PERFUSION IMAGING

The Impact of Myocardial Flow Reserve on the Detection of Coronary Artery Disease by Perfusion Imaging Methods: An NHLBI WISE Study

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ABSTRACT

Myocardial flow reserve (MFR) is not routinely assessed in myocardial perfusion imaging (MPI) studies but has been hypothesized to affect test accuracy when assessing disease severity by coronary vessel lumenography. Magnetic resonance imaging (MRI) is an emerging diagnostic technique that can both perform MPI and assess MFR. We studied women (n = 184) enrolled in the Women’s Ischemia Syndrome Evaluation (WISE) study with symptoms suggesting ischemic heart disease. Tests performed were coronary angiography and MPI by both MR and gated radionuclide single photon emission computed tomography (gated-SPECT). The MFR index was calculated using the MR data acquired at baseline and under vasodilation (dipyridamole) conditions. The study was structured with a pilot and an implementation phase. During the pilot phase (n = 46) data were unmasked and an MFR threshold was defined to divide patients into those with an adequate (A_MFR) or inadequate (I_MFR) MFR index. During the implementation phase, the MFR index threshold was prospectively applied to patients (n = 138). In the implementation phase, MPI ischemia

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detection accuracy compared to severe (≥ 70%) coronary artery diameter narrowing by angiography was higher in the AMR vs. the IMR group for MRI (86% vs. 70%, p < 0.05) and gated-SPECT (89% vs. 67%, p < 0.01). The IMR group (n = 55, 30% of study population) had a higher resting rate-pressure product compared with the AMR group (10,599 ± 2871 vs. 9378 ± 2447 bpm mm Hg, p < 0.01), consistent with higher resting myocardial flow. When compared with each other, MRI and gated-SPECT MPI showed no difference in accuracy among MFR groups. Myocardial perfusion patterns in the IMR group may have resulted in atypical perfusion patterns, which either masked or mimicked epicardial coronary artery disease.

Key Words: Magnetic resonance; Myocardium; Perfusion; Coronary artery disease; Radionuclide; SPECT.

INTRODUCTION

Severe coronary artery disease can be detected by imaging myocardial perfusion under stress conditions during administration of a vasodilator, and in extreme cases, at rest. Exercise is widely regarded as the best stress, but a large number of patients are unable to achieve an adequate level of exercise (Amanullah et al., 1996; Elhendy et al., 1998; Iskandrian, 1991). Vasodilators such as dipyridamole and adenosine are used to induce myocardial hyperemia for myocardial perfusion imaging (MPI) (Meyers and Wintch, 1997; Takeishi et al., 1998). Myocardial flow reserve (MFR), defined as the ratio of myocardial blood flow during hyperemia to myocardial blood flow at rest, can be highly variable (Hasdai et al., 1997; Vassalli and Hess, 1998). Failure to achieve an adequate MFR has been hypothesized to result in lower test accuracy for noninvasive MPI methodologies, and consequently, physiological indicators have been sought to predict the vasodilation level achieved. Until recently, the decrease in systolic blood pressure was accepted as the best predictor of achievement of a high level of vasodilation (Ogilby et al., 1992), but it has been shown not to influence accuracy for radionuclide single photon emission computed tomography (gated-SPECT) MPI studies (Aksut et al., 1995a; Amanullah et al., 1997a,b).

Myocardial perfusion distribution and MFR can be simultaneously assessed using a magnetic resonance (MR) first-pass contrast agent approach (Cullen et al., 1999; Davis et al., 1996; Dromigny-Badin et al., 1998; Haacke et al., 1995; Jerosch-Herold et al., 1998; Pattynama and de Roos, 1995; Reeder et al., 1999). In the study presented here, we compare first-pass MR MPI, gated-SPECT MPI, and coronary angiography. We hypothesized that an MR-derived MFR index would identify the group of patients in which MPI results better correspond to coronary angiography. This study was conducted as part of the National Heart, Lung and Blood Institutes (NHLBI)-sponsored Women’s Ischemia Syndrome Evaluation (WISE), established to improve gender-specific noninvasive detection of ischemic heart disease in women (Bairey Merz et al., 1999).

METHODS

Patients

Women presenting with suspected ischemic heart disease were candidates for study if they were referred for routine diagnostic coronary angiography (Bairey Merz et al., 1999). Written informed consent was obtained from all participants using a form approved by the University of Alabama at Birmingham Institutional Review Board. The study was structured with a pilot phase (n = 64) to permit protocol refinement prior to the implementation phase (n = 165). Excluded from analysis during the pilot were seven patients with coronary artery bypass grafts, because angiographic results could not be unambiguously assessed. Of the remaining 57 patients, complete data were not acquired in 11 or 19.3% (five due to MR technical failure, five due to claustrophobia within the MR scanner, and one due to an incomplete radionuclide study). During the implementation phase, complete data were not acquired in 27 or 16.4% (10 due to MRI technical failure, eight due to claustrophobia, four due to incomplete radionuclide data, and five due to incomplete catheterization data). Analysis of pilot phase (n = 46) and implementation phase (n = 138) data are reported here (total n = 184).

Gated-SPECT MPI

The gated-SPECT examination was performed in parallel with the MRI examination and was either preceded or followed by a coronary angiogram (Fig. 1).
A baseline gated-SPECT examination was obtained (Analytical Development Associates Corporation, Milpitas, CA). Following this, patients were sent to the MRI suite where at three minutes following infusion of dipyridamole (0.56 mg/kg over 4 minutes) technetium-99m sestamibi (MIBI) was administered. Following the MRI study, patients returned to the nuclear cardiology laboratory for hyperemic gated-SPECT imaging. During the pilot phase, thallium-201 was used for the baseline and MIBI used for post dipyridamole. During the implementation phase, MIBI (low dose/high dose) was used for both baseline and hyperemic gated-SPECT MPI (DePuey et al., 1999).

MR MPI

An 18–22 gauge needle was inserted into the left antecubital vein and connected to a power injector (Spectris® MR Injection System, Medrad Inc., Pittsburgh, PA). A Philips MR scanner was used to image (ACS 1.5 T, 10mT/m/s, Philips Medical Systems, Best, The Netherlands). All images were acquired with a body coil. Perfusion imaging was performed in the short-axis orientation using a bolus injection of gadolinium (0.04 mmol/kg at a rate of 4–6 ml/sec) followed by a 10-ml saline flush administered using the power injector. During the pilot phase Magnevist (Berlex, Wayne, NJ) was used as the contrast agent. Thereafter, ProHance (Bracco, Princeton, NJ) was used due to its lower viscosity. For the implementation phase, two short-axis slices (at mid and apical locations) were acquired with heartbeat resolution up to 95 BPM or at alternate heartbeats for higher rates using a modified key-hole acquisition method (gradient echo imaging, TR/TE/flip 7/3.5/20°, 32 lines dynamically acquired and inserted into a 128 × 128 matrix), with T1 contrast generated by a 90° radio-frequency pulse applied 150 ms prior to data acquisition for each slice (Walsh et al., 1995). Images were acquired using a field of view ranging from 250 to 400 mm. Hyperemia was initiated with administration of dipyridamole (described above) and at 5 minutes post dipyridamole infusion the hyperemic MR perfusion study was initiated. Aminophylline was administered to patients complaining of bothersome headache or nausea (49% of cases) and after reestablishing the resting state, a 12-lead EKG was obtained.

Quantitative Coronary Angiography (QCA)

Conventional diagnostic coronary angiography was performed on all study patients. Coronary angiograms were digitally recorded and analyzed at the WISE core angiography laboratory (Rhode Island Hospital, Providence, RI) using computer-assisted quantitative methods. For the purpose of this study, a stenosis of $\geq 70\%$ luminal diameter reduction in either the proximal, mid, or distal portion of any coronary artery or its major branch was considered severe.
MRI MPI Analysis

Quantitative analysis of the MR perfusion data was conducted with a specially designed computer program developed using Matlab (The MathWorks, Inc. Natick, MA). Images were registered manually by adjusting the horizontal and vertical registration of each frame, and an apodization (low pass band filter with roll off) noise reduction filter was applied in the Fourier domain. The filter resulted in an approximate doubling of the signal to noise ratio (SNR) and the reduction of the influence of misregistration-related signal changes. The left ventricular blood pool and six myocardial regions (anterior, anterolateral, inferolateral, inferior, inferoseptal, and anteroseptal) were analyzed to extract the linear slope during the initial signal increase as well as the starting and peak signal intensities (Kraitchman et al., 1996; Wilke et al., 1997). To extract the slope, base, and peak signals, a line was manually fitted to the upslope signal (typically 4–6 time points), and the base and peak positions of the upslope data were manually identified. Normalized slope ($\text{slope}_N$) was calculated by division by the left ventricular blood pool slope, and the net signal gain (SG) determined by subtracting the initial from the peak signal intensity (Vallee et al., 1999). The myocardial flow reserve index was calculated for each myocardial region as the ratio of the normalized hyperemic time-intensity slope to the normalized baseline time-intensity slope. The pilot phase data were used to establish conditions to categorize patients as having an adequate MFR index (AMFRI) or an inadequate MFR index (IMFRI). If $2$ out of $12$ myocardial regions had an MFRI $\leq 0.5$, then the patient was categorized as having an AMFRI; otherwise, the patient was categorized as having an IMFRI. The quality of the MRI perfusion data sets were qualitatively judged in a masked manner using a 1–4 grading system (4 being the best).

Myocardial Flow Reserve and Stenosis Detection

Detection of perfusion defects was performed using the pilot phase hyperemic data by taking the product of $\text{slope}_N$ and SG, as this was expected to be a more robust disease indicator than using each parameter separately (Wilke et al., 1997). A myocardial region was identified as being underperfused by MR criteria if

$$\text{(SG} \times \text{slope}_N)_{\text{region}} < (\text{SG} \times \text{slope}_N)_{\text{max}} \times F$$

where $(\text{SG} \times \text{slope}_N)_{\text{max}}$ is the maximum value for all regions over all slices and $F$ is an MFRI-dependent coefficient. During the implementation phase, the sensitivity and specificity of detection of perfusion defects (taking QCA as the standard for comparison) were investigated by manually adjusting the value of $F$ in the above equation to achieve adequate sensitivity and specificity. To accommodate the possibility that the criterion for disease detection was different between MFRI groups, the fraction ($F$) was determined separately for each group. The values of $F$ were determined to be $0.3$ for the $A_{\text{MFRI}}$ group and $0.2$ for the $I_{\text{MFRI}}$ group and were fixed for each group before the beginning of the implementation phase (average threshold values for ischemia were $77.7$ and $51.8$ for the $A_{\text{MFRI}}$ and $I_{\text{MFRI}}$ groups, respectively).

Gated-SPECT MPI Analysis

Gated-SPECT data were analyzed by two or more experience readers masked from the results of angiography and MRI. Readers had access to the functional data from gated-SPECT (including wall motion assessment and ejection fraction). A qualitative assessment was made using a 19-segment model assessed in the short- and long-axis views. Regions were assessed as normal, transient defect, or fixed defect.

Statistical Methods

The Fisher exact test was used to compare differences among proportions, the two-tailed Student’s t-test was used to analyze continuous data, and a p value $\leq 0.05$ was considered significant. Analysis was performed using the SPSS statistical package (Chicago, IL) running on a PC. Patients’ family history, demographic information, and medication use were determined by questionnaire. When data were not known for a category, patients were excluded from that comparison and population percentages were calculated for the remaining population.

RESULTS

Data from QCA, gated-SPECT, and MRI were available for analysis in a total of 184 patients (46 from the pilot phase and 138 from the implementation phase). Patient characteristics, risk factors, medication use, and extent of severe coronary artery disease are summarized in Table 1. The $I_{\text{MFRI}}$ and $A_{\text{MFRI}}$ groups had many similar characteristics but were significantly different in use of
angiotensin-converting enzyme (ACE) inhibitors (47% vs. 30%, p < 0.05) and prevalence of single vessel coronary artery disease (20% vs. 9%, p < 0.05), respectively.

**Perfusion Imaging Comparisons**

For the AMFRI and IMFRI groups, the sensitivity, specificity, and accuracy of MPI compared to the presence of severe epicardial coronary artery disease by QCA are given in Table 2 for the pilot, implementation, and combined data sets. During the implementation phase, accuracy was significantly higher for the AMFRI group compared with the IMFRI group for both gated-SPECT (89% vs. 67%, p < 0.01) and MR (86% vs. 70%, p < 0.05). Examples of the higher contrast generally seen in images in the AMFRI MR images compared with the IMFRI images are shown in Fig. 2. Interestingly, for the AMFRI group, gated-SPECT exhibited an increase in accuracy between the pilot and implementation phases, i.e., between the hybrid and the MIBI-only protocols (67% vs. 89%, p < 0.05). However, for the IMFRI group, no significant difference was found in the accuracy of the gated-SPECT analysis between the two phases (68% vs. 67%, p = NS). Combining data for pilot and implementation phases, the accuracy was significantly different between AMFRI and IMFRI groups for both gated-SPECT (84% vs. 67%, p < 0.001) and MRI (83% vs. 58%, p < 0.001).

A direct comparison of MRI and gated-SPECT perfusion analysis is given in Table 3, where gated-SPECT was regarded as the standard for comparison. In the pilot and implementation phases there were no significant differences noted in accuracy of disease detection between AMFRI and IMFRI groups (82% vs. 76%, p = NS in the implementation phase). Further, the AMFRI and IMFRI groupings did not exhibit any differences in image quality (average image quality

### Table 1. Patient profile (n = 184).

<table>
<thead>
<tr>
<th>Population descriptors</th>
<th>Full population n = 184</th>
<th>IMFRI n = 55</th>
<th>AMFRI n = 129</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race: minority or nonwhite</td>
<td>32%</td>
<td>36%</td>
<td>29%</td>
</tr>
<tr>
<td>Race: white</td>
<td>68%</td>
<td>64%</td>
<td>70%</td>
</tr>
<tr>
<td>Body surface area (m²), mean ± stdn.</td>
<td>1.795 ± 0.18</td>
<td>1.791 ± 0.17</td>
<td>1.797 ± 0.19</td>
</tr>
<tr>
<td>Age (years), mean ± stdn.</td>
<td>59 ± 11</td>
<td>61 ± 11</td>
<td>58 ± 11</td>
</tr>
<tr>
<td>Triglycerides (mg/dl), mean ± stdn.</td>
<td>164 ± 113</td>
<td>163 ± 102</td>
<td>164 ± 118</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl), mean ± stdn.</td>
<td>203 ± 47</td>
<td>207 ± 54</td>
<td>202 ± 44</td>
</tr>
<tr>
<td>HDL (mg/dl), mean ± stdn.</td>
<td>57 ± 14</td>
<td>55 ± 12</td>
<td>57 ± 14</td>
</tr>
<tr>
<td>LDL (mg/dl), mean ± stdn.</td>
<td>114 ± 41</td>
<td>119 ± 46</td>
<td>111 ± 39</td>
</tr>
<tr>
<td>Medication used prior to testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>35%</td>
<td>47%</td>
<td>30%</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>47%</td>
<td>57%</td>
<td>42%</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>31%</td>
<td>26%</td>
<td>33%</td>
</tr>
<tr>
<td>Statins pharmaceuticals</td>
<td>28%</td>
<td>26%</td>
<td>29%</td>
</tr>
<tr>
<td>Nitrates</td>
<td>46%</td>
<td>57%</td>
<td>42%</td>
</tr>
<tr>
<td>Hormone replacement within 3 months</td>
<td>64%</td>
<td>63%</td>
<td>65%</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former cigarette smoker</td>
<td>31%</td>
<td>33%</td>
<td>30%</td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>20%</td>
<td>24%</td>
<td>18%</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>65%</td>
<td>69%</td>
<td>63%</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>67%</td>
<td>75%</td>
<td>63%</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>26%</td>
<td>35%</td>
<td>22%</td>
</tr>
<tr>
<td>History of dyslipidemia</td>
<td>60%</td>
<td>62%</td>
<td>59%</td>
</tr>
<tr>
<td>Extent of coronary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 Vessel disease</td>
<td>86%</td>
<td>78%</td>
<td>89%</td>
</tr>
<tr>
<td>1 Vessel disease</td>
<td>12%</td>
<td>20%</td>
<td>9%</td>
</tr>
<tr>
<td>2 Vessel disease</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>3 Vessel disease</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Quantities are significantly different between AMFRI and IMFRI groups (p < 0.05).*
value 2.40 ± 0.94 vs. 2.61 ± 0.95, p ≠ NS). When the accuracy of MR MPI was examined for each image quality grouping, no significant trend among groups was noted for either QCA or gated-SPECT as the standard of comparison (results not shown).

Hemodynamic parameters for the AMFRI and IMFRI groups are summarized in Table 4. The IMFRI group had higher baseline systolic blood pressure (149 ± 22 vs. 137 ± 23 mm Hg, p < 0.001), a higher baseline pulse pressure (73 ± 19 vs. 62 ± 17 mm Hg, p < 0.001), a higher baseline rate-pressure product (10,599 ± 2871 vs. 9378 ± 2447 mm Hg/s, p < 0.01), and a greater number of cardiac risk factors (2.9 ± 1.1 vs. 2.5 ± 1.0, p < 0.05).

To investigate the influence of the change in systolic blood pressure between baseline and vasodilation, patients (n = 178) were grouped into those demonstrating a large decrease (≥10 mm Hg) and those demonstrating a lesser or even a positive change in systolic blood pressure (Aksut et al., 1995b). Patients exhibiting a large decrease in systolic blood pressure (n = 48 or 27%) vs. the small or positive change group showed no significant difference in accuracy for either

Table 2. Perfusion imaging accuracy for severe coronary artery disease detection.

<table>
<thead>
<tr>
<th></th>
<th>Pilot (%) n = 46</th>
<th>Implementation (%) n = 138</th>
<th>Combined (%) n = 184</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sen</td>
<td>Spc</td>
<td>Acc</td>
</tr>
<tr>
<td>SPEC AMFRI</td>
<td>60</td>
<td>68d</td>
<td>67d</td>
</tr>
<tr>
<td>SPEC IMFRI</td>
<td>71</td>
<td>66</td>
<td>68</td>
</tr>
<tr>
<td>SPECT total</td>
<td>67</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>MRI AMFRI</td>
<td>80</td>
<td>68</td>
<td>71a</td>
</tr>
<tr>
<td>MRI IMFRI</td>
<td>43</td>
<td>40</td>
<td>41a</td>
</tr>
<tr>
<td>MRI total</td>
<td>58</td>
<td>56</td>
<td>57</td>
</tr>
</tbody>
</table>

Sensitivity (Sen), specificity (Spc), accuracy (Acc), and distribution (Dist) of patients among categories for gated-SPECT and quantitative MRI detection of perfusion deficits compared to severe stenosis (≥70%) detection by catheterization. The a, b, and c, indicate that quantities are significantly different between AMFRI and IMFRI groups within each category at the p < 0.05, 0.01, and 0.001 levels, respectively. The d indicates significant differences between the pilot and implementation phases (p < 0.05).

Figure 2. Sequential MR perfusion images depicting contrast agent passage for (top panel) a patient with an AMFRI and (lower panel) for a patient with an IMFRI, each patient having a severe stenosis of the left circumflex coronary artery. A region of perfusion deficit (arrowed) is seen well delineated in the AMFRI case but with lower contrast in the IMFRI case. From left to right, images depict contrast in (1) the right ventricle, (2) during early phase of passage of agent, and (3) at a late stage of passage through the myocardium.
Additionally, the average decrease in systolic blood pressure was not significantly different between AMFRI and IMFRI groups (Table 4).

DISCUSSION

While attempts have been made by other investigators to increase MFR by use of more potent vasodilators, it has not been determined if augmentation of MFR was achieved when tested using gated-SPECT imaging (Watanabe et al., 1997). To our knowledge, the data presented here is the first demonstration of the influence of MFR on accuracy of severe coronary artery disease detection by perfusion imaging methodologies. In the implementation phase, accuracy was higher in the AMFRI group compared with the IMFRI group for both gated-SPECT (89% vs. 67%, p \( < 0.01 \)) and MR (86% vs. 70%, p \( < 0.05 \)). It is clear that for both MR and radionuclide modalities, changes are necessary in the testing protocol to ensure that the MFRI information is incorporated in data assessment.

The percentage of IMFRI patients (24% in the implementation phase) was similar to the distribution found in previous investigations of myocardial perfusion reserve in patients (Geltman et al., 1990). It has been shown by others that performing MPI without suspending use of antianginal medication can result in reduced test sensitivity (Sharir et al., 1998); note that the use of ACE inhibitors in the IMFRI group was higher than in the AMFRI group (47% vs. 30%, p \( < 0.05 \)). Additionally, use of nitrates and beta blockers tended to be higher in the IMFRI group and the use of one or more of these three drugs was present more often in the IMFRI group than in the AMFRI group (85% vs. 68%, p \( < 0.05 \)). These results were observed despite the fact that use of medication was suspended for \( \geq 12 \) hrs before testing, possibly indicating that the effects of these drugs persisted for longer than \( 12 \) hrs, or perhaps that their use could be associated with as yet unknown physiological conditions that lead to a reduced MFR. Alternately, the medication-use data is consistent with the interpretation that the IMFRI patients had more severe disease symptoms. However, this cannot be extracted from our records, since all patients reported chest pain consistent with myocardial ischemia and resulted in a physician referring them for coronary angiographic testing.

The threshold used to discriminate between adequate and inadequate MFRI was a minimum of two segments having an MFRI of \( \geq 1.5 \). The average MFRI in the \( \text{AMFRI} \) group was \( 1.98 \pm 0.36 \) and \( 1.00 \pm 0.04 \) (p \( < 0.001 \)) in the IMFRI group. In the adequate group the MFRI is close to 2, which is similar in magnitude to the myocardial flow reserve reported by other modalities. Myocardial flow reserve cannot be directly compared with coronary velocity reserve, where of values of \( \geq 2 \) are common, due to the interaction between the epicardial coronary arteries and the microvasculature (Baumgart et al., 1998).

When using QCA as the standard for comparison, the specificity and accuracy of the gated-SPECT analysis for the AMFRI group increased between the pilot and the implementation phases (i.e., between the hybrid and MIBI-only protocols), while accuracy in the IMFRI group was not increased between phases. This may indicate that the increased accuracy of the higher energy MIBI agent vs. thallium is limited in the absence of an adequate myocardial flow response.

When compared to QCA, both MRI and gated-SPECT MPI exhibited differences in accuracy among MFRI groups (Table 2). However, when using gated-SPECT as the standard for comparison, MR MPI analysis did not demonstrate any significant difference in disease detection between AMFRI and IMFRI groups (Table 3). These findings suggest that myocardial perfusion patterns for AMFRI

### Table 3. MRI perfusion imaging accuracy with gated-SPECT as the standard.

<table>
<thead>
<tr>
<th></th>
<th>Pilot (%) n = 46</th>
<th>Implementation (%) n = 138</th>
<th>Combined (%) n = 184</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MRI AMFRI</strong></td>
<td>Sen  66, Spc 73, Acc 70, Dist 52</td>
<td>Sen 46, Spc 88, Acc 82, Dist 76</td>
<td>Sen 54, Spc 86, Acc 80, Dist 70</td>
</tr>
<tr>
<td><strong>MRI IMFRI</strong></td>
<td>Sen 50, Spc 42, Acc 45, Dist 48</td>
<td>Sen 50, Spc 87, Acc 76, Dist 24</td>
<td>Sen 50, Spc 71, Acc 64, Dist 30</td>
</tr>
<tr>
<td><strong>MRI total</strong></td>
<td>Sen 58, Spc 59, Acc 59, Dist 100</td>
<td>Sen 48, Spc 88, Acc 80, Dist 100</td>
<td>Sen 52, Spc 82, Acc 75, Dist 100</td>
</tr>
</tbody>
</table>

Sensitivity (Sen), specificity (Spc), accuracy (Acc), and distribution (Dist) of patients among categories for quantitative MRI detection of perfusion deficits compared to detection of perfusion defects by gated-SPECT. The * indicates significant differences between the pilot and implementation phases (p \( < 0.05 \)).
Table 4. Patient characteristics among $A_{MFRI}$ and $I_{MFRI}$ groups (n = 184).

<table>
<thead>
<tr>
<th></th>
<th>B SBP (mm Hg)</th>
<th>H SBP (mm Hg)</th>
<th>$\Delta$SBP (mm Hg)</th>
<th>B HR (BPM)</th>
<th>H HR (BPM)</th>
<th>$\Delta$HR (BPM)</th>
<th>$&gt;95$ BPM</th>
<th>B PP (mm Hg)</th>
<th>H PP (mm Hg)</th>
<th>B RPP (mm Hg/s)</th>
<th>H RPP (mm Hg/s)</th>
<th>No. of risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{MFRI}$</td>
<td>137</td>
<td>135</td>
<td>-2.2</td>
<td>68</td>
<td>85</td>
<td>17</td>
<td>19%</td>
<td>62</td>
<td>62</td>
<td>9378</td>
<td>11,445</td>
<td>2.5</td>
</tr>
<tr>
<td>(n = 129)</td>
<td>+ 23</td>
<td>+ 23</td>
<td>+ 11</td>
<td>+ 12</td>
<td>+ 12</td>
<td>+ 9</td>
<td>+ 17</td>
<td>+ 18</td>
<td>+ 18</td>
<td>+ 2447</td>
<td>+ 2455</td>
<td></td>
</tr>
<tr>
<td>$I_{MFRI}$</td>
<td>149</td>
<td>144</td>
<td>-5.2</td>
<td>71</td>
<td>86</td>
<td>15</td>
<td>24%</td>
<td>73</td>
<td>69</td>
<td>10,599</td>
<td>12,382</td>
<td>2.9</td>
</tr>
<tr>
<td>(n = 55)</td>
<td>+ 22</td>
<td>+ 25</td>
<td>+ 16</td>
<td>+ 15</td>
<td>+ 15</td>
<td>+ 10</td>
<td>+ 19</td>
<td>+ 20</td>
<td>+ 2871</td>
<td>+ 3069</td>
<td>+ 1.1</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.001</td>
<td>0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.01</td>
<td>0.05</td>
<td>0.01</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

B indicates baseline, H indicates hyperemic conditions, HR is the heart rate, PP is the pulse pressure, RPP is the rate pressure product, SBP is the systolic blood pressure, $\Delta$ indicates the differences between rest and hyperemia, $>95$ BMP represents the percentage of patients in which the MRI acquisition increased from single to alternate heart beat time resolution due to the heart rate exceeding 95 BPM, and p is the significance level of the difference between $A_{MFRI}$ and $A_{MFRI}$ groups.
patients are dominated by the stenotic status of the epicardial coronary arteries, while for I_MFRI patients myocardial perfusion patterns are dominated by other factors.

MFR Correlates

Previously, in the absence of a direct measurement of MFR using gated-SPECT, the degree of decrease in systolic blood pressure was expected to predict test accuracy. In this study, however, no significant difference in accuracy was noted for patients having a $\geq 10$ mm Hg fall in blood pressure compared to others.

While no single hemodynamic parameter predicted MFR, there were distinct hemodynamic conditions associated with the I_MFRI and A_MFRI groups. Differences were noted in the baseline hemodynamic state, with the I_MFRI group having a baseline rate pressure product (RPP) similar to the vasodilation RPP of the A_MFRI group. This suggests that the I_MFRI Patients have, on average, a higher baseline oxygen demand. Such conditions are consistent with higher resting myocardial flow, which necessarily places a limit on the MFR that can be achieved. This adds supportive evidence to observations by others that an inadequate MFR is likely to be the result of an elevated perfusion level at baseline, resulting in a diminished ability to increase perfusion levels during vasodilation (Kaski and Elliott, 1995). Since gated-SPECT analysis incorporates resting and vasodilation data sets, it is expected to be influenced by a low MFR response, even in cases where a normal or high perfusion state is achieved at vasodilation. However, the MRI diagnosis reported here was based on the vasodilation data set and thus the baseline state did not influence diagnosis. Since the I_MFRI group is characterized by high resting RPP levels, it suggests that in this group myocardial perfusion patterns may be elevated relative to normal conditions, possibly as an adaptive response to disease, which may either mask or mimic perfusion disease.

No individual risk factor was significantly different among groups; even so, the average number of risk factors for coronary artery disease (CAD) was higher in the I_MFRI group, suggestive of a higher likelihood of the presence of disease, consistent with the observations of others (Table 4) (Laine et al., 1998; Mellwig et al., 1998; O’Rourke and Mancia, 1999; Tanaka et al., 1998). This fact, combined with the noted elevated systolic and pulse blood pressures in the I_MFRI group, is consistent with the interpretation that the coronary vasculature’s resistance is higher in the I_MFRI group. Whether this inferred increased resistance is at the epicardial or microvascular level is unknown, but a recent study in a similar population demonstrated abnormalities in the endothelium (Al Suwaidi et al., 2000).

Notably, the patient population was one with a high normalcy rate by QCA (89%), and those with severe CAD predominantly had single vessel disease. The distribution of patients with single vessel disease was higher in the I_MFRI group compared with the A_MFRI group (20% vs. 9%, $p < 0.05$). The accuracy of perfusion imaging in patients with single vessel disease is typically lower than that for patients with multiple vessel disease. For the implementation phase data, the accuracies reported here for gated-SPECT (83%) and MR (82%) are comparable to other studies involving similar populations with low prevalence of severe disease. In patients with three-vessel disease, where perfusion may be low but balanced, assessment of both the MFRI and perfusional status is likely to be compromised due to the limited extent of normal regions available for comparison. In such cases, a quantitative MR perfusion assessment approach may be of most value.

Many techniques that are designed to detect stenotic lesions in the coronary vasculature, including MPI, fractional flow reserve angiography, and intravascular ultrasound, rely on attainment of an adequate MFR (Abizaid et al., 1998; De Bruyne et al., 2000; Pijls et al., 1995). The assumption inherent in these approaches is that a low MFR is governed primarily by the extent and severity of coronary artery lesions and occurs in myocardial territories distal to lesions. However, it has been shown that MFR may be reduced even in territories remote from an isolated epicardial coronary lesion (Beanlands et al., 1995). Thus, myocardial flow reserve may be limited either by local stenosis characteristics or by a more global attenuation of the hyperemic response, which in turn may be further limited by elevated resting flow. We have shown that when using QCA as the standard, patients experiencing a low MFR were assessed with low accuracy by MPI for two independent modalities, MRI and gated-SPECT. While decreased MFR was associated with higher prevalence of CAD, CAD risk factors, and increased medication use, it was not predictive of severe epicardial CAD. Thus, the level of MFR should be independently assessed when applying techniques that assess the coronary vasculature.

Limitations

The MR analysis was performed in a limited number of tomographic planes (two in the implementation phase) and contrast agent was administered via the antecubital vein, whereas better accuracy is expected with an
increased number of tomographic slices and a central line injections (Wilke et al., 1993). The population studied had a low prevalence of severed CAD, and thus assessment of sensitivity among MFR groups could not show significant differences. Nevertheless, the population is an important one, in that it represents patients at intermediate risk for CAD. Dipyridamole was used as the vasodilator agent, which is known to have a lower maximum vasodilation effect than adenosine. However, the variability of the vasodilation level achieved by adenosine is comparable to that produced by dipyridamole, and thus, some patients are still expected to experience an inadequate MFR even with use of the more potent agent.

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