslopes at rest (□) and stress (■) for the different segments (S1 to S6, clockwise) (see Figure 2) for patients without CAD. Note the significantly lower values of the inferior segments (S3, S4) in comparison to the anterior (S1, S6). Right, Mean±SD for the relative alteration of the upslope during adenosine stress in patients without CAD.

of CAD (sensitivity, 74%; specificity, 58%; accuracy, 65.5%) by using all 5 slices, and 62 patients (sensitivity, 70%; specificity, 78%; accuracy, 74%) were diagnosed by using the 3 inner slices. Sensitivity was 79% for 1-vessel disease, 88% for 2-vessel disease, and 77% for 3-vessel disease.

Discussion

MR perfusion measurements allow diagnosing hemodynamically relevant CAD with high diagnostic accuracy. A MPRI can be assessed from alterations of the upslope of the first-pass SI curves after injection of a gadolinium-DTPA bolus at rest and during adenosine stimulation. A diagnostic accuracy of 89% was achieved when segments in the 3 inner slices were below the ischemic threshold using a ROC analysis.

Since the first studies reporting the feasibility of MR to determine myocardial perfusion from the first pass of a contrast agent bolus,[6,7] MR techniques have developed rapidly and now allow the acquisition of several slices each heartbeat with high spatial resolution. Some investigators have recently examined the value of MR perfusion measurements to detect myocardial ischemia in small or selected patient collectives[10,11,18,20–22] and found similar results as reported in the present study. In the present study, no comparison to other techniques assessing myocardial perfusion (SPECT, PET) was performed, but the MR results were compared with those of invasive angiography. Even though

this approach has the disadvantage to assess different pathophysiologies (perfusion versus epicardial stenosis), there are also advantages: in clinical routine, the decision whether or not to proceed to revascularization is most frequently based on invasive angiography, and SPECT and PET imaging have inherent drawbacks, potentially yielding false-positive or false-negative results.

In a recent study,[12] MR perfusion measurements were compared with those from PET and angiography. Diagnostic accuracy in comparison to angiography was slightly lower than in the present study. This may be owing to a different evaluation strategy, taking only the upslope during vasodilation into account and defining different thresholds for different segments. In addition, images were acquired every second heartbeat only, which might introduce an error owing to temporal undersampling.

In our analysis, the calculation of a perfusion reserve index from the upslopes at rest and stress after correction for the upslope in the LV allowed for the best detection of CAD. This approach was superior to the assessment of the upslope at stress alone or the simple division of the upslope at stress through the upslope at rest. The calculation of a perfusion reserve, rather than using the upslopes at stress, is a way to correct for signal differences within the image. Because a surface coil was used for image acquisition, different signal intensities were gained in the anterior and inferior myocardial regions. This may be corrected for by using different thresholds for different myocardial regions, as suggested by Schwitter et al.[12] However, different placement of the surface coil or different patient anatomy may require different thresholds in different patients. Our approach led to similar perfusion reserve indexes for all myocardial regions, independent of the distance from the coil. A similar approach has been recently reported in healthy volunteers and 25 patients with documented CAD, yielding a sensitivity of 69% and specificity of 89% versus values for angiography.[23] These numbers are lower than those reported in the present study, probably because no correction for the LV input function was performed.

A potential alternative approach may be a stress scan followed by scar imaging to detect myocardial infarction. Although this approach may improve visual assessment, it does not allow calculation of perfusion reserve and was not performed in the current study.

Evaluating only the 3 inner slices resulted in a higher accuracy for the detection of significant CAD than did the evaluation of all 5 slices, which may be explained by several
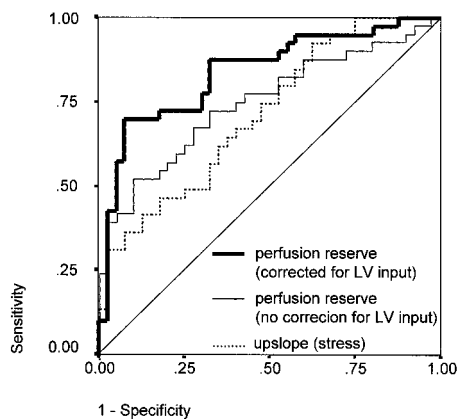
Figure 4. ROC analyses for different parameters. Evaluation of the upslope at stress, calculation of a perfusion reserve index, and correction for LV input function for the ability to differentiate between patients with and without significant CAD.

TABLE 2.   ROC Analyses

Variable	AUC	SE	*P* vs MIN5	CI	Sensitivity	Specificity
MIN5	0.824	0.047	...	0.732–0.917	84	70
MIN3	0.923	0.034	<0.001	0.857–0.989	86	87
SSM5	0.862	0.043	0.086	0.778–0.946	86	80
SSM3	0.933	0.032	<0.001	0.871–0.996	88	90

MIN5 indicates minimal MPRI for 5 slices; MIN3, minimal MPRI for 3 slices; SSM5, second smallest MPRI for 5 slices; SSM3, smallest MPRI for 3 slices; and SE, standard error of area.

reasons. The ischemic area induced by most coronary artery stenoses is usually not limited to a small basal or apical area but extends to the equatorial level. The apical slice is visualized during systole, whereas all other slices are visualized more within diastole, and thus, intracapillary blood volume is lower. In addition, the apical slice has more partial volume effects owing to the conical shape of the LV. The basal slice is frequently influenced by the outflow tract and thus has more regional inhomogeneities. These factors led to more overlap between ischemic and nonischemic segments of the outer 2 slices.

The analysis of the second smallest value is a way to reduce the probability of outliers to influence the results. This approach led to an increase of the AUC, indicating that outliers are an important problem for the imaging approach used. This may be owing to 2 reasons. First, the imaging sequence was optimized to cover a large area of the heart by visualizing 5 slices per heartbeat, which is more than in studies reported previously. This necessitated the use of a long EPI train to accelerate data acquisition, an approach that also induces artifacts. Second, a very small bolus of contrast agent was used to minimize the influence of the rest scan on the stress scan and to allow generating a valid LV input function without signal clipping owing to high contrast-agent concentrations.[24] Such a small bolus, on the other hand, generates only mild visual differences and relatively low signal-to-noise ratios. Accordingly, the results from the visual assessment were disappointing. Better visual results can most probably be achieved by using higher doses of contrast agent and performing the stress study first. This approach, however, will most likely not allow semiquantification.

In future studies, sequences should be applied that either visualize 3 slices only with better spatial resolution or use other approaches (eg, faster gradients, parallel imaging) to allow to overcome the limitations encountered in the present study for visualizing the apical and basal slice.

Patient Population

Only patients with suspected CAD without previous angiography who were referred for a diagnostic coronary angiography were included into the study. Care was taken to also include patients with moderate pretest likelihood of CAD. The results of MR perfusion imaging had no impact on the decision whether or not to proceed to angiography, resulting in a relatively low prevalence of CAD (51%), which allows generalizing the results on an outpatient population. Possible problems of MR perfusion measurements may occur in patients with low ejection fraction or significant valvular disease, as these pathologies influence the compactness of the contrast agent bolus. In addition, patients with diabetes mellitus and arterial hypertension were excluded, as these patients have a high likelihood for perfusion defects, despite normal epicardial coronary arteries. The value of MR perfusion measurement in these patients remains to be evaluated in a different study and may show a lower accuracy.

For measurements of flow reserve, it is essential to induce maximal vasodilation. We made every effort to achieve this goal by using a potent vasodilator and excluding patients who did not adhere to the patient instructions and had taken medications or consumed substances reducing the effects of adenosine.

Limitations

Generating the SI time curves for calculation of the upslope from the MR images is time consuming. Even though care was taken to visualize the first pass of the contrast agent bolus during breath-holding, manual segmentation of the myocardium and correction for diaphragmatic motion had to be
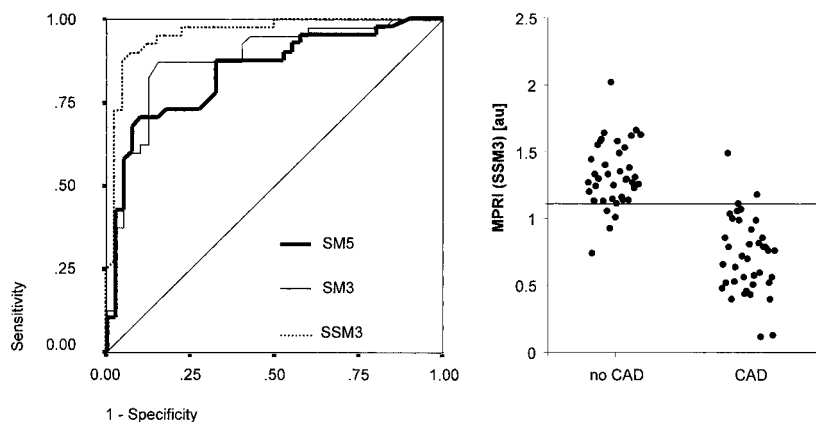
Figure 5. ROC analyses for the ability of different parameters do detect significant CAD: assessment of the smallest value of 5 slices (SM5), of the 3 inner slices only (SM3), and the second smallest value of 6 segments in 3 slices (SSM3).

performed in 84% of the patients. Such a manual segmentation is tedious, allows user influence, and reduces the use of this technique for clinical routine measurements.

A drawback of the contrast agents used for MR perfusion measurements at the current time is the rapid diffusion into the extracellular space. This may also explain the smaller increase of perfusion reserve (factor, ≈1.5) in comparison to the literature, in which an increase of factor 4 to 5 was reported. In the future, intravascular contrast agents, which are currently under development, may be a step toward quantitative analysis.[25] In addition, the relation between the perfusion reserve indices calculated in this study and the true alterations of flow needs to be determined.

Diagnostic accuracy may be further improved by a separate analysis of endocardial and epicardial segments because a reduction of endocardial perfusion is the most sensitive parameter for a reduction of blood flow.[26] In a recent study, such an analysis of subendocardial data has been shown to allow the detection of patients with syndrome X.[27] In the present study, the inner 10% and outer 30% of the myocardium were excluded from the analysis to avoid influence from the blood pool and to generate a stronger weighting of the subendocardium. However, spatial resolution did not allow for a differentiation into endocardium and epicardium.

The use of a retrospective analysis to calculate the ROC curves may lead to an optimistic estimate of the accuracy of the technique. However, ongoing studies in our institution do not show significant differences when prospectively applying the reported cutoff value.

Currently, a general limitation to MR perfusion imaging is the use of different technical approaches by different vendors and different centers, which inhibit comparison of results and limit multicenter trials.

Conclusions

MR can be used for the assessment of myocardial perfusion reserve and allows an accurate detection of significant CAD. It may be used to screen patients with suspected CAD and avoid cardiac catheterization in patients with negative MR. For an adequate accuracy, however, semiquantification is required. Before MR perfusion measurements can be routinely used in clinical practice, further improvement and automatization of quantification algorithms is required.

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