Noninvasive Detection of Myocardial Ischemia From Perfusion Reserve Based on Cardiovascular Magnetic Resonance

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Background—Myocardial perfusion reserve can be noninvasively assessed with cardiovascular MR. In this study, the diagnostic accuracy of this technique for the detection of significant coronary artery stenosis was evaluated.

Methods and Results—In 15 patients with single-vessel coronary artery disease and 5 patients without significant coronary artery disease, the signal intensity–time curves of the first pass of a gadolinium-DTPA bolus injected through a central vein catheter were evaluated before and after dipyridamole infusion to validate the technique. A linear fit was used to determine the upslope, and a cutoff value for the differentiation between the myocardium supplied by stenotic and nonstenotic coronary arteries was defined. The diagnostic accuracy was then examined prospectively in 34 patients with coronary artery disease and was compared with coronary angiography. A significant difference in myocardial perfusion reserve between ischemic and normal myocardial segments (1.08\(\pm\)0.23 and 2.33\(\pm\)0.41; \(P<0.001\)) was found that resulted in a cutoff value of 1.5 (mean minus 2 SD of normal segments). In the prospective analysis, sensitivity, specificity, and diagnostic accuracy for the detection of coronary artery stenosis (\(\geq 75\%\)) were 90\%, 83\%, and 87\%, respectively. Interobserver and intraobserver variabilities for the linear fit were low (\(r=0.96\) and 0.99).

Conclusions—MR first-pass perfusion measurements yielded a high diagnostic accuracy for the detection of coronary artery disease. Myocardial perfusion reserve can be easily and reproducibly determined by a linear fit of the upslope of the signal intensity–time curves. (Circulation. 2000;101:1379-1383.)

Key Words: magnetic resonance imaging perfusion coronary disease

In principle, the reduction of myocardial perfusion is a sensitive indicator for myocardial ischemia because myocardial blood flow is directly correlated to myocardial oxygen supply. Such measurements are superior to coronary angiography for the detection of myocardial ischemia because the functional relevance rather than the morphological appearance of a stenosis is assessed. Furthermore, the analysis of perfusion may permit the estimation of collateralization. Clinical routine measurements of myocardial perfusion are performed with single-photon emission computed tomography (SPECT) or with positron emission tomography (PET). Sensitivity and specificity for the detection of significant coronary artery disease with SPECT or PET range from 83\% to 95\% and 53\% to 95\%\(^{-1,4}\). However, these techniques have a rather low spatial resolution and are not suitable for the detection of subendocardial perfusion defects, which by themselves are extremely sensitive to the occurrence of myocardial ischemia.\(^3\) In addition, the requirement of radioactive markers prohibits the use of these techniques for follow-up examinations, and SPECT imaging is limited by attenuation artifacts.\(^1\) PET has a higher sensitivity and specificity than SPECT\(^1,4\) but is burdened by its limited availability.

MR tomography allows an analysis of myocardial perfusion by the use of the first pass of a T1-shortening contrast agent bolus.\(^6\,\,\,7\) Several studies have shown in principle that an analysis of myocardial perfusion with MR is possible and may even permit a quantitative assessment of myocardial blood flow.\(^1,16\) The concept of myocardial perfusion measurements from the first pass of a contrast agent has been extensively validated in experimental animals.\(^7,8,13,14,17\) Under optimal conditions, such as injection of the contrast agent into the left atrium or the use of an intravascular contrast agent, a close correlation to microsphere or coronary flow measurements was found.\(^1,14\) In healthy control subjects and in small numbers of patients, the concept also has been shown to be
useful. To reduce the error introduced by diffusion of the extracellular tracer used in humans and to improve sensitivity, the determination of perfusion reserve was suggested and has been shown to be beneficial. However, to date, no easy and reproducible way that enables a clear identification of ischemic myocardial segments has been reported.

Thus, the aim of this study was to define a threshold value for ischemic regions by myocardial perfusion reserve. This was measured by cardiovascular MR to differentiate the myocardium supplied by a stenotic coronary artery from the myocardium supplied by a nonstenotic coronary artery. Also, we aimed to determine prospectively the diagnostic accuracy of this cutoff value for the detection of significant coronary artery stenosis in patients with suspected coronary artery disease.

Results
Dipyridamole stress MR perfusion imaging was successfully performed in all patients of group A and in 34 of the 40 (85%) patients of group B (see Methods). In group B, 3 (7.5%) patients were excluded because of claustrophobia. In 3 (7.5%) patients, ECG triggering was insufficient because of frequent premature ventricular complexes (n=2) or atrial fibrillation, which developed at the beginning of the MR examination (n=1). Neither the dipyridamole infusion nor the placement of the central venous catheter caused any serious side effects requiring active treatment; however, the usual side effects of dipyridamole were observed. In all patients, it was possible to perform the second MR perfusion measurement during dipyridamole infusion. In 19 (3%) of the 648 signal intensity (SI) curves of all evaluated myocardial segments, curve fitting was not possible because of artifacts or noise.

Validation
Interobserver and intraobserver variabilities for the determination of the upslope yielded excellent correlations (r=0.96 and 0.99, respectively). Relative differences were 8.3±9.9% and 3.9±4.7%, respectively (Figure 1).

In group A, no significant difference between myocardial segments supplied by stenotic coronary arteries (median area stenosis 94%) and contralateral myocardial segments supplied by normal coronary arteries was found at rest (1.6±0.7 vs 1.6±0.8). After dipyridamole infusion there was a significant difference between the ischemic and the nonischemic myocardial segments (2.1±0.9 vs 2.9±1.0; P<0.05) (Figure 2). However, because of an overlap of the 2 groups at rest and during dipyridamole stimulation, no cutoff could be defined from these values.

Myocardial perfusion reserve after dipyridamole infusion resulted in highly significant differences between myocardial segments supplied by stenotic coronary arteries (1.08±0.23) and nonstenotic coronary arteries (2.34±0.41; P<0.001) (Figure 3). A cutoff value of ≤1.5 was defined.

In group B, 60 coronary artery stenoses were found by angiography (left anterior descending [LAD] 20, left circumflex [LCX] 21, right coronary artery [RCA] 19, median area stenosis 89%). Thirteen (38%) patients had single-vessel disease and 16 (47%) had double-vessel disease. In 5 (15%) patients, triple-vessel disease was found despite previously expected double-vessel disease.

In this group, myocardial perfusion reserve was 1.16±0.29 in the ischemic segments and 2.17±0.62 in the nonischemic segments (P<0.001). Fifty-four of the 60 segments supplied by stenotic coronary arteries and 35 of the 42 segments supplied by nonstenotic coronary arteries were correctly classified by the use of the defined myocardial perfusion reserve cutoff value of 1.5,
resulting in a sensitivity of 90%, a specificity of 83%, and a diagnostic accuracy of 87% (Table 1).

**Discussion**

MR perfusion imaging can be used to detect coronary artery stenosis with high diagnostic accuracy. In this study, a sensitivity of 90% and a specificity of 83% for the detection of significant coronary artery stenosis was reached in 34 patients by the use of a previously defined threshold for ischemic myocardial regions. A linear fit of the upslope of the first-pass of a gadolinium-DTPA bolus before and after dipyridamole infusion enabled an easy and reproducible determination of the myocardial perfusion reserve.

In this study, a new and easy approach for the determination of myocardial perfusion reserve was used. In contrast to previous studies, which applied a γ-variate fit,13,16,18,19 a linear fit of the upslope of the SI-time curves of the first-pass bolus of a contrast bolus injection was performed. The concept of a γ-variate fit was used for the quantification of myocardial perfusion in PET2,20,21 and may be applied to intravascular contrast agents and a well-defined input function. MR studies have produced very good results in animal models.13,14,17 However, several limitations appertain in patients. Currently available contrast agents rapidly leak out of the vascular bed and diffuse into the extracellular space, such as the myocardium. Thus, the resultant signal intensity (SI)-time curve is a combination of perfusion and diffusion, both of which are influenced by blood flow.22,23 The early part of the SI-time curve is mainly influenced by perfusion and to a lesser extent by diffusion, and the latter parts are increasingly influenced by diffusion. Another problem of the γ-variate fit is the need for ≥6 data points during the washout (downslope) of the contrast agent to allow for reliable calculation.18 To guarantee such a downslope, a small and compact contrast agent bolus must pass through the myocardium. In the experimental animal, this can be achieved by left atrial injection. However, in patients this may not be possible, particularly as ischemic myocardial segments show a slower passage of the contrast agent,24 which results in a stronger influence of diffusion and a less pronounced or even nonexistent downslope.

To circumvent these problems with a γ-variate function and to minimize the influence of diffusion on the results, a linear fit of the upslope of the SI-time curves rather than mean transit time, maximal signal intensity, downslope, or time to maximal signal intensity was used for the present analysis. The linear fit was highly reproducible, with excellent interobserver and intraobserver variabilities, and could be performed in 97% of all evaluated myocardial segments.

To achieve a compact bolus and good myocardial SI-time curves, only a small amount of contrast agent was used and injected through a central vein catheter. Patients with significant valvular disease or low ventricular ejection fraction were excluded from the study to improve bolus arrival in the myocardium. The placement of a central venous catheter is not practical for routine diagnosis. However, because the upslope of the SI curves was used to calculate myocardial perfusion reserve, a peripheral gadolinium-DTPA injection should be feasible. Our first observations with the use of peripheral injection underline this expectation.

The myocardial perfusion reserve for segments supplied by stenotic coronary arteries and segments supplied by nonstenotic coronary arteries found in this study are in good agreement with values reported previously with PET2,20,24–26 or Doppler coronary flow reserve measurements when segments remote to the territory of a coronary artery stenosis in patients with single-vessel disease were studied.27,28 The resultant cutoff value of 1.5 for myocardial perfusion reserve is less than the lower normal value found in the literature measured by different techniques in healthy control subjects.20,21,24,29 This can be explained by the reduced vasodilatory response and thus reduced myocardial perfusion reserve in segments supplied by nonstenotic coronary arteries in patients with coronary artery disease when compared with healthy control subjects. The goal of the study was to differentiate the segments supplied by stenotic coronary arteries from those supplied by nonstenotic coronary arteries. This was successfully achieved by the cutoff value used in this study. Another reason for the lower cutoff value, when compared with the literature, was the use of dipyridamole for vasodilation, which is less potent, shows a more variable response than adenosine,30 and might result in submaximal vasodilation. In general, there is a wide range of myocardial perfusion reserve values in the literature that can be attributed to methodological reasons and to the interindividual physiological variation of myocardial perfusion reserve that is seen even in healthy subjects, which is mainly the result of variations of myocardial perfusion at rest. This is influenced by the resistance of the small vessels, collateralization, hemodynamic parameters, perfusion pressure, intramyocard-

**TABLE 1. Diagnostic Accuracy of MR Perfusion Measurements**

<table>
<thead>
<tr>
<th>CAD+</th>
<th>CAD-</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPR+</td>
<td>54</td>
</tr>
<tr>
<td>MPR-</td>
<td>6</td>
</tr>
</tbody>
</table>

Sensitivity = 90% Specificity = 83%

MPR+ indicates myocardial perfusion reserve ≤1.5; MPR−, myocardial perfusion reserve >1.5; CAD+, coronary artery stenosis ≥75%; and CAD−, coronary artery stenosis <75%.
dial pressure, the severity of the coronary artery stenosis, and age.29,31

In this study, coronary angiography was used as the reference method for the detection of coronary artery stenosis. Because coronary angiography detects luminal morphology rather than the functional significance of a stenosis, “false-positive” MR results might in fact be “false-negative” angiograms. Three of the 7 segments that had a “false-positive” reduction of myocardial perfusion reserve showed ≥1 stenosis <75% area reduction of the corresponding coronary artery on quantitative angiography. Furthermore, 2 false-positive segments were found in 1 patient with diffuse atherosclerosis of the nonstenotic coronary arteries.

Limitations

The major limitation of this study was the use of a single-slice technique. Thus, the myocardium was only partially visualized and significant myocardial ischemia might have been missed. However, only patients with ≥75% stenosis of a major coronary artery were regarded as having significant coronary artery disease. Thus, rather large ischemic areas are to be expected, which explains the high sensitivity of the present study. In future studies, the value of multislice techniques32 must be assessed.

A possible limitation is the combined use of nonischemic segments from patients with single-vessel disease and patients without significant coronary artery disease for the definition of the ischemic threshold. However, myocardial perfusion reserve in nonischemic segments of patients with single-vessel disease and patients without significant stenosis did not differ significantly, probably a result of the fact that the latter also had coronary atherosclerosis. In addition, these patients often show a high coronary risk profile and thus must be differentiated from patients without coronary artery disease.

In the current study, we have shown that MR first-pass perfusion measurements yield a high diagnostic accuracy for the detection of coronary artery disease. Myocardial perfusion reserve can be easily and reproducibly determined from the upslope of the SI-time curves.

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References


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