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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_{MFRI}) or inadequate (I_{MFRI}) 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 A_{MFRI} vs. the I_{MFRI} group for MRI (86% vs. 70%, $p < 0.05$) and gated-SPECT (89% vs. 67%, $p < 0.01$). The I_{MFRI} group ($n = 55$, 30% of study population) had a higher resting rate-pressure product compared with the A_{MFRI} group ($10{,}599 \pm 2871$ 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 I_{MFRI} 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 MRI 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).

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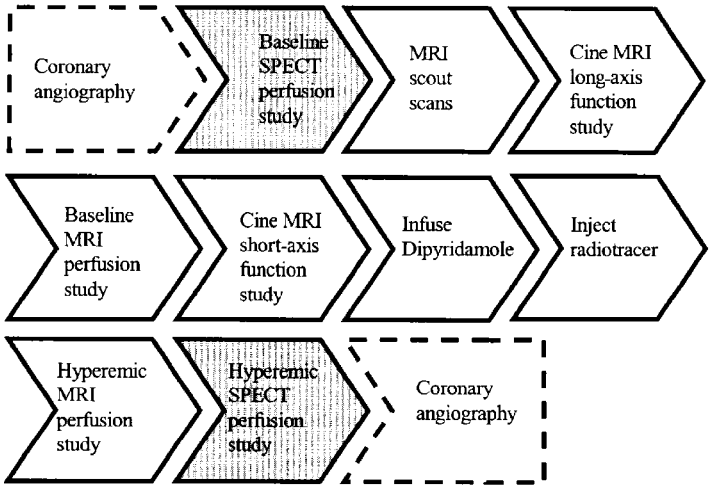

Figure 1. Flow chart indicating the order of the three examinations: coronary angiography, gated-SPECT, and MRI. Shaded boxes indicate activities performed in the nuclear medicine department, and the dashed boxes indicate that the coronary angiogram was performed either before or after the other examinations.

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 ($Slope_N$) 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 (A_{MFRI}) or an inadequate MFR index (I_{MFRI}). If ≥ 2 out of 12 myocardial regions had an MFRI ≥ 1.5, then the patient was categorized as having an A_{MFRI}, otherwise, the patient was categorized as having an I_{MFRI}. 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 $Slope_N$ 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

$$(SG \times Slope_N)_{region} < (SG \times Slope_N)_{max} \times F \qquad (1)$$

where $(SG \times Slope_N)_{max}$ 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_{MFRI} group and 0.2 for the I_{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_{MFRI} and I_{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 <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_{MFRI} and A_{MFRI} groups had many similar characteristics but were significantly different in use of

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Table 1. Patient profile (n = 184).

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

[a] Quantities are significantly different between A_{MFRI} and I_{MFRI} groups ($p < 0.05$).

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 A_{MFRI} and I_{MFRI} 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 A_{MFRI} group compared with the I_{MFRI} 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 A_{MFRI} MR images compared with the I_{MFRI} images are shown in Fig. 2. Interestingly, for the A_{MFRI} 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 I_{MFRI} 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 A_{MFRI} and I_{MFRI} 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 A_{MFRI} and I_{MFRI} groups (82% vs. 76%, p = NS in the implementation phase). Further, the A_{MFRI} and I_{MFRI} groupings did not exhibit any differences in image quality (average image quality

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

	Pilot (%) n = 46				Implementation (%) n = 138				Combined (%) n = 184			
	Sen	Spc	Acc	Dist	Sen	Spc	Acc	Dist	Sen	Spc	Acc	Dist
SPEC A_{MFRI}	60	68[d]	67[d]	52	67	91[a,d]	89[b,d]	76	64	87[a]	84[c]	70
SPEC I_{MFRI}	71	66	68	48	40	71[a]	67[b]	24	58	70[a]	67[c]	30
SPECT total	67	68	67	100	57	86	83	100	62	82	79	100
MRI A_{MFRI}	80	68	71[a]	52	67	88	86[a]	76	71	84[b]	83[c]	70
MRI I_{MFRI}	43	40	41[a]	48	40	75	70[a]	24	42	63[b]	58[c]	30
MRI total	58	56	57	100	57	85	82	100	57	78	76	100

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 A_{MFRI} and I_{MFRI} 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 ($p < 0.05$).

value 2.40 ± 0.94 vs. 2.61 ± 0.95, $p \neq$ 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 A_{MFRI} and I_{MFRI} groups are summarized in Table 4. The I_{MFRI} 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 ($10,599 \pm 2871$ 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

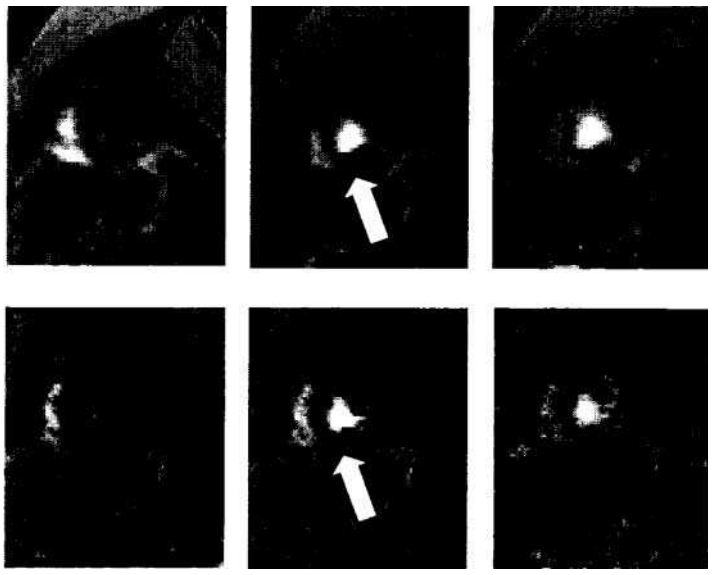

Figure 2. Sequential MR perfusion images depicting contrast agent passage for (top panel) a patient with an A_{MFRI} and (lower panel) for a patient with an I_{MFRI}, each patient having a severe stenosis of the left circumflex coronary artery. A region of perfusion deficit (arrowed) is seen well delineated in the A_{MFRI} case but with lower contrast in the I_{MFRI} 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.

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

	Pilot (%) n = 46				Implementation (%) n = 138				Combined (%) n = 184			
	Sen	Spc	Acc	Dist	Sen	Spc	Acc	Dist	Sen	Spc	Acc	Dist
MRI A_{MFRI}	66	73	70	52	46	88	82	76	54	86	80	70
MRI I_{MFRI}	50	42	45[a]	48	50	87	76[a]	24	50	71	64	30
MRI total	58	59	59	100	48	88	80	100	52	82	75	100

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 [a] indicates significant differences between the pilot and implementation phases ($p < 0.05$).

gated-SPECT (75% vs. 81%) or MRI (73% vs. 78%). Additionally, the average decrease in systolic blood pressure was not significantly different between A_{MFRI} and I_{MFRI} 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 A_{MFRI} group compared with the I_{MFRI} 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 I_{MFRI} 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 I_{MFRI} group was higher than in the A_{MFRI} group (47% vs. 30%, $p < 0.05$). Additionally, use of nitrates and beta blockers tended to be higher in the I_{MFRI} group and the use of one or more of these three drugs was present more often in the I_{MFRI} group than in the A_{MFRI} group (85% vs. 68%, $p < 0.05$). These results were observed despite the fact that use of medication was suspended for ≥ 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 I_{MFRI} 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 ≥ 1.5. The average MFRI in the A_{MFRI} group was 1.98 ± 0.36 and 1.00 ± 0.04 ($p < 0.001$) in the I_{MFRI} 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 >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 A_{MFRI} group increased between the pilot and the implementation phases (i.e., between the hybrid and MIBI-only protocols), while accuracy in the I_{MFRI} 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 A_{MFRI} and I_{MFRI} groups (Table 3). These findings suggest that myocardial perfusion patterns for A_{MFRI}

Table 4. Patient characteristics among A_{MFRI} and I_{MFRI} groups (n = 184).

	B SBP (mm Hg)	H SBP (mm Hg)	ΔSBP (mm Hg)	B HR (BPM)	H HR (BPM)	ΔHR (BPM)	>95 (BPM)	B PP (mm Hg)	H PP (mm Hg)	B RPP (mm Hg/s)	H RPP (mm Hg/s)	No. of risk factors
A_{MFRI}	137	135	−2.2	68	85	17	19%	62	62	9378	11,445	2.5
(n = 129)	±23	±23	±11	±12	±12	±9		±17	±18	±2447	±2455	±1.1
I_{MFRI}	149	144	−5.2	71	86	15	24%	73	69	10,599	12,382	2.9
(n = 55)	±22	±25	±16	±15	±15	±10		±19	±20	±2871	±3069	±1.1
p	0.001	0.05	NS	NS	NS	NS	NS	0.001	0.05	0.01	0.05	0.05

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, Δ 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.

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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 ≥ 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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