Validation of Magnetic Resonance Myocardial Perfusion Imaging With Fractional Flow Reserve for the Detection of Significant Coronary Heart Disease

Stuart Watkins, BSc, MBChB, MRCP, MD; Ross McGeoch, MBChB, MRCP; Jonathan Lyne, BSc, MB Chir, MRCP; Tracey Steedman, BSc; Richard Good, BA, MBBS, MRCP; Mairi-Jean McLaughlin, MBChB, MRCGP; Tony Cunningham; Vladimir Bezlyak, PhD; Ian Ford, BSc, PhD; Henry J. Dargie, MBChB, FRCP; Keith G. Oldroyd, MBChB, MD, FRCP

Background—Magnetic resonance myocardial perfusion imaging (MRMPI) has a number of advantages over the other noninvasive tests used to detect reversible myocardial ischemia. The majority of previous studies have generally used quantitative coronary angiography as the gold standard to assess the accuracy of MRMPI; however, only an approximate relationship exists between stenosis severity and functional significance. Pressure wire–derived fractional flow reserve (FFR) values \( \leq 0.75 \) correlate closely with objective evidence of reversible ischemia. Accordingly, we have compared MRMPI with FFR.

Methods and Results—One hundred three patients referred for investigation of suspected angina underwent MRMPI with a 1.5-T scanner. The stress agent was intravenous adenosine \( 140 \mu g \cdot kg^{-1} \cdot min^{-1} \), and the first-pass bolus contained 0.1 mmol/kg gadolinium. In the following week, coronary angiography with pressure wire studies was performed. FFR was recorded in all patent major epicardial coronary arteries, with a value \( < 0.75 \) denoting significant stenosis. MRMPI scans, analyzed by 2 blinded observers, identified perfusion defects in 121 of 300 coronary artery segments (40%), of which 110 had an FFR \( \leq 0.75 \). We also found that 168 of 179 normally perfused segments had an FFR \( \geq 0.75 \). The sensitivity and specificity of MRMPI for the detection of functionally significant coronary heart disease were 91% and 94%, respectively, with positive and negative predictive values of 91% and 94%.

Conclusion—MRMPI can detect functionally significant coronary heart disease with excellent sensitivity, specificity, and positive and negative predictive values compared with FFR. (Circulation. 2009;120:2207-2213.)

Key Words: angiography • coronary disease • fractional flow reserve, myocardial • imaging • magnetic resonance imaging • perfusion

Magnetic resonance myocardial perfusion imaging (MRMPI) with pharmacological stress is a relatively new method for the noninvasive detection of reversible myocardial ischemia. A number of studies have compared it with more established techniques such as single-photon emission computerized tomography (SPECT),\(^1\)-\(^3\) positron emission tomography,\(^4\),\(^5\) and invasive coronary angiography (CA).\(^1\)-\(^15\) It has a number of advantages over the other noninvasive techniques, including high spatial and temporal resolution, no exposure to ionizing radiation, no attenuation or scatter artifacts, and no image orientation constraints. Conventional exercise testing has a sensitivity of 67% and specificity of 72% for correctly identifying patients with significant coronary heart disease (CHD) who have not had a previous myocardial infarction.\(^16\) In a pooled analysis of 79 studies, SPECT demonstrated a mean sensitivity of 86% and specificity of 74%, varying according to which radioisotope was used.\(^17\) The combination of dobutamine stress and myocardial contrast echocardiography provides a sensitivity of 91% and specificity of 70%, which is comparable to SPECT.\(^18\) Multislice CT CA is now challenging conventional diagnostic CA with a sensitivity and specificity of 92% in a recent pooled analysis of studies using 64-slice CT.\(^19\) However, neither conventional invasive or CT coronary angiography can accurately predict the functional significance of coronary stenosis.\(^20,21\) The sensitivity and specificity of MRMPI for the detection of significant coronary disease were recently evaluated in a meta-analysis of 1516 patients from 24 studies and found to be 91% (95% confidence interval, 88 to 94) and 81% (95% confidence interval, 77 to 85), respectively.\(^22\) The majority of
these studies used quantitative CA (QCA) or visual assessment of the degree of stenosis as the gold standard test.

Clinical Perspective on p 2213

We undertook the present study to determine the sensitivity, specificity, and positive and negative predictive values of MRMPI compared with an invasive assessment of functional significance, namely pressure wire–derived fractional flow reserve (FFR). FFR can reliably identify flow-limiting stenosis in an epicardial coronary artery and has previously been validated against a variety of noninvasive techniques, including positron emission tomography. It is independent of heart rate, blood pressure, and left ventricular contractility and takes into account the contribution of collateral flow to myocardial perfusion. An FFR value <0.75 confirms that the stenosis interrogated has the potential to induce reversible myocardial ischemia.

Methods

Study Population

We recruited 103 patients between November 2004 and April 2006. All patients had been referred to a single cardiologist for investigation of suspected angina; after assessment CA was thought to be indicated. Exclusion criteria included myocardial infarction with evidence of ongoing myocardial ischemia in the preceding 48 hours, previous coronary artery bypass grafting, pregnancy, atrial fibrillation, and standard contraindications to MR imaging (MRI), adenosine, and gadolinium. Patients were scheduled for an MRMPI scan in the week before CA. At the time of CA, FFR was measured in all major patent epicardial coronary arteries. Before the MRMPI scan and CA, patients were asked to abstain from methylxanthine-containing substances for 24 hours. The study protocol was approved by the local research ethics committee.

MRI Protocol

Before scanning, two 18-gauge venous cannula were inserted. ECG and noninvasive blood pressure monitoring was established. A Siemens Sonata 1.5-T scanner (Erlangen, Germany) with a 6-channel anterior chest coil and spinal coils within the gantry table was used. Long- and short-axis cine images were obtained with a retrospectively gated fast imaging with steady precession sequence. Maximal hyperemia was achieved with intravenous adenosine (140 μg · kg⁻¹ · min⁻¹) through an 18-gauge cannula in the left antecubital fossa. At steady-state hyperemia, the FFR was recorded on the RadAnalyzer Xpress (Radi Medical Systems). This is calculated by dividing the mean distal coronary pressure measured with the pressure wire by the mean aortic pressure measured through the guide catheter. This procedure was repeated for all 3 major epicardial coronary arteries. Arteries were recorded as having significant flow-limiting disease if they had an FFR value <0.75, if they were occluded or subtotally occluded, or if there was angiographically severe left main stem disease.

QCA Studies

QCA was performed with GE automated edge detection software, which calibrates using the coronary guide catheter as its reference diameter (Centricity Cardiology CA1000, GE Healthcare, Dornstadt, Germany). Two observers were blinded to patient details, pressure wire results, MRMPI findings, and patient outcome. Both observers marked the region of interest within a coronary artery that they thought was the most severe region of coronary arterial disease. The software then calibrated the minimal luminal diameter, reference vessel diameter at stenosis, lesion length, and ideal vessel diameter at stenosis. From these results, the percent diameter stenosis (DS) was calculated. The 2 observers performed this calculation for at least 3 coronary arteries per patient, depending on circulatory dominance and number of occluded arteries.

Power Calculation and Statistical Analysis

To maximize information, significant CHD was assessed on an artery rather than a patient basis. Because we assessed 3 arteries per patient, there was a possibility of a loss of information associated with any correlation in the correctness of the assessment of arteries in the same patient. The study aimed to recruit sufficient subjects to generate 90 normal arteries and at least 150 abnormal arteries. Assuming an underlying sensitivity and specificity of 80% and no loss of information resulting from correlation of results from the same subjects, this would have allowed sensitivity to be estimated with an SE of 3.3% and specificity with an SE of 4.2%. Even with an information loss equivalent to a 33% reduction (one third of arteries) in the same subjects, this would have allowed sensitivity to be estimated with an SE of 4.0% and specificity with an SE of 5.2%.

Statistical analysis was performed with R version 2.7. Sensitivity, specificity, and positive and negative predictive values were calculated with 95% confidence intervals, taking into account both within- and between-subject components of variance. Confidence intervals were calculated using the methods of Donner and Klar. Results are presented in terms of mean and SD. The Cohen κ statistic was used to assess agreement between the 2 observers.

Results

One hundred sixty-six patients were screened to participate in the study. Of these 166, 11 (7%) were excluded because of...
asthma/chronic obstructive pulmonary disease with reversibility, 1 (0.6%) had prolonged first-degree atrioventricular block, 8 (5%) had atrial fibrillation, 12 (7%) had previous coronary artery bypass grafting performed, and 20 (12%) refused to take part (12 had claustrophobia and 8 gave no reason). Five patients (3%) agreed to take part in the study but withdrew on arrival for their MRI scan (3 felt claustrophobic, 1 suffered anxiety while reading the consent form, and 1 had a new diagnosis of asthma and was on steroids). One hundred three patients were finally recruited into the study; however, the data from 2 patients (2%) were excluded because of delays between the MRMPI scan and the CA. The demographics of the final 101 patients are summarized in Table 1. Nine patients (9%) had Canadian Cardiovascular Society angina grade 1, 43 (43%) had grade 2, 24 (23%) had grade 3, and 25 (25%) had severe grade 4 angina. Two patients with severe renal impairment were included in this study before the concerns relating to the use of gadolinium-containing contrast agents in this group of patients arose.

**MRMPI Scans**

The technical quality of all MRMPI scans was thought to be adequate for visual diagnostic purposes (Figure 1). One hundred twenty-two perfusion defects were reported, of which 49 (40.2%) were in the left anterior descending coronary artery territory, 32 (26.2%) in the left circumflex/obtuse marginal artery territory, and 41 (33.6%) in the right coronary artery territory. Agreement between observers was assessed on the identification of abnormal perfusion per patient, which produced a κ of 0.97, indicating excellent agreement. Agreement was also calculated for the extent of CHD (normal or 1-, 2-, or 3-vessel disease) and was 0.76, indicating substantial agreement. Both observers agreed on the pattern of CHD in 84 scans (83.2%), and the third observer adjudicated on the remaining 17 (16.8%).

**QCA Results**

QCA was performed on 334 coronary arteries. At least 3 arteries were studied in all but 1 patient, in whom we were unable to identify the left circumflex coronary artery. We chose a 50% DS cutoff for stenoses of the left main stem and a 70% DS cutoff for the other epicardial coronary arteries as indicating significant disease. No significant disease was found in 42 patients (42%), 1-vessel disease was seen in 43 patients (42%), 2-vessel disease was found in 15 patients (15%), and 3-vessel disease was noted in 1 patient (1%). The overall mean DS for all stenoses was 44.3% (SD, 32.0%), and mean lesion length was 12.3 mm (SD, 8.9 mm). The spread of severity of disease by DS is shown in Figure 2.

**FFR Results**

FFR results were obtained from 260 coronary arteries. Of the 101 patients, the FFR was obtained in 4 arteries per patient in 5 patients (5%), 3 arteries in 63 patients (62%), 2 arteries in 22 patients (22%), and 1 artery in 7 patients (7%); no FFR values were obtained in 4 patients (4%). The median FFR was 0.88 (mean, 0.81; SD, 0.19; quartile 1 to 3, 0.71 to 0.95). As shown in Table 2, 121 arteries (40%) had an FFR <0.75 (including occluded and suboccluded arteries). There were 36 completely occluded arteries and 17 subtotally occluded arteries with long areas of severe complex disease that were considered positive for the purpose of the comparison with MRMPI but in which FFR could not be measured. Included in this group were 3 patients with severe left main stem disease...
in whom FFR was not measured to minimize patient risk. Four arteries without any identifiable plaque had no FFR measurements because of difficulties with selective cannulation of the coronary ostia. Tables 2 and 3 also presents the data using an FFR \( \leq 0.8 \) cutoff, which has recently been used in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial.\(^{29}\) The range of FFR results is presented in Figure 2.

**MRMPI Versus FFR**

In this analysis, only the 3 largest epicardial arteries per patient were considered. Table 2 highlights these data using the conventional FFR cutoff of \(<0.75\) and the more conservative FFR cutoff of \(\leq 0.8\). One hundred ten coronary territories demonstrated a perfusion defect with FFR \(<0.75\) (true positive). There were 11 territories with a perfusion defect and FFR \(\geq 0.75\) (false positive). When the higher FFR cutoff of 0.8 was used, the number of false-positive results fell to 3. One hundred sixty-eight territories showed no perfusion defect and an FFR \(\leq 0.75\) (true negative). In 11 territories, there was no perfusion defect, but the relevant artery had an FFR \(<0.75\) (false negative). There was a large increase in false-negative results (11 to 26) when the 0.8 cutoff was used. The sensitivity, specificity, and positive and negative predictive values of MRMPI for the detection of functionally significant CHD are presented in Table 3. Patient-level data are presented in Table 4.

**MRMPI Versus QCA**

We used a 70% DS cutoff value as in multiple previous studies.\(^{3,9,12,14,15}\) There were 72 territories with perfusion defects and a DS in the corresponding artery \(\geq 70\%\). Fifty territories had abnormal perfusion and a DS \(<70\%\). There were 178 territories with no perfusion defect and a DS \(<70\%\); however, only 2 territories had no perfusion defect with a DS \(\geq 70\%\). These data are summarized in Table 2 and confirm the previous finding that percent DS is a suboptimal indicator of physiologically significant disease. The majority (39 of 68) of nonoccluded coronary arteries with an FFR \(<0.75\) had a percent DS \(<70\%\).

**Per-Patient Analysis of MRMPI for the Detection of Significant Coronary Artery Disease**

We assessed the diagnostic accuracy of MRMPI on a per-patient basis using an FFR \(<0.75\) as the cutoff for the
Table 2. MRMPI Compared With FFR at 2 Cutoff Values (0.75 and 0.8) and Degree of Stenosis by QCA

<table>
<thead>
<tr>
<th></th>
<th>FFR &lt;0.75</th>
<th>FFR ≥0.75</th>
<th>Total</th>
<th>FFR ≤0.8</th>
<th>FFR &gt;0.8</th>
<th>Total</th>
<th>DS ≥70%</th>
<th>DS &lt;70%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive MRMPI</td>
<td>110</td>
<td>11</td>
<td>121</td>
<td>118</td>
<td>3</td>
<td>121</td>
<td>72</td>
<td>50</td>
<td>122</td>
</tr>
<tr>
<td>Negative MRMPI</td>
<td>11</td>
<td>168</td>
<td>179</td>
<td>26</td>
<td>153</td>
<td>179</td>
<td>2</td>
<td>178</td>
<td>180</td>
</tr>
<tr>
<td>Total</td>
<td>121</td>
<td>179</td>
<td>300</td>
<td>144</td>
<td>300</td>
<td>74</td>
<td>228</td>
<td>302</td>
<td></td>
</tr>
</tbody>
</table>

Results are expressed per coronary artery territory.

diagnosis of physiologically significant coronary artery disease. Of the 76 patients with a perfusion defect on their MRMPI scan, 74 (97%) had an FFR <0.75 in at least 1 coronary artery. There were 2 false-positive scans with FFR ≥0.75 in all coronaries. Of the 25 patients with no perfusion defects on MRMPI, 21 (84%) had FFR values ≥0.75 in all coronaries, and there were 4 false-negative patients. Therefore, in 101 patients, there was a false-positive rate per patient of 2% and a false-negative rate of 4%. On a per-patient analysis, MRMPI has a sensitivity, specificity, and positive and negative predictive values of 95%, 91%, 97%, and 84%, respectively.

Discussion

Multiple studies have assessed the ability of MRMPI to detect reversible myocardial ischemia with QCA or visual estimation of stenosis severity as the gold standard. Other studies used nuclear perfusion methods such as SPECT and positron emission tomography. We have compared MRMPI to the invasive gold standard of FFR. The most important finding in this study is the excellent sensitivity, specificity, and positive and negative predictive values of MRMPI compared with FFR using both per–coronary territory and per-patient analyses. Our results were also excellent compared with prior studies using MRMPI and suggest that the value of MRMPI may have been underestimated. Two previous studies have compared MRMPI with FFR. In the first study, however, patient numbers were small (n = 43), and FFR was measured in only 33% of arteries. Analysis of the MRMPI scans in this study was performed with a semiquantitative measure of upslope-derived myocardial perfusion reserve index with a cutoff value of 1.5 compared with the purely visual analysis performed in the present study. This small study also noted an improvement compared with the previous sensitivities and specificities, achieving values of 88% and 90%. Costa et al also published a small study in 2007 that prospectively compared quantitative myocardial perfusion reserve with FFR. This study enrolled 37 consecutive patients but compared FFR and myocardial perfusion reserve in only 44 coronary segments. The sensitivity of MRMPI was 92.9% when a myocardial perfusion reserve cutoff of 2.04 was used, which is in keeping with the findings of Rieber et al and our own study. The specificity, however, was only 56.7%, which is far lower than that measured in both the Rieber et al study and the present study. Costa et al believe that this may have been secondary to the high prevalence of hypertension, diabetes mellitus, and hypercholesterolemia causing microcirculatory dysfunction.

We highlight the well-known limitations of QCA in assessing the functional significance of coronary artery disease. Figure 2 shows that a large number of arteries have physiologically significant disease (FFR <0.75); however, the DS by QCA was <70%. The length of disease within these arteries may have a larger role in the severity of flow reduction. The sensitivity and negative predictive value with QCA are excellent, but the specificity and positive predictive value are poor.

In this study, we intentionally did not include a semiquantitative analysis of myocardial perfusion reserve. The currently available commercial software is expensive, and analysis remains time consuming. The majority of centers continue to use visual analysis for the assessment of clinical myocardial perfusion scans. Comparing the rest and stress scans together on a viewing platform allows the recognition of perfusion defects and discrimination from artifacts. The argument remains that patients with 3-vessel disease and balanced hypoperfusion would be missed by this method. Nine of our patients had proven 3-vessel disease. As shown in Table 4, visual analysis correctly diagnosed 3-vessel disease in 5 patients and 2-vessel disease in 3 patients, and 1 patient was thought to be normal. On a per-patient basis, the 2 observers had excellent agreement, and by individual coronary perfusion territories, agreement was substantial. Recognizing the limitation of visual analysis, we believe that quantification of myocardial perfusion reserve using MRMPI is worthy of further study.

Table 3. Diagnostic Ability of MRMPI

<table>
<thead>
<tr>
<th></th>
<th>FFR &lt;0.75</th>
<th>FFR ≥0.75</th>
<th>DS ≥70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, %</td>
<td>90.9</td>
<td>81.9</td>
<td>97.3</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>93.9</td>
<td>98.1</td>
<td>78.1</td>
</tr>
<tr>
<td>PPV, %</td>
<td>90.9</td>
<td>97.5</td>
<td>59.0</td>
</tr>
<tr>
<td>NPV, %</td>
<td>93.9</td>
<td>85.5</td>
<td>98.9</td>
</tr>
</tbody>
</table>

The sensitivity, specificity, and positive and negative predictive values of MRMPI for the detection of significant coronary artery disease using the various methods are also presented. Values in parentheses are 95% confidence intervals.

Table 4. Number of Coronary Arterial Territories With Functionally Significant Disease (FFR <0.75) Compared With the Number of Territories Demonstrating Hypoperfusion on the MRMPI Scan Per Patient

<table>
<thead>
<tr>
<th>Arterial Territories per Patient With Perfusion Defect, n</th>
<th>Arteries Per Patient With FFR &lt;0.75, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>21 3 0 1 25</td>
</tr>
<tr>
<td>1</td>
<td>2 34 2 0 38</td>
</tr>
<tr>
<td>2</td>
<td>0 3 19 3 25</td>
</tr>
<tr>
<td>3</td>
<td>0 1 4 5 10</td>
</tr>
<tr>
<td>Total</td>
<td>23 41 25 9 98</td>
</tr>
</tbody>
</table>

The data from 3 patients with results for only 2 arterial territories were excluded from this table.
nition of artifacts is critical for accurate analysis of scans because artifacts with rapid image acquisition usually manifest themselves as dark subendocardial rims and may mimic perfusion defects.32

FFR has a number of advantages in evaluating a noninvasive test for the detection of significant coronary artery disease. It can reliably identify flow-limiting stenosis and has been validated against what is probably the best current gold standard, positron emission tomography. Most of the published studies describing the predictive accuracy of FFR measurements have been done in the setting of stable angina, but the technique has been validated in the setting of unstable angina and recent (>5 days) myocardial infarction.33–35 The majority of our patients had stable angina, but 25% were unstable and 23% had a previous myocardial infarction. There is unpredictable variability in all biological measurements, so any cutoff value cannot be expected to have absolute precision. Increasing the FFR cutoff to the upper limit of the “gray zone” (0.8) led to a reduction in the number of false positives with an increase in false negatives; however, the diagnostic performance remained very good, with sensitivity, specificity, and positive and negative predictive values of 82%, 98%, 98%, and 86%.

The present study has some limitations. FFR was measured in only 81% of major epicardial coronary arteries. However, collating with occluded arteries provides us with 92% of the data points. Despite the excellent results of MRMPI for the accurate detection of physiologically significant coronary artery disease, there are some important limitations. Claustrophobia remains problematic; however, new open scanners are available. Adenosine is contraindicated in asthmatics and patients with high-degree atioventricular block, but A2a-specific agonists are now available, and exercise within the magnetic field is possible with specially adapted nonferromagnetic exercise bicycles.36–38 Another limitation is that we cannot be certain that we have correctly assigned all myocardial segments to the appropriate coronary artery; for example, in patients with codominant circulation, it can be difficult to know which vessel provides the majority of the blood supply to the inferior wall.

Conclusion

This is one of the largest studies performed to assess the clinical utility of MRMPI in the diagnosis of significant coronary artery disease. MRMPI can detect functionally significant CHD with excellent sensitivity, specificity, and positive and negative predictive values compared with FFR.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

The diagnosis of myocardial ischemia with magnetic resonance myocardial perfusion imaging (MRMPI) has a number of potential advantages over other available noninvasive tests. The majority of previous studies have assessed the clinical utility of MRMPI by comparing it with quantitative coronary angiography, which at intermediate degrees of stenosis has been shown to be a poor indicator of the functional severity of coronary heart disease. The present study in 101 patients with suspected angina is the largest study to assess the accuracy of MRMPI compared with an invasive physiological measurement of the significance of coronary artery disease, namely fractional flow reserve. Fractional flow reserve values of <0.75 have been shown to indicate functionally significant coronary heart disease. Visual analysis of MRMPI scans was compared with fractional flow reserve and quantitative coronary angiography. We have shown that with fractional flow reserve as the gold standard, MRMPI can detect functionally significant coronary heart disease with a sensitivity and specificity of 91% and 94% and positive and negative predictive values of 91% and 94%, respectively. Comparing MRMPI with quantitative coronary angiography led to a reduction in specificity and positive predictive value. We have shown that MRMPI is an excellent test for the diagnosis of significant coronary heart disease compared with the invasive gold standard of fractional flow reserve. It is hoped that our study will promote the use of MRMPI as a radiation-free alternative test for the noninvasive detection of reversible myocardial ischemia.
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