Regional myocardial perfusion reserve determined using myocardial perfusion magnetic resonance imaging showed a direct correlation with coronary flow velocity reserve by Doppler flow wire

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Aims
Quantitative analysis of rest–stress myocardial perfusion magnetic resonance imaging (MRI) can provide assessments of regional myocardial perfusion reserve (MPR). The purpose of this study was to compare regional MPR determined by myocardial perfusion MRI with coronary flow reserve (CFR) by intracoronary Doppler flow wire.

Methods and results
Twenty patients with suspected coronary artery disease (CAD) were studied. Average peak velocity was measured by Doppler flow wire in the resting state and during adenosine triphosphate (ATP) stress in 36 coronary arteries. CFR measurements for each patient were performed in the culprit and one non-culprit non-stenotic artery. First-pass, contrast-enhanced myocardial perfusion MR images were obtained in the resting state and during ATP stress within the week before the Doppler wire procedure. Regional myocardial blood flow (MBF) was quantified in 16 myocardial segments by analysing arterial input and myocardial output using a Patlak plot method. MPR was calculated as stress MBF divided by rest MBF. CFR measured by Doppler flow wire was compared with MPR in the myocardial segments corresponding to vessel territories. The average MPR measured by perfusion MRI was 1.77 ± 0.62 for the culprit arteries and 3.45 ± 0.78 for the non-culprit arteries, respectively (P < 0.001). The averaged CFR by Doppler flow wire was 1.72 ± 0.44 in the culprit arteries and 3.14 ± 0.74 in the non-culprit arteries, respectively (P < 0.001). For both culprit and non-culprit vessel groups, significant direct correlations were observed between MR assessments of MPR and Doppler assessments of CFR (culprit artery: $R = 0.87$, Non-culprit artery: $R = 0.86$)

On Bland–Altman analysis, the mean differences between MPR determined by myocardial perfusion MRI and CFR measured by Doppler wire were 0.05 in culprit arteries (95% limit of agreement: −0.65 to 0.56) and 0.36 in non-culprit arteries (95% limit of agreement: −1.24 to 0.44). The sensitivity and specificity of MR measurement of MPR for predicting physiologically significant reduction of Doppler CFR (<2) was 88% (95% CI 61.7–98.5) and 90% (95% CI 68.3–98.8), respectively.

Conclusion
The current results using Doppler flow wire as a reference method demonstrated that quantitative analysis of stress–rest myocardial perfusion MRI can provide a non-invasive assessment of reduced MPR in patients with CAD.

Keywords
Cardiac magnetic resonance • Myocardial blood flow • Myocardial perfusion reserve • Doppler flow wire • Coronary flow reserve

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Introduction

Catheter coronary angiography has been used to evaluate coronary artery disease (CAD) and is considered to be the gold standard for determining the severity of coronary artery stenosis. However, anatomic evaluation of the degree of stenosis does not always adequately determine the functional significance of a stenosis. Previous studies using intracoronary Doppler flow wire demonstrated that assessment of coronary flow velocity reserve (CFR: the ratio of hyperaemic blood flow to resting blood flow) is useful in determining the functional significance of stenosis in the epicardial coronary arteries and in evaluating microvascular disease. However, intracoronary Doppler flow wire is invasive and only available during cardiac catheterization. Stress myocardial perfusion scintigraphy has been widely used, mainly for qualitative assessment of altered regional myocardial perfusion in patients with CAD.

Recently, first-pass contrast-enhanced myocardial perfusion magnetic resonance imaging (MRI) has emerged as a method that can measure the presence and extent of hypoperfusion caused by flow-limiting CAD. Rest–stress perfusion MR images have been evaluated with semi-quantitative approaches, such as an upslope analysis of myocardial time–intensity curve, or with a visual assessment. Quantitative evaluation of myocardial blood flow (MBF) and myocardial perfusion reserve (MPR) with myocardial perfusion MRI may provide a more objective evaluation of myocardial ischaemia and microvascular disease.

The purpose of this study was to evaluate the relationship between regional MPR determined by myocardial perfusion MRI and CFR measured by intracoronary Doppler flow wire, the gold standard for assessing CFR, and to determine if quantitative analysis of MPR by stress–rest myocardial perfusion MRI can provide a non-invasive prediction of reduced CFR in patients with CAD.

Methods

Study subjects

We studied 108 patients with known or suspected CAD who underwent cardiac magnetic resonance study that include both stress–rest perfusion MRI and late gadolinium enhanced (LGE) MRI. Inclusion criteria were percutaneous coronary intervention (PCI) candidate, cardiac MRI was performed within the week before coronary angiography, and single-vessel disease on coronary angiography. Patients with histories of myocardial infarction (MI), acute MI, unstable angina, previous coronary artery bypass grafting, irregular heart rhythm (atrial fibrillation, frequent premature atrial complexes, etc.), pacemaker, intracranial clip, or contraindication to receiving adenosine triphosphate (ATP) were excluded from this study. The study protocol was approved by the institutional ethical committee, and written informed consent was obtained from all subjects. There were no patients who refused to give their consent. Eventually, 20 patients (18 men and two women; mean age, 68 ± 9 years) who met our study criteria were enrolled (Table 1). No PCI was performed between myocardial perfusion MRI and intracoronary Doppler flow measurements. We did not observe visible collateral vessels on coronary angiography in these 20 subjects evaluated in this study. No clinical modification or therapy change occurred between the myocardial perfusion MRI and the intracoronary Doppler study. The severity of stenosis of the coronary artery on the coronary angiography was expressed as percent diameter reduction using the classifications of the American Heart Association (AHA).

Intracoronary Doppler wire

Coronary flow velocity by intracoronary Doppler wire was measured in the resting state and during ATP stress in 20 patients. In each patient, intracoronary Doppler measurements were taken in the culprit arteries and non-culprit arteries without significant stenoses on the coronary angiography. Doppler flow measurements failed in two culprit and two non-culprit arteries. Consequently, CFR was evaluated in 36 coronary arteries (left anterior descending artery: LAD 16; left circumflex coronary artery: LCX 11; and right coronary artery: RCA 9).

A 0.014-in. intracoronary Doppler flow wire (Flowire Cardiometrics Inc., Mountain View, CA, USA) was used to measure coronary flow velocity. The procedure using the intracoronary Doppler flow wire has been described previously. Briefly, an intracoronary Doppler flow wire was passed through the catheter to a position distal to the stenosis. Intracoronary flow velocity measurements were then performed in the resting state and during ATP (160 μg/kg/min) stress with monitoring of symptoms, blood pressure (BP), heart rate (HR) and electrocardiography (ECG) (Figure 1). Pharmacological stress was achieved by injecting ATP (160 μg/kg/min) in the left antecubital vein for 4 min. The ratio of hyperaemic average peak velocity to resting average peak velocity...
resting average peak velocity was calculated as the CFR. CFR was
determined in an average of stable consecutive three beats at rest
and during maximal vasodilatation induced by ATP infusion. In this
study, a physiologically significant reduction in the CFR was defined
as CFR of 2.0 or less, based on previous results. We also
used the cut-off value of 3.0, in order to confirm that the value of
MPR measurement by MRI for predicting altered CFR is not under-
mined by the different setting of cut-off value.

Magnetic resonance imaging
First-pass contrast-enhanced myocardial perfusion MR images during
ATP stress and in the resting state were obtained using a 1.5 T MR
imager (Signa CV/i, 1.5T, GE Medical system, Waukesha, WI, USA)
and four-element cardiac receiver coils. A four-lead electrocardiogram
(VCG) was used for cardiac gating. Initial scout images were obtained
in three orthogonal directions to determine the position of the heart
and diaphragm. Then trans-axial cine MR images and vertical long-axis
cine MR images of the left ventricle (LV) were acquired. Myocardial
perfusion MR images were acquired with steady-state perfusion MR
sequence with non-slice-selective preparation (five to six short-axis
imaging slices, repetition time of 3.0 ms, echo time of 1.2 ms, flip
angle of 45°, time between saturation preparation pulse and centre
of k-space acquisition of 180 ms, field of view of 36 × 32 cm, acqui-
sition matrices of 128 × 96, section thickness of 8 mm). For both
stress and rest perfusion MRI, gadolinium contrast medium (Gadopen-
tetate dimeglumine, Magnevist, Schering, Berlin, Germany) was injected
into the right antecubital vein at a dose of 0.05 mmol/kg and a flow rate
of 4 mL/s, followed by a 20-mL saline flush. Dynamic MR images were
acquired for 1 min. The patients were instructed to begin holding their
breath at the start of the image acquisition and to maintain the breath
hold as long as possible. In order to correct for the nonlinear relation-
ship between the blood concentration of MR contrast medium and MR
signal intensity during first-pass, the dual bolus method was employed
by injecting a bolus of contrast medium diluted to 10% with saline
(0.005 mmol/kg) via an antecubital vein at a rate of 4 mL/s, followed
by a 20-mL saline flush prior to perfusion MRI that does not cause sat-
uration of the blood signal.

Pharmacological stress was achieved by injecting ATP (160 µg/kg/min)
in the left antecubital vein for 4 min. Symptoms, BP, HR, and ECG
were monitored while the patients were in the magnet, and any serious
adverse reaction caused by the pharmacological stress was recorded
throughout MRI examination. Three minutes after starting ATP adminis-
tration, the acquisition of stress myocardial perfusion MR images
were initiated and ATP was continuously injected during the acquisition
of stress perfusion MRI. Rest myocardial perfusion MRI was acquired at
least 10 min after finishing stress myocardial perfusion MRI.

Assessment of regional myocardial blood
flow and myocardial perfusion reserve
Rest--stress first-pass myocardial perfusion MR images were analysed
using an image analysis workstaton (Virtual Place, Aze, Tokyo, Japan).
 Epicardial and endocardial contours of the LV myocardium were
manually determined to obtain myocardial time–intensity curves, and the region of interest was placed in the LV chamber to generate blood time–intensity curve (Figure 2). The LV myocardium was divided into 16 segments, consisting of six basal segments, six mid-ventricular segments, and four apical segments based on an AHA 17-segment model excluding the apical segment. Signal saturation of the LV blood signal was corrected using a dual bolus method. Patlak plot analysis was performed using a blood time–intensity curve as an input function and a regional myocardial time–intensity curve as an output function. The Patlak plot method is based on a two-compartment model and describes the $K_1$ of one-way transfer of contrast material from the LV blood to the myocardium. The mass balance of Gd-DTPA is described by the following first-order differential equation:

$$\frac{dC_{myo}(t)}{dt} = K_1 C_a(t) - k_2 C_{myo}(t)$$

where $C_{myo}(t)$ and $C_a(t)$ are the relative concentrations of Gd-DTPA in the myocardium and LV blood. In the early phase after the arrival of contrast agent in the myocardium, it is assumed that $C_{myo}(t)$ is negligibly small compared with $C_a(t)$. Then, the solution to Equation (1) is:

$$\frac{dC_{myo}(t)}{dt} = K_1 C_a(t).$$

The plot of $Y(t) = C_{myo}(t)$ against $X(t) = \int_0^t C_a(t)dt$ yields a straight line with a slope of $K_1$ (Patlak plot):

$$K_1 = \frac{C_{myo}(T)}{\int_0^T C_a(t)dt}.$$  

This linear relationship is no longer maintained after the amount of Gd-DTPA transferred from myocardial tissue back to the blood pool increases. The range of this linear relationship was automatically optimized using an algorithm that maximizes the correlation coefficient of the smallest square fitting. After calculating perfusion parameter $K_1$ in 16 myocardial segments, MBF was calculated as $K_1$ divided by the extraction fraction of Gd-DTPA, using the extraction fraction values in the literatures. MPR was determined as stress MBF divided by rest MBF.

**Figure 2** Quantitative analysis of myocardial perfusion magnetic resonance images using the Patlak plot method. Epicardial and endocardial contours of the left ventricular (LV) myocardium were manually determined to generate myocardial time–intensity curves. A region of interest was placed in the LV chamber to generate a blood time–intensity curve. Patlak plot analysis was performed using blood input function and myocardial output functions.
The coronary artery territories were decided individually based on the coronary angiogram. The location of the stenosis defined by coronary angiogram was used to guide the selection of MPR values from specific myocardial slices corresponding to the stenosis location (proximal, middle, or distal). This allowed a more stenosis-specific comparison among MPR assessments and some patients in this study had a non-balanced type of coronary artery. Thus, in an ostial stenosis, we considered MPR values from three slices, whereas for stenosis located at proximal and middle areas, only MPR values from the middle and apical slices were averaged for comparison.23

Statistical analysis
All data were expressed as mean ± SD and percentage. Group data were analysed using the two-sided paired or unpaired Student’s t test as appropriate. Linear regression analysis was used to compare the MPR by stress perfusion MRI and CFR by Doppler wire in culprit artery and non-culprit artery groups. Bland–Altman analysis was also used to evaluate the agreement between the two methods, and the limits of the agreement (mean ± 1.96 times the SD of the differences) were determined in culprit artery group and non-culprit artery group. A difference with a P-value <0.05 was considered to be statistically significant. If the P-value is <0.001, P-value was expressed P <0.001.

Results
Haemodynamic data
Systolic BP, diastolic BP, and HR in the resting state and during stress were summarized in Table 2. There were no significant differences in HR, systolic BP, and diastolic BP at rest or during ATP stress between MRI and Doppler flow wire studies.

The mean value of coronary flow reserve and myocardial perfusion reserve
Figure 3 is a representative image of the regional MPR map in a subject without significant CAD and in a patient with stress-induced ischaemia in the anteroseptal wall. The rest MBF quantified by rest perfusion MRI was 0.87 ± 0.17 mL/min/g in the territories corresponding to the culprit arteries, and 0.89 ± 0.19 mL/min/g in those corresponding to the non-culprit arteries (P = 0.98). The average MPR measured by MRI was 1.77 ± 0.62 for the culprit arteries and 3.45 ± 0.78 for the non-culprit arteries, respectively (P < 0.001). The averaged CFR by Doppler flow wire was 1.72 ± 0.44 in the culprit arteries and 3.14 ± 0.74 in the non-culprit arteries, respectively (P < 0.001).

Table 2 Haemodynamic parameters recorded at rest and during ATP stress

<table>
<thead>
<tr>
<th></th>
<th>Rest–stress perfusion MRI</th>
<th>Intracoronary Doppler study</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Heart rate (per min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>68 ± 7</td>
<td>68 ± 10</td>
<td>0.88</td>
</tr>
<tr>
<td>ATP stress</td>
<td>78 ± 7</td>
<td>79 ± 8</td>
<td>0.73</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>145 ± 11</td>
<td>148 ± 18</td>
<td>0.53</td>
</tr>
<tr>
<td>ATP stress</td>
<td>142 ± 10</td>
<td>141 ± 18</td>
<td>0.85</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>67 ± 8</td>
<td>72 ± 8</td>
<td>0.11</td>
</tr>
<tr>
<td>ATP stress</td>
<td>69 ± 9</td>
<td>68 ± 7</td>
<td>0.75</td>
</tr>
</tbody>
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Values are mean ± SD. ATP, adenosine triphosphate; MRI, magnetic resonance imaging.

The accuracy of myocardial perfusion reserve measurement by magnetic resonance imaging in predicting reduced coronary flow reserve by intracoronary Doppler flow wire
Reduced MPR (r < 0.20) assessed by MRI had a sensitivity of 87.5% (95% CI 61.7–98.5), a specificity of 90.0% (95% CI 68.3–98.8), a positive predictive value (PPV) of 87.5% (95% CI 61.7–98.5), and a negative predictive value (NPV) of 90.0% (95% CI 68.3–98.8) in predicting a reduction of CFR (<2.0) by Doppler flow wire. Reduced MPR (r < 3.0) had a sensitivity of 80.8% (95% CI 60.7–93.5), a specificity of 100% (95% CI 69.2–100), a PPV of 100% (95% CI 83.9–100), and NPV of 66.7% (95% CI 38.4–88.2) in predicting reduction of CFR (<3.0).

Discussion
In the present study, we found a significant correlation between regional MPR determined by quantitative analysis of myocardial perfusion MRI and CFR measured by Doppler flow wire in patients with CAD. In addition, a Physiologically significant reduction of...
CFR (<2) by intracoronary Doppler wire can be predicted with high sensitivity (88%) and specificity (90%) using non-invasive MR assessment of MPR. While Doppler flow wire assessment of CFR is useful in determining the functional significance of coronary artery stenosis in patients with CAD, this approach is invasive.\(^1\) The high sensitivity and specificity observed in this study indicates that quantitative analysis of MPR can be used as a non-invasive method for assessing altered CFR in patients with CAD.
Quantitative analysis of myocardial perfusion MRI was performed by analysing arterial input and myocardial output functions in our study. Previous studies demonstrated that quantitative evaluation of MPR with myocardial perfusion MRI provided a more objective evaluation of myocardial ischaemia and microvascular disease. The ability of quantitative perfusion MR imaging to assess haemodynamic significance of CAD has been studied by several investigators. Costa et al. determined the relation between MPR and fractional flow reserve (FFR) in patients with suspected CAD by quantitative analysis of perfusion MRI. They found that reduced MPR ≤ 2.04 has a sensitivity of 93% and a specificity of 57% in predicting a coronary segment with FFR ≤ 0.75. In a study reported by Futamatsu et al., they found a significant correlation between MPR and FFR. However, the correlation coefficient between MPR and FFR was lower (r = 0.41) than the value between MPR and CFR in our current study. MPR and CFR indicate the augmentation of coronary blood flow by vasodilator stress and are similarly influenced by microcirculation status, while FFR is closely related to the haemodynamic significance of narrowing in the epicardial coronary arteries and is less sensitive to microcirculation. The relation between myocardial perfusion reserve index (MPRI) by perfusion MRI and CFR by Doppler flow measurement was reported in a recent study by Barmeyer et al. They used a semi-quantitative upslope method for determining MPRI and found a linear correlation between MPRI and CFR with an r value of 0.44. Compared with Marmeyer’s report, we used a quantitative analysis of myocardial perfusion to calculate MPR and determined the relation between MPR and CFR.

There are several different approaches for detecting the reduction of perfusion reserve or flow reserve in coronary circulation, including intracoronary Doppler flow wire, positron emission tomography (PET), single photon emission computed tomography (SPECT), and myocardial contrast echo (MCE). Doppler flow wire allows for direct measurement of CFR. As previously mentioned, this method is invasive and is only available during catheterization of the coronary artery. PET with myocardial perfusion tracers such as oxygen 15 water, NH3, and Rubidium has been recognized as the most established method for the quantitative assessment of regional MBF. However, myocardial perfusion PET is not readily available for routine clinical assessments of CAD patients. In contrast, myocardial perfusion MRI can be performed in many hospitals with MR imagers, and the cost of an MR study is lower than that of myocardial perfusion PET. MCE is another approach that has recently emerged as a method that can provide quantitative assessment of MBF. A volumetric model of ultrasound contrast agent kinetics allows the quantification of MBF, which was in good agreement with CFR by intracoronary Doppler wire in patients with CAD. The Ultrasound imager for the MCE procedure is widely available in cardiology departments and can be performed at a lower cost compared with other modalities. However, the MCE procedure is operator-dependent, and quantitative analysis of MBF and MPR is typically performed using apical four-chamber and two-chamber images, because MBF and MPR quantification on the short-axis view is often difficult due to poor image quality from the parasternal short-axis views. When compared with MCE, myocardial perfusion MRI is less operator-dependent and images of the LV can be obtained on the short axis, because the MRI signal is not influenced by lung or bone.

We used ATP instead of adenosine because adenosine was not approved for clinical use in our country when we started the current study. Adenosine 5’-triphosphate (ATP) is a precursor of adenosine, and intravenous ATP and adenosine have the similar...
vasodilatory effects. While the augmentations of coronary flow by ATP and adenosine may not be identical, we used ATP for both stress myocardial perfusion MRI and Doppler flow wire study. Therefore, the relationship between MPR measured by perfusion MRI and CFR by intracoronary Doppler flow wire can be adequately assessed using ATP.

Clinical implications

Evaluation of the functional severity of flow-limiting CAD is important in making appropriate therapeutic decisions, including coronary angioplasty in patients with CAD. This study was designed to determine if quantitative analysis of MPR by stress–rest myocardial perfusion MRI could provide a non-invasive prediction of reduced CFR in patients with CAD. Reduced MPR (<2.0) on MRI had a sensitivity of 88%, a specificity of 90%, a PPV of 88%, and a NPV of 90% in predicting a significant reduction of CFR. Quantitative evaluation of MPR using myocardial perfusion MRI may provide objective evaluation of flow-limiting stenosis in coronary artery and microvascular disease.

The quantification of MPR with stress–rest MRI may be useful in assessing the effectiveness of drug therapy and other therapeutic procedures. In addition, since reduced MPR has been shown to correlate with long-term risk of CAD, MR assessment of MPR may provide non-invasive risk stratification of the patients.42

Study limitations

There are several limitations to be noted in our study. First, the number of patients in this study was limited. Thus, the importance of MPR assessments with stress–rest perfusion MRI in patients with suspected CAD needs to be validated in future studies with a larger number of patients. However, CFR measurement using intracoronary Doppler wire is an invasive procedure and it is difficult to perform Doppler flow measurements in a large number of subjects. The consistencies observed between MPR by MRI and CFR by Doppler wire in our study would be of value for the future studies using quantitative myocardial perfusion MRI. Secondly, Doppler CFR was calculated as the ratio of baseline to hyperaemic coronary blood flow velocities instead of the ratio of blood flow volume. However, the possibility remains that the lumen diameter of the coronary artery at the site of the Doppler measurements increased during intravenous ATP infusion. One previous study reported that the CFR measured by an intracoronary Doppler correlated strongly with the regional MPR by PET.43 In addition, CFR by an intracoronary Doppler was influenced by both epicardial coronary arterial stenoses and microvascular disease, and is dependent on heart rate. Assessment of CFR cannot differentiate flow-limiting stenosis in the epicardial coronary artery and microvascular disease. Consequently, FFR is now widely used for therapeutic decision making in patients with coronary arterial stenoses. Although we have demonstrated an excellent correlation between MPR and CFR in this study, MPR by stress perfusion MRI has the same intrinsic limitations as CFR. Thirdly, in this study, MBF was calculated as $K_r$ divided by the extraction fraction of Gd-DTPA, by using the extraction fraction values in the literatures. Further study is needed to investigate the relationship between MBF and the extraction fraction. Fourthly, while the mean differences between MPR and CFR were small in the culprit artery and non-culprit artery groups, the 95% limits of agreement between MPR and CFR by the Bland–Altman analysis was not narrow enough. Therefore, MPR value calculated by stress–rest perfusion MRI may not be directly used interchangeably with CFR value by Doppler wire. Finally, in this study, patients continued to take their usual medications when MR and Doppler studies were performed. Therefore, the MPR and CFR could have been influenced by these medications. Since, the major objective of this study was to determine the correlation between the MR MPR and Doppler CFR, continuous medication during the study period does not invalidate our findings.

Conclusions

Quantitative analysis of stress–rest myocardial perfusion MRI can provide non-invasive detection of reduced MPR in patients with CAD. The high sensitivity and specificity of MRI-determined MPR in predicting a significant reduction of Doppler CFR indicated that MR measurement of MPR can be used as a non-invasive method to Doppler flow wire in assessing reduced CFR in patients with CAD.

Conflict of interest: none declared.

References


