New Methods

A Myocardial Perfusion Reserve Index in Humans Using First-Pass Contrast-Enhanced Magnetic Resonance Imaging

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OBJECTIVES

The purpose of this study was to evaluate a myocardial perfusion reserve index (MPRI) derived from a quantitative magnetic resonance imaging (MRI) technique in normal human volunteers and patients with coronary artery disease and to relate MPRI to coronary artery stenosis severity measured with quantitative arteriography.

BACKGROUND

Magnetic resonance imaging could be a useful noninvasive tool in the investigation of ischemic heart disease. However, there have been few studies in humans to quantify myocardial perfusion and myocardial perfusion reserve using MRI and none in patients with coronary disease.

METHODS

Twenty patients with angiographically proven coronary artery disease and five normal volunteers underwent both resting and stress (adenosine 140 \( \mu \text{g/kg} \text{min}^{-1} \)) first-pass contrast-enhanced MRI examinations (using 0.05 mmol/kg of gadopentetate dimeglumine. Using a tracer kinetic model, the unidirectional transfer constant (\( K_i \)), a perfusion marker for the myocardial uptake of contrast, was computed in each coronary arterial territory. The ratio of \( K_i \) for the rest and stress scans was used to calculate the MPRI. Percent reduction in luminal diameter of coronary lesions was measured using an automated edge-detection algorithm.

RESULTS

Myocardial perfusion reserve index was significantly reduced in patients compared with normal subjects (2.02 ± 0.7 vs. 4.21 ± 1.16, \( p < 0.02 \)). For regions supplied by individual vessels, there was a significant negative correlation of MPRI with percent diameter stenosis (\( r = -0.81, \ p < 0.01 \)). Importantly, regions supplied by vessels with <40% diameter stenosis (non–flow limiting) had a significantly higher MPRI than regions supplied by stenoses of “intermediate” severity, that is, >40% to 59% diameter stenosis (2.80 ± 0.77 and 1.93 ± 0.38, respectively, \( p < 0.02 \)). However, even regions supplied by vessels with <40% diameter stenosis had a significantly lower MPRI than volunteers (\( p < 0.01 \)).

CONCLUSIONS

A myocardial perfusion reserve index derived from first-pass MRI studies can distinguish between normal subjects and patients with coronary artery disease. Furthermore, it provides useful functional information on coronary lesions, particularly where the physiologic significance cannot be predicted accurately from the angiogram. (J Am Coll Cardiol 1999;33: 1386–94) © 1999 by the American College of Cardiology
Methods

Study population. The study was approved by the local ethical committee, and all patients and volunteers gave written, informed consent. We studied 20 patients (17 men and three women; mean ± SD, 61 ± 8 years of age), who had undergone cardiac catheterization for chest pain with a positive treadmill test. We also studied five healthy male volunteers (mean age 28 ± 6 years), who all had a low risk for coronary disease based on history and examination. Patients were ineligible for enrollment if they had intracranial clips, a pacemaker, cochlear or intraocular implants, a history of metal fragments in the eye, claustrophobia or a contraindication to receiving adenosine. Any substances that might interfere with the action or metabolism of adenosine, such as caffeine, chocolate or theophylline, were withheld 24 h before the study.

Study design. All patients underwent the MRI examination within two weeks after their coronary angiogram. The patients and volunteers underwent both a resting and a stress MRI examination separated by 24 h, to allow any residual intramyocardial MRI contrast agent from the rest study to dissipate. The stress examination was conducted using adenosine at a dose of 140 µg/kg−1/min−1.

Magnetic resonance imaging technique. Magnetic resonance imaging was performed using a 1.0-T Siemens Magnetom Impact scanner (Siemens, Erlangen, Germany). The standard body coil was used both for radiofrequency transmission and reception of the signal. The patients had precordial electrocardiographic electrodes applied for cardiac gating of the images before being positioned at the isocenter of the magnet. After obtaining scout views, three double-oblique short-axis planes through the left ventricle were acquired sequentially: 1) basal, 2) mid–left ventricular (through the papillary muscles) and 3) apical, using an inversion recovery snapshot-FLASH sequence (13). This sequence uses a 180° inversion pulse to provide T1 contrast, followed by a FLASH acquisition with a very short echo time (2 ms) and repetition time (4.7 ms). The flip angle of the excitation pulses was 8°, with a 64 × 64 data matrix, a 250-mm field of view and slice thickness of 10 mm. Image acquisition commenced 300 ms after the inversion pulse (TI = 300 ms) and was gated to the electrocardiogram to occur during mid-diastole, thus minimizing motion artifacts. An image at each anatomic position was acquired approximately every six heartbeats, with a total of 20 images at each of the three levels. Perfusion was assessed by injecting the contrast agent Gd-DTPA (0.05 mmol/kg−1 body weight), via the antecubital vein after the fifth image. The TI was chosen such that before contrast injection the sequence gives low signal intensity throughout the myocardium. As the contrast agent reaches the heart, myocardium enhances, and the images give an approximate visual indication of tissue perfusion. Care was taken to make a copy of the scout images of the left ventricle to show the exact position of the short-axis oblique slices, so that they could be repositioned as accurately as possible the following day for the stress scan.

The stress images were acquired in an identical fashion, except that adenosine 140 µg/kg−1/min−1 was commenced via an intravenous line, for 3 min before starting the MRI. Gadopentetate dimeglumine was injected via a separate line to prevent any adverse bolus effects from adenosine, such as bradycardia.

Measurement of Ki for Gd-DTPA and myocardial perfusion reserve index. Gadopentetate dimeglumine is a small hydrophilic molecule, which after intravenous injection and passage to the heart passes across the myocardial capillary membranes into the extravascular compartment. The transport of Gd-DTPA across the capillary can be described by the first order differential equation (14):

$$\frac{d[Gd]_{myo}(t)}{dt} = K_i [Gd]_a(t) - \frac{1 - Hct}{\lambda}[Gd]_{myo}(t).$$  \[1\]
A full description of this model and its derivation has previously been described (9,10). [Gd]_{myo}(t) is the concentration of Gd-DTPA in the myocardium at time t, and [Gd]_{a}(t) is the input function (arterial blood concentration of Gd-DTPA). K_i is the unidirectional influx constant determining the transport of Gd-DTPA across the capillary membrane; Hct is the hematocrit; \lambda is the volume of distribution of Gd-DTPA within the myocardium, which is equivalent to the interstitial space volume fraction, assuming Gd-DTPA is a freely diffusible substance in the extracellular space. The solution to equation 1 is a convolution of the impulse response function with the arterial input function:

\[ [Gd]_{myo}(t) = [Gd]_{a}(t) \otimes K_e e^{-\frac{t}{\lambda}}, \]

where \( \otimes \) denotes the convolution operator, and the term

\[ K_e e^{-\frac{t}{\lambda}}, \]

is the impulse response of myocardium. K_i can therefore be determined by a deconvolution of the measured arterial and myocardial concentration of Gd-DTPA.

K_i is related to the extraction fraction (E) across the capillary membrane and blood perfusion (F) in the following equation (15,16):

\[ K_i = EF \]

Although E cannot easily be measured, by determining K_i we have a parameter that is related to perfusion, and since E is a dimensionless constant, the unit of measurement for K_i is ml/g \cdot 1/min. There is evidence that E stays relatively constant for a wide range of pathologic and physiologic states (11), so the ratio of K_i during adenosine stress to K_i at rest was used to calculate the myocardial perfusion reserve index (12).

Measurement of regional myocardial [Gd] and input function. For each patient there were 20 images at each level showing the signal intensity changes before, during and after the contrast injection. After transferring the images to a computer (Sun Microsystems, Mountainview, California), the program Analyze (Mayo Foundation, Rochester, Minnesota) was used to measure signal intensity changes in the myocardium, which was divided radially into 10 regions of interest (ROIs). The relationship between signal intensity and [Gd-DTPA] is nonlinear. However, [Gd]_{myo} can be computed for a specified region of interest if myocardial relaxation rate (R_i) is measured, since R_i is linearly related to Gd-DTPA concentration as in the following equation, assuming fast exchange between intracellular and extracellular compartments (17):

\[ R_i^{myo}(t) = R_i^{myo}(0) + \beta_{myo} [Gd]_{myo}(t). \]

R_i^{myo}(t) is the time course of the myocardial relaxation rate; R_i^{myo}(0) is the myocardial relaxation rate before contrast injection, and \( \beta_{myo} \) is the relaxivity of Gd-DTPA, which was assumed to be 4.3 mmol/l \cdot s^{-1} (18). Myocardial relaxation rate measurement using the snapshot FLASH sequence is known to suffer from inaccuracies particularly due to magnetization saturation when the overall sequence repetition time is shortened. Our group has shown that errors of between 10% and 25% may be introduced at higher heart rates. Consequently, our method for measuring R_i from signal intensities included corrections for these errors, and is described in detail elsewhere (19).

The input function [Gd]_{a}(t) was similarly computed from the signal intensity changes in the ventricular cavity of the basal slice, which is nearest to the left ventricular outflow tract. The left ventricular concentration of Gd-DTPA was assumed to be representative of the [Gd] in blood entering the aortic sinus and coronary arteries. The relaxivity of Gd-DTPA in blood was assumed to be the same as the relaxivity of Gd-DTPA in myocardial tissue water.

Having derived plots of R_i against time for all 20 myocardial ROIs and also for the left ventricular (LV) cavity, K_i was determined for each ROI, using a deconvolution algorithm written in the “C” programming language. This was done for both the rest and adenosine stress data and the myocardial perfusion reserve index calculated for each ROI as the ratio of the stress to the rest K_i values.

Quantitative coronary arteriography. Selective coronary arteriography of the right and left coronary arteries in multiple views was performed according to the Judkins technique. The angiograms were analyzed by an automated edge contour detection system (Quantor QCA, Siemens, Erlangen, Germany) that has been previously validated (20) (this software was formally known as the new generation of Cardiovascular Angiography Analysis System [CAAS II] Pie Medical Equipment, Maastricht, The Netherlands). After selecting the projection showing maximal severity, the luminal diameter of the stenosed artery along with adjacent reference segments were measured in the end-diastolic frame. The severity of the stenosis was expressed as a percent reduction of the internal diameter in relation to the estimated diameter interpolated from the diameters at the proximal and distal boundaries of the stenosis. The lesions were assigned to one of four categories of severity: 1) <40% narrowing was considered hemodynamically insignificant, 2) 40% to 59% mild, 3) 60% to 79% moderate and 4) ≥80% severe.

The coronary angiograms were also analyzed by an experienced cardiac radiologist blinded to the MRI perfusion data using the Green Lane Score (21). This system enabled the territory of distribution and the corresponding regions of interest of each coronary artery to be accurately assigned depending on variations in coronary anatomy. A typical circulation consisted of regions 8 to 2 assigned to the left anterior descending artery, regions 3 and 4 to circumflex and regions 5 to 7 to right coronary artery (Fig. 1).

In calculating the perfusion reserve index for each artery, it was decided to use only the basal and papillary slices, since partial volume effects were significant toward the apex, causing signal from the left ventricular blood to be super-
imposed on the myocardium. Due to the potential overlap between differing coronary arterial territories, the $K_i$ values for a ROI were calculated for the two most central ROIs allotted to each artery. The resulting $K_i$ from these ROIs were averaged, to give $K_i$ for each artery before stress. The resultant area was therefore approximately 20% of the circumference of the short-axis oblique slice; this reduced statistical noise that would have resulted from too small a region of interest. The same ROIS were chosen from the stress study to calculate $K_i$ during stress.

**Statistical analysis.** Data are presented as mean ± SD. A one-way analysis of variance (ANOVA) was used to compare simultaneously mean resting and adenosine stress $K_i$ values and the MPRI for the four categories of stenosis severity. Group means were compared using paired and unpaired Student $t$ test as appropriate. Linear regression analysis was used to detect correlation between angiographic severity grade represented as percent diameter stenosis and myocardial perfusion reserve index.

### RESULTS

**Patient characteristics.** Eleven patients had previously suffered a myocardial infarction based on clinical history, the presence of pathologic Q waves on the resting electrocardiogram and the presence of regional wall motion abnormalities on left ventricular angiography. Regions of interest in infarct-related territories were excluded owing to possible effects on regional flow reserve, resulting in lesions in 47 coronary vessels for analysis. Where there was more than one stenosis in the same vessel, the more severe stenosis was graded.

**Coronary arteriographic findings.** Of 47 non–infarct-related vessels, 13 were left anterior descending coronary arteries, 14 were right coronary arteries and 20 were left circumflex coronary arteries. The mean coronary percent diameter stenosis was $49 ± 21\%$. Twelve arteries were graded as $<40\%$ diameter stenosis, 21 arteries $40\%$ to $59\%$, 11 arteries $60\%$ to $79\%$ and 3 arteries $≥80\%$.

**Hemodynamic findings.** The hemodynamic findings during the rest and stress studies are summarized in Table 1. The heart rate increased significantly during adenosine stress in the patient and volunteer groups (from $64.7 ± 13.2$ to $76.6 ± 14.9$ beats per minute in patients, $p < 0.01$; and from $58.5 ± 12.1$ to $95.3 ± 23.2$ beats per minute in volunteers, $p < 0.01$). Mean aortic blood pressure was significantly lower during stress in the patient group compared with rest ($p < 0.03$); systolic and mean aortic blood pressure were also significantly lower in the volunteer group during stress compared with rest ($p < 0.01$ and $p < 0.02$, respectively). However, the rate–pressure product increased significantly during adenosine in both patients and volunteers (from $8,901.2 ± 2,151.7$ to $10,127.3 ± 2,950.9$ in patients, $p < 0.03$; and from $7,553.8 ± 1,821.0$ to $11,758.6 ± 3,157.2$ in volunteers, $p < 0.02$). However, there were no significant differences in resting heart rate, systolic, diastolic and mean arterial blood pressure, and rate–pressure product between the patient and normal volunteer groups, and there were no significant differences in rate–pressure product between patients and normal volunteers during adenosine stress.

**Unidirectional transfer constant values and myocardial perfusion reserve in normal volunteers and patients.** At rest, the mean $K_i$ in normal volunteers was $0.54 ± 0.13\, \text{ml/g}^{-1}\text{min}^{-1}$, which increased to $2.29 ± 0.85\, (p < 0.01)$ with adenosine stress, resulting in an average myocardial

### Table 1. Hemodynamic Findings

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 20)</th>
<th>Volunteers (n = 5)</th>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Stress</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64.7 ± 13.2</td>
<td>76.6 ± 14.9*</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>137.0 ± 14.1</td>
<td>130.6 ± 17.6</td>
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<tr>
<td>Diastolic BP (mm Hg)</td>
<td>83.6 ± 9.7</td>
<td>80.8 ± 9.9</td>
</tr>
<tr>
<td>Rate–pressure product</td>
<td>8,901.2 ± 2,151.7</td>
<td>10,127.3 ± 2,950.9‡</td>
</tr>
<tr>
<td>Mean aortic BP (mm Hg)</td>
<td>101.4 ± 10.2</td>
<td>97.4 ± 9.3‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>58.5 ± 12.1</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>128.6 ± 5.4</td>
<td>123.0 ± 5.0*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>83.6 ± 2.2</td>
<td>79.2 ± 1.9</td>
</tr>
<tr>
<td>Rate–pressure product</td>
<td>7,553.8 ± 1,821.0</td>
<td>11,758.6 ± 3,157.2§</td>
</tr>
<tr>
<td>Mean aortic BP (mm Hg)</td>
<td>98.6 ± 2.8</td>
<td>93.8 ± 1.3§</td>
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*p < 0.01 vs. rest; †p < 0.05 vs. patients; ‡p < 0.03 vs. rest; §p < 0.02 vs. rest.

BP = blood pressure; beats/min = heart rate in beats per minute. Stress is during adenosine $140\, \mu g/kg^{-1}\text{min}^{-1}$. 

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**Figure 1.** Schematic of left ventricular short-axis oblique slice, showing allocation of the 10 regions of interest to the three coronary arteries in a typical circulation. Left anterior descending artery (LAD) represents regions 8 to 2; circumflex artery (CX) represents regions 3 and 4, and right coronary artery (RCA) represents regions 5 to 7.
perfusion reserve index of 4.21 ± 1.16. Figure 2 shows a typical example of the increase in \( K_i \) with stress across all 10 regions of interest, in one of the normal volunteers (mid–lv slice). In patients the mean \( K_i \) value at rest, in regions supplied by all 47 coronary arteries, was similar to that of the normal volunteers (0.60 ± 0.28 ml/g/min, \( p = \text{NS} \)), but was lower during hyperemia (1.17 ± 0.59, \( p < 0.05 \)). Hence MPRI (2.02 ± 0.70) was significantly lower than in normal volunteers (\( p < 0.02 \)). Figure 3 shows a typical response to stress in a patient, revealing significant reduction of the ratio of \( K_i \) during stress to \( K_i \) at rest in the posterior and anteroseptal walls, due to right coronary and left anterior descending coronary artery disease.

The basal \( K_i \) rate in patients remained relatively constant irrespective of the stenosis severity (Table 2). However, during hyperemia, for vessels with 40% or more reduction in luminal diameter there was a progressive reduction in \( K_i \) and MPRI as stenosis severity increased. For vessels with 80% or more reduction in luminal diameter, the MPRI approached unity. There was a significant inverse and linear relationship of MPRI with the percent diameter stenosis on coronary arteriography (\( r = -0.81, p < 0.01 \), see Fig. 4). Importantly, despite moderate variability of MPRI with stress at each level of stenosis severity, regions supplied by vessels with <40% reduction in luminal diameter (hemodynamically insignificant) had a significantly higher MPRI than those between 40% and 59% (2.80 ± 0.77 and 1.93 ± 0.38, respectively, \( p < 0.01 \)). However, regions supplied by vessels with hemodynamically insignificant stenoses (<40% diameter) still had lower MPRI than in the normal volunteers (2.80 ± 0.77, \( p < 0.01 \)).

**DISCUSSION**

The physiologic impact of coronary artery disease at the myocardial level can be difficult to assess from coronary angiography, due to confounding factors such as collateral vessels (22), microcirculatory dysfunction (7) and the uncertain relationship between the severity of a coronary artery stenosis and its flow-limiting effects (5). Thus quantification of myocardial perfusion and perfusion reserve is of interest to investigators to assess the “end organ” effects of the summation of these factors. At present the only clinically validated method for measuring myocardial perfusion is PET (7), which is time-consuming, only available in specialist research faculties due to its more limited use generally and involves exposure to ionizing radiation, precluding its use in longitudinal studies. Magnetic resonance imaging perfusion assessment is an attractive alternative, since in addition to its noninvasive, nontoxic nature, it also has good spatial resolution and has the potential to assess other features of the heart such as coronary anatomy (23), coronary flow (24) and myocardial wall motion changes (25) in one examination. Other investigators have assessed the ability of first-pass contrast studies with gadolinium chelates to demonstrate myocardial perfusion abnormalities in patients with ischemic heart disease, both at rest and during stress. These approaches have centered around measuring signal intensity changes and the slope of the intensity versus time curves from myocardium. Many of these studies did not measure an input function with which to “normalize” the resultant signal intensities in each myocardial region before and after stress. Consequently, although regional differences in perfusion may be detected at rest (26) and particularly on the stress images (27,28), where areas of low signal intensity are interpreted as areas of hypoperfusion, and there is evidence of reduction in the up-slope during the wash-in of the contrast (29,30), comparison with rest images and also between patients is difficult. These studies are also limited by the nonlinear relationship between signal intensity to [Gd] and rapid leakage of the contrast agents into the extracellular space. One approach has attempted to

![Figure 2](image-url)  
*Figure 2.* Histogram plots of individual resting and stress unidirectional transfer constant \( (K_i) \) values in all 10 regions of interest in a normal subject at the papillary level, showing a uniform increase in \( K_i \) in all coronary territories with adenosine stress.

![Figure 3](image-url)  
*Figure 3.* Histogram plots of all individual resting and stress unidirectional transfer constant \( (K_i) \) values in all 10 regions of interest in a patient at the papillary level, showing significant reduction of the ratio of \( K_i \) during stress to \( K_i \) at rest in the posterior and anteroseptal walls, due to right coronary and left anterior descending coronary artery disease.
overcome these difficulties using a perfusion model based on analysis of the myocardial signal intensity changes in the wash-in portion of a first-pass bolus study (31), using the left ventricular cavity signal intensity changes as an input function. The rate of contrast wash-in was found to be linearly related to perfusion, with good agreement in animal models with microsphere measurements of blood flow. Nevertheless, this depends on a uniform and rapid injection of contrast with a power injector into a venous catheter line situated in the superior vena cava to minimize the effect of extracellular leakage and changes in myocardial blood volume, which otherwise introduce inaccuracy to the perfusion parameter value. It also assumes linearity of signal intensity with [Gd], which does not hold true near the peak values of signal intensity in the blood pool (31).

The measurement of the unidirectional transfer constant Kᵢ is another approach that attempts to overcome these problems. The model is not so dependent on a rapid bolus technique and so does not require the relatively invasive injections described with other studies (29,31), and can be performed through a standard peripheral intravenous line. However, its estimation depends on accurate measurement of R₁. Our group has shown that errors of up to 25% in the value of R₁ can be introduced in cardiac gated dynamic scanning, particularly at higher heart rates (19). These potential errors were removed during the analysis. Thus, this represents the first report to apply this more rigorous method to patients with coronary artery disease as part of a stress protocol to calculate a myocardial perfusion reserve index.

### Estimation of myocardial blood flow and perfusion reserve index in normal subjects.

The average resting Kᵢ value in normal subjects (0.54 ml/g⁻¹/min⁻¹) is very similar to values measured by other investigators (9,10). To calculate absolute myocardial perfusion, the extraction fraction (E) needs to be known. The extraction fraction has been measured using MRI methods in canine myocardium with values of between 0.5 and 0.6 (32). In humans, Kᵢ and E have been measured using the single-injection, residue detection method by injection of technetium-99–labeled DTPA into the left coronary artery, during diagnostic coronary angiography (33). In patients (n = 12) with a normal coronary angiogram, Kᵢ was found to be 0.66 ± 0.12 ml/g⁻¹/min⁻¹ and E, 0.55 ± 0.09. Perfusion was therefore calculated as 1.21 ± 0.7 ml/g⁻¹/min⁻¹. If we assume an E value of 0.55, the myocardial blood flow estimate for the normal subjects in our study is 0.98 ± 0.38 ml/g⁻¹/min⁻¹. Estimates of myocardial blood flow in normal subjects from PET studies were 1.13 ± 0.26 ml/g⁻¹/min⁻¹ (8), 1.00 ± 0.22 ml/g⁻¹/min⁻¹ (34) and 0.98 ± 0.27 ml/g⁻¹/min⁻¹ (35). Thus, our values are in good agreement with these studies.

Perfusion reserve index in the normal subjects was estimated to be 4.21 ± 1.16, which is similar to what would be expected from the physiologic effect of adenosine on the circulation, which raises the coronary blood flow three to fivefold (1). Positron-emission tomography measurement of flow reserve is of a similar level in normal subjects (3.16 ± 1.4, n = 21) (8). In the only other study where a similar Kety model was used to calculate the ratio of Kᵢ during dipyridamole stress to rest in eight normal volunteers, the ratios ranged from 2 to 3.2 (12). This has led to the comment (31) that the E value may decrease with increasing flow, since these MPRI values were considered to be less than those measured with PET. However, data from experiments with canine myocardium suggest E stays relatively constant for a wide range of physiologic and pathologic states (11). The results from our study in normal subjects are somewhat higher than those of the previous MRI study (12), but direct comparison is difficult, since

<table>
<thead>
<tr>
<th>Percent Diameter Stenosis of Coronary Lesion</th>
<th>&lt;40% (n = 12)</th>
<th>40% to 59% (n = 21)</th>
<th>60% to 79% (n = 11)</th>
<th>≥80% (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>0.50 ± 0.24</td>
<td>0.62 ± 0.29</td>
<td>0.72 ± 0.32</td>
<td>0.45 ± 0.06</td>
</tr>
<tr>
<td>Adenosine</td>
<td>1.40 ± 0.76</td>
<td>1.20 ± 0.50</td>
<td>1.09 ± 0.52</td>
<td>0.49 ± 0.10</td>
</tr>
<tr>
<td>MPRI</td>
<td>2.80 ± 0.77</td>
<td>1.93 ± 0.38*</td>
<td>1.51 ± 0.24*</td>
<td>1.1 ± 0.28*†</td>
</tr>
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</table>

* p < 0.01 vs. <40%; †p < 0.01 vs. 40 to 59%.

MPRI = the myocardial perfusion reserve index measured with magnetic resonance imaging.

![Figure 4](image_url)
there were methodological differences in the way $R_1$ was measured. Also, no age range is given for the normal subjects in the study by Fritz-Hansen, which may have affected the results, since flow reserve is known to decrease with increasing age (36). Also one needs to note that the same degree of variability as seen in MRI measurements of MPRI is also seen with PET (8), which may reflect differences in the responsiveness of individual subjects to pharmacologic vasodilation (37).

**Myocardial perfusion reserve index measurements in patients.** Resting myocardial $K_i$ values in regions supplied by stenosed coronaries were similar on average to the normal volunteers. Furthermore, the resting $K_i$ values showed no significant decrease despite any increasing severity of stenosis (Table 2). This is consistent with previous observations, which have shown that even in patients with complete coronary occlusion but normal regional wall motion, basal flow is maintained, presumably due to a well-maintained collateral circulation (8,38).

Overall, the mean MPRI in patients was significantly lower than in normal subjects. Furthermore, the MPRI decreased with increasing percent diameter stenosis severity, and was inversely and negatively correlated. This is in agreement with a variety of animal (4) and human studies (8,39), which show a reduction of the myocardial perfusion reserve and its analogue coronary vasodilator reserve, with an increase in stenosis severity. Importantly, there was a significant difference in MPRI in lesions <40% and 40% to 59%. It is known from human myocardial perfusion reserve studies using PET that the perfusion reserve starts to decrease at 40% reduction in luminal diameter of coronary arteries (8). Our data would suggest that the MPRI as measured by MRI can distinguish between vessels that are non–flow-limiting (<40%) and what would be considered “intermediate” severity, that is, 40% to 59%. This may prove to be clinically useful, since the physiologic significance of “intermediate” lesions can be difficult to predict from the angiogram.

However, it needs to be acknowledged that the overall correlation of MPRI with severity of coronary stenoses, although similar to that seen with PET (8,39), was moderate ($r^2 = 0.65$). There are several factors that could contribute to this, in part technical, relating to the accuracy of both MRI perfusion estimation (see the following) and quantitative arteriography, and in part biological. Although an advance over visual estimation, quantitative arteriography has recognized technical limitations in accurate measurement of lesional severity. Diffuse intimal atherosclerosis proximal and distal to the stenosis can cause difficulty in defining the normal reference segment of coronary artery. However, biologic factors, such as variability in the extent of collateral circulation (22) and especially the presence of and extent of microvascular dysfunction (40), could also have a significant effect on flow reserve independent of the level of maximal stenosis severity. It is of interest that the myocardial perfusion reserve index in regions supplied by vessels with non–flow-limiting stenoses (<40% diameter stenosis) was significantly lower than in the normal volunteer subjects. This may be a reflection of impaired endothelial-dependent vasodilator capacity in patients with established atherosclerosis (41). It has been demonstrated that the presence of “significant” epicardial coronary disease is a marker of global atherosclerosis (42), so it is likely that many of these patients would have a reduced flow reserve even in coronaries with non–flow-limiting disease. However, our control subjects were younger than the patients, and since age may affect myocardial perfusion reserve (36), further studies are needed to confirm this difference.

**Study limitations.** The perfusion model used for the calculation of [Gd-DTPA] is subject to a number of assumptions. The use of $K_i$ as a perfusion parameter depends on the stability of the $E$ value during rest and stress studies, and also for ischemic and normally perfused tissue. This has not been fully established. Attempts to separate extraction and perfusion with MRI measurements is currently difficult (10), and more research is needed to validate the use of the MRI technique to assess the effect of varying conditions on $E$ and $F$ independently. There are undoubtedly some errors in calculation of the input function. This is because the relaxation times of blood and myocardium before the contrast injection are different. With the inversion time of 300 ms, myocardial $R_1$ will be reliably measured, since at this time the longitudinal magnetization would just be crossing the null point, which coincides with the central phase encoding line of k space (this determines tissue contrast), and so the resultant change in signal intensity from the Gd-DTPA injection can be used to estimate the $R_1$ value. However, since blood in the LV cavity relaxes more slowly, the central phase encoding line of k space occurs before null point has occurred, resulting in slight inaccuracies in the precontrast $R_1$ value. It is not possible to measure the input function with a differing TI, since it is measured at the same time as myocardial $R_1$. The relaxation of myocardium after Gd-DTPA injection is also assumed to be the same in blood and myocardium, and any changes of the relaxivity of Gd-DTPA in myocardium would be very difficult to measure in vivo in humans. Finally, we have not validated this technique against a gold standard of perfusion measurement, and further studies, particularly using PET and MRI in direct comparison, are needed.

**Conclusions.** We have demonstrated the feasibility of performing myocardial perfusion estimation and perfusion reserve index measurement in human subjects, using contrast-enhanced magnetic resonance imaging. The technique produces results that are concordant with measurements reported using other techniques, particularly PET. The measurement of perfusion reserve index is inversely correlated with stenosis severity, and gives some indication of the functional severity of a lesion as the stenosis severity increases. In view of the noninvasive and nontoxic nature of
MRI, in addition to the fact that it has superior spatial resolution to PET, it may have considerable clinical importance in the future. However, further research and validation of the tracer kinetic model are needed to develop a robust clinical protocol for widespread application.

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