Background: Fractional flow reserve (FFR) measured on catheterization is now widely used for the diagnosis of functional myocardial ischemia in patients with coronary artery disease (CAD). FFR, however, is invasive and carries potential procedural complications. Therefore, the aim of this study was to compare the diagnostic capability in functionally significant stenosis identified on FFR, between cardiac magnetic resonance myocardial perfusion imaging (CMR-MPI), single-photon emission computed tomography MPI (SPECT-MPI), and dobutamine stress echocardiography (DSE) in patients with CAD.

Methods and Results: A total of 25 patients who had at least 1 angiographic stenosis ≥50% on coronary angiography was studied. CMR-MPI, SPECT-MPI and DSE were done before FFR measurement. FFR was measured in all 3 major epicardial coronary arteries. Out of 71 vascular territories excluding 4 territories due to inadequate imaging, 29 (41%) had FFR <0.80. The sensitivity of CMR-MPI was significantly higher than that of SPECT-MPI and DSE (P=0.02 and P=0.001, respectively). The area under the receiver operating characteristic curve (AUC) for CMR-MPI (AUC, 0.92) was significantly greater than for SPECT-MPI (AUC, 0.73; P=0.006) and DSE (AUC, 0.69; P<0.001).

Conclusions: CMR-MPI performed well in the detection of functionally significant stenosis defined according to FFR, and had the highest diagnostic sensitivity among the 3 modalities tested in patients with CAD. (Circ J 2014; 78: 2468–2476)

Key Words: Cardiac magnetic resonance; Dobutamine stress echocardiography; Fractional flow reserve; Ischemia; Single-photon emission computed tomography

Imaging

Cardiac Magnetic Resonance Performs Better in the Detection of Functionally Significant Coronary Artery Stenosis Compared to Single-Photon Emission Computed Tomography and Dobutamine Stress Echocardiography

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Imaging
2 (FAME 2) trial found that FFR-guided PCI plus OMT could improve outcome as compared to OMT alone. Therefore, FFR has emerged as an attractive diagnostic tool for assessing myocardial ischemia and guiding PCI in patients with coronary artery disease (CAD), and is widely used in many cardiac intervention laboratories. FFR, however, is invasive and is associated with potential procedural complications. Cardiac magnetic resonance (CMR) myocardial perfusion imaging (MPI), single-photon emission computed tomography MPI (SPECT-MPI), and dobutamine stress echocardiography (DSE) are non-invasive imaging modalities that are also widely used to assess the presence and extent of myocardial ischemia and determine the need for PCI. There are often discrepancies, however, in the assessment of the presence or absence and location of myocardial ischemia among these modalities in clinical practice. Previous studies have determined and compared the diagnostic performance of these modalities for the detection of significant CAD, with CAG as the reference standard. In recent years, several studies have evaluated the individual diagnostic performance of CMR-MPI, SPECT-MPI, and DSE for the detection of significant CAD using FFR as the reference standard. To our knowledge, however, no systematic comparison of these 3 imaging modalities has been done in the same patient. We thus compared the diagnostic performance of CMR-MPI, SPECT-MPI, and DSE for guiding PCI in CAD patients with functional ischemic reference values based on FFR.

Methods

Subjects and Study Design
This was a prospective, single-center, comparative diagnostic accuracy study at Hokkaido University Hospital, Japan. From July 2011 to July 2013, 25 patients (a total of 75 vessel territories) with at least 1 angiographic stenosis ≥50% on conventional CAG who were deemed suitable to undergo PCI were recruited. All patients underwent CMR, SPECT, and DSE before FFR measurement. Exclusion criteria were unstable angina pectoris, significant left main coronary artery stenosis, prior Q-wave myocardial infarction, coronary artery bypass grafting, critical aortic stenosis, congenital heart disease, CMR or adenosine infusion, and renal insufficiency (glomerular filtration rate ≤30 ml·min⁻¹·1.73 m⁻²). The study was approved by the institutional ethics committee and written informed consent was obtained from all patients.

Preparation
Patients were told to refrain from having caffeine-containing beverages, and taking nitrates and calcium channel blockers for at least 24 h, and β-blockers for 48 h before stress imaging and FFR.

CAG and FFR Measurement
All patients underwent CAG via the femoral approach. A 26-Fr guiding catheter was used. At least 2 orthogonal views were obtained after 1 mg i.c. isosorbide dinitrate infusion. The projection showing the most severe narrowing was used for quantitative coronary angiography (QCA; CAAS 5.9, Pie Medical, Maastricht, The Netherlands). Using the guiding catheter as a scaling device, measurements of the percentage diameter stenosis were calculated. Stenosis ≥50% of the luminal diameter of QCA was considered to be significant. Severity was graded as intermediate (50–70%) or severe (≥70%). FFR was measured using a 0.014-in. coronary sensor-tipped angioplasty guidewire (Certus; St. Jude Medical Systems, Uppsala, Sweden) in all 3 major epicardial coronary arteries. FFR was defined as the ratio of mean distal coronary pressure and mean aortic pressure measured under maximum coronary hyperemia, induced by 160µg·kg⁻¹·min⁻¹ continuous i.v. adenosine triphosphate (ATP). The stenosis was considered functionally significant for FFR <0.80.

CMR
CMR acquisition was performed using a 3-T whole-body scanner (Achieva Tx; Philips Medical Systems, Best, The Netherlands) with a 32-channel phased-array receiver torso-cardiac coil. The magnetic resonance imaging (MRI) perfusion sequence was performed with an electrocardiography (ECG)-triggered and breath-hold technique at the 3 short-axis planes. Gadolinium contrast medium was given at 0.03 mmol/kg with a flow rate of 4.0 ml/s, followed by a 20-ml saline flush at the same flow rate. MRI was performed with the turbo field-echo technique with saturation recovery (SR) magnetization preparation; repetition time/echo time 4.0/1.9 ms; flip angle, 18°; number of slices, 4; slice thickness, 8 mm; slice gap, 10 mm; field of view, 380×380 mm; matrix, 224×224; SR delay time, 200 ms; and sensitivity encoding parallel imaging (SENSE) factor, 2. Dynamic MRI was obtained for left ventricular short axis slices. The scanning was repeated continuously every 2 cardiac cycles. The subjects were instructed to hold their breath as long as possible and to breathe shallowly thereafter. The perfusion sequence was started concurrently with the injection of gadolinium contrast medium. For the stress state, dynamic MRI perfusion was performed 5 min after ATP (160µg·kg⁻¹·min⁻¹).

CMR was evaluated independently by 2 experienced observers. The observers had no knowledge of the patient’s CCA and FFR results. The stress and rest perfusion scans were viewed simultaneously, and areas of perfusion defect were assigned to coronary artery territory using the 16 segments of the 17-segment American Heart Association (AHA) model adjusted for arterial dominance (excluding the apical cap segment 17). Segments 1, 2, 7, 8, 13, 14 were assigned to the left anterior descending coronary artery (LAD) territory. Segments 3, 4, 9, 10, and 15 were generally assigned to the right coronary artery (RCA), and segments 5, 6, 11, 12, and 16 were assigned to the left circumflex artery (LCX). In patients with left coronary artery dominance the inferior and infero-lateral segments were assigned to the LCX territory, and all 4 apical segments were assigned to the LAD territory. In patients with RCA dominance, the inferior, infero-lateral, and apical inferior segments were assigned to the RCA territory, with the remaining 3 apical segments assigned to the LAD territory. CMR-MPI was considered abnormal if the contrast signal intensity was reduced over ≥3 consecutive image frames in comparison to non-ischemic myocardial segments, or an endocardial to epicardial perfusion gradient within a segment was present and the perfusion defect was not located within scar tissue as determined on corresponding late gadolinium-enhanced (LGE) imaging. The observers evaluated the presence or absence of myocardial ischemia in individual vessel territories. The final decision was reached via consensus.

For semi-quantitative visual interpretation, perfusion defect in each of the 16 segments was graded on a 4-point scale ranging from 0 to 3 (0, normal; 1, inconclusive; 2, subendocardial defect; 3, transmural defect). The regional perfusion score (PSr) was then calculated as the sum of individual segmental scores for each vessel territory and used for receiver operating characteristic (ROC) analysis.
SPECT
SPECT was performed using a 1-day stress-rest protocol. Pharmacological stress was induced by infusion of ATP at a rate of 160 µg·kg⁻¹·min⁻¹ and the dose was increased to 10, 20, 30 and a peak of 40 µg·kg⁻¹·min⁻¹ for at least 3 min at each stage. In patients not achieving 85% of the age-predicted maximum heart rate, atropine was given i.v. with the continuation of dobutamine, starting with 0.25 mg and repeated up to a maximum of 1.0 mg. The criteria for stopping dobutamine infusion included achievement of age-predicted submaximum heart rate (heart rate ≥[220–age in years]×0.85), newly developed wall motion abnormalities (WMA), ST segment depression or elevation >0.2 mV on ECG, severe chest pain, systolic blood pressure >220 mmHg, significant ventricular or supraventricular arrhythmias, or serious side-effects of dobutamine.

Left ventricular long- and short-axis views from the parasternal window, and left ventricular long-axis as well as 4- and 2-chamber views from the apical window were acquired for comparison during the 4 stages of stress test. Images were evaluated by 2 experienced observers. The observers had no knowledge of the patient’s QCA and FFR results. The presence or absence of myocardial ischemia in individual vessel territories. The final decision was reached via consensus. For semi-quantitative visual interpretation, WMA in each of the 16 segments was graded on a 4-point scale ranging from 0 to 4 (0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; 4, absent radiotracer distribution).

Segmental scores were summed for each vessel territory, resulting in PSr under stress (regional summed stress score; SSSr) and rest (regional summed rest score; SRSr) conditions. The difference of SSSr and SRSr was defined as the regional summed difference score (SDSr). In the present study, we excluded patients with previous Q-wave myocardial infarction. SDSr was a suitable predictor of pathological FFR (<0.75) in patients without prior myocardial infarction. In fact, in ROC analysis, the area under the curve (AUC) for SDSr (AUC, 0.733) was slightly larger than for SSSr (AUC, 0.725). Therefore, we used SDSr for ROC analysis (Figure S1).

DSE
Dobutamine was given i.v. at an initial dose of 5 µg·kg⁻¹·min⁻¹ and the dose was increased to 10, 20, 30 and a peak of 40 µg·kg⁻¹·min⁻¹ for at least 3 min at each stage. In patients not achieving 85% of the age-predicted maximum heart rate, atropine was given i.v. with the continuation of dobutamine, starting with 0.25 mg and repeated up to a maximum of 1.0 mg. The criteria for stopping dobutamine infusion included achievement of age-predicted submaximum heart rate (heart rate ≥[220–age in years]×0.85), newly developed wall motion abnormalities (WMA), ST segment depression or elevation >0.2 mV on ECG, severe chest pain, systolic blood pressure >220 mmHg, significant ventricular or supraventricular arrhythmias, or serious side-effects of dobutamine.

Table 1: Patient Characteristics (n=25)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.5±7.2</td>
</tr>
<tr>
<td>Male</td>
<td>14 (56.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.5±3.4</td>
</tr>
<tr>
<td>Smoking</td>
<td>10 (40.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (64.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15 (60.0)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>19 (76.0)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td>Familial history of IHD</td>
<td>12 (48.0)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>6 (24.0)</td>
</tr>
</tbody>
</table>

Angina classification
- Asymptomatic: 4 (16.0)
- CCS class I: 11 (44.0)
- CCS class II: 6 (24.0)
- CCS class III: 4 (16.0)

Medication
- Aspirin: 20 (80.0)
- β-blocker: 10 (40.0)
- Statin: 19 (76.0)
- Calcium channel blocker: 11 (44.0)
- Nitrate: 6 (24.0)
- ACEI: 3 (12.0)
- ARB: 8 (32.0)

Data given as mean±SD or n (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CCS, Canadian Cardiovascular Society; IHD, ischemic heart disease.
Non-Invasive Test for Functionally Significant CAD

Angiographic, FFR, CMR, SPECT, and DSE data are summarized in Table 2. Forty-one vessel territories (58%) had angiographic stenosis ≥50%. FFR measurement was performed in 71 vessel territories, excluding 4 territories due to inadequate imaging. One coronary artery was totally occluded. FFR=0.50 was allocated to this vessel. The overall mean diameter stenosis was 53 ± 21% and was significantly different between the 2 groups for FFR ≥ 0.8 and <0.8 (71.3 ± 10.9% and 38.4 ± 16.1%, P<0.001). FFR ranged from 0.5 to 1.0, with a mean FFR of 0.84 ± 0.15. In 29/71 territories (41%), FFR was significantly reduced (FFR <0.80), whereas 42 territories (59%) had FFR >0.80. Among a total of 25 patients, 14 (56%) had angiographic multi-vessel disease (MVD) and 11 (44%) had angiographic single-vessel disease (SVD). Meanwhile, 7 (28%) had functional MVD based on FFR criteria, 13 (52%) had functional SVD and 5 (20%) had no functional disease. CMR-PSr measured on CMR-MPI was significantly higher in the vessel version 9.3 (SAS Institute).

Results

A total of 56% of the patients were male, and mean age was 67.5 ± 7.2 years (Table 1). Twenty-one patients (84%) had stable angina, while the remaining 4 patients (16%) had no typical angina and were scheduled for CAG for clinical reasons. Sixteen patients (64%) had hypertension, 15 (60%) had diabetes mellitus and 19 (76%) had dyslipidemia. Twenty patients (80%) received aspirin, 19 (76%) received statins and 10 (40%) received β-blockers.

No patient experienced life-threatening or serious adverse reaction during pharmacologic stress. DSE was not done in 1 patient due to cerebral aneurysm, which was contraindicated for dobutamine stress. In 3 patients, the age-predicted sub-maximum heart rate could not be achieved due to severe chest pain and newly developed WMA in DSE.

CAG and FFR Measurement

Angiographic, FFR, and DSE data are summarized in Table 2. Forty-one vessel territories (58%) had angiographic stenosis ≥50%. FFR measurement was performed in 71 vessel territories, excluding 4 territories due to inadequate imaging. One coronary artery was totally occluded. FFR=0.50 was allocated to this vessel. The overall mean diameter stenosis was 53±21% and was significantly different between the 2 groups for FFR ≥0.8 and <0.8 (71.3±10.9% and 38.4±16.1%, P<0.001). FFR ranged from 0.5 to 1.0, with a mean FFR of 0.84±0.15. In 29/71 territories (41%), FFR was significantly reduced (FFR <0.80), whereas 42 territories (59%) had FFR >0.80. Among a total of 25 patients, 14 (56%) had angiographic multi-vessel disease (MVD) and 11 (44%) had angiographic single-vessel disease (SVD). Meanwhile, 7 (28%) had functional MVD based on FFR criteria, 13 (52%) had functional SVD and 5 (20%) had no functional disease. CMR-PSr measured on CMR-MPI was significantly higher in the vessel version 9.3 (SAS Institute).
SPECT-MPI (90% vs. 79% and 79%), but it did not reach statistical significance (P=0.32 and P=0.21, respectively). The overall accuracy of CMR-MPI tended to be higher than that of SPECT-MPI and DSE (85% vs. 75% and 74%), but these differences were also not statistically significant (P=0.11 and P=0.06, respectively). The overall agreement between FFR and CMR-MPI was good (κ=0.69), which tended to be better than that between FFR and both SPECT-MPI and DSE (κ=0.48 and 0.42, respectively), but it did not reach statistical significance (P=0.11 and P=0.05, respectively).

The sensitivity of SPECT-MPI in patients with functional MVD was lower than that in patients with functional SVD territories with FFR <0.8 than in those with FFR ≥0.8 (8.34±0.61 vs. 2.71±0.51, P<0.001), SDSr on SPECT-MPI and peak WMSIr on DSE were also significantly higher in the vessel territories with FFR <0.8 than those with FFR ≥0.8.

### Diagnostic Performance on Vessel-Based Analysis

The diagnostic performance of CMR-MPI, SPECT-MPI, and DSE in detecting functionally significant coronary artery stenosis is summarized in Table 3. The overall sensitivity of CMR-MPI was significantly higher than that of SPECT-MPI and DSE (P=0.02 and P=0.001, respectively). The overall specificity of DSE tended to be higher than that of CMR-MPI and SPECT-MPI (90% vs. 79% and 79%), but it did not reach statistical significance (P=0.32 and P=0.21, respectively). The overall accuracy of CMR-MPI tended to be higher than that of SPECT-MPI and DSE (85% vs. 75% and 74%), but these differences were also not statistically significant (P=0.11 and P=0.06, respectively). The overall agreement between FFR and CMR-MPI was good (κ=0.69), which tended to be better than that between FFR and both SPECT-MPI and DSE (κ=0.48 and 0.42, respectively), but it did not reach statistical significance (P=0.11 and P=0.05, respectively).

The sensitivity of SPECT-MPI in patients with functional MVD was lower than that in patients with functional SVD
Non-Invasive Test for Functionally Significant CAD

Figure 2. (A) Cardiac magnetic resonance myocardial perfusion imaging (CMR-MPI) shows a reversible transmural perfusion defect at anterior wall (white arrow); single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) is concordant (white arrow), indicating anterior reversible ischemia, and coronary angiography (CAG) confirms a significant stenosis in the left anterior descending coronary artery (white arrowhead). (B) CMR-MPI shows a reversible subendocardial perfusion defect at the anteroseptal, septal, inferoseptal, and inferior wall (white arrow), but SPECT-MPI could not visualize significant perfusion defect during stress, and CAG confirms significant stenosis in all 3 coronary arteries (white arrowhead). LCA, left coronary artery; RCA, right coronary artery.

Figure 3. Receiver operative characteristic (ROC) curves for diagnostic performance of cardiac magnetic resonance myocardial perfusion imaging (CMR-MPI), single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI), and dobutamine stress echocardiography (DSE) in detecting functionally significant coronary artery disease on a per-vessel base (fractional flow reserve <0.8). Area under the ROC curve (AUC) for CMR-MPI was significantly larger than that for SPECT-MPI and DSE. CI, confidence interval.
different territories with left ventricular myocardium. Therefore, it can identify only the coronary territory supplied by the most severe stenosis. In patients with diffuse 3-vessel CAD, balanced overall reduction of CFR can lead to false-negative results. Therefore, SPECT-MPI may be limited in identifying individual vessel territories with myocardial ischemia in patients with MVD. The sensitivity of SPECT-MPI in MVD for visualizing individual functionally significant coronary artery stenosis was 53%, which is similar to the Forster et al study (62%). In contrast, CMR-MPI was more accurate in the detection of significant CAD in patients with MVD.

This favorable diagnostic performance of CMR-MPI is also due to the superior spatial resolution compared with SPECT-MPI, which makes it possible to distinguish subendocardial and transmural ischemia. In other words, CMR-MPI could detect myocardial ischemia at an earlier stage as subendocardial perfusion, even in patients with MVD. In this study, CMR-MPI could detect subendocardial perfusion defects that could not be identified on SPECT-MPI in 5 vessel territories, confirming higher sensitivity as compared with SPECT-MPI.

Diagnostic Performance of DSE
DSE had a significantly lower sensitivity compared with that of CMR-MPI. The temporal development of myocardial ischemia caused by coronary artery stenosis, leads initially to perfusion abnormalities detected on CMR-MPI, followed by WMA detected on DSE, known as the ischemic cascade. WMA often occurs in the setting of more advanced myocardial blood flow impairment. Furthermore, a previous experimental study using dobutamine stress myocardial contrast echocardiography showed that the circumferential extent of perfusion abnormalities is greater than that of WMA. The spatiotemporal disparity between perfusion abnormalities and WMA might be responsible for the suboptimal DSE results in the present study.

Generally, DSE could perform better in the diagnosis of significant stenosis in LAD than in non-LAD territories, but no statistically significant improvement in diagnostic performance in the LAD territory was observed in the present study. Sensitivity and specificity of DSE for detection of functionally significant stenosis defined according to FFR were 41% and 100% in LAD, and 64% and 88% in non-LAD territories, respectively. These unexpected results might be due to the patient characteristics such as gender, obesity, and the number of coronary arteries with stenosis, all of which might affect the diagnostic performance of DSE. The number of patients, however, was too small to further analyze the effects of these different factors. We thus could not accurately assess the differences in diagnostic capabilities of the 3 modalities between LAD and non-LAD lesions.

Clinical Implications
This study has shown that CMR-MPI has excellent diagnostic performance in the detection of functional ischemia of CAD defined according to FFR. Previous studies showed that patients with non-pathologic CMR have low likelihood (<1%) of a major cardiac event during follow-up of 2 years. Therefore, CMR could be used to assess the clinical relevance of stenotic lesion detected on CAG and facilitate accurate decision-making for PCI, with similar accuracy to invasive FFR measurements. There is insufficient evidence, however, that PCI based on minor ischemia such as subendocardial area detected only on CMR-MPI can indeed improve the prognosis of stable CAD patients, and further studies are needed to confirm this.
Study Limitations
This study had several limitations. First, we were unable to completely assign all myocardial segments to the appropriate coronary artery perfusion territory. Second, there was a high proportion of patients with diabetes mellitus and hypertension. Diabetes mellitus and hypertension often result in a microvascular autonomic dysfunction not detectable on FFR\textsuperscript{20} but which can potentially reduce CFR, which might increase false-positive results. Third, we used only MPI to compare perfusion assessments between CMR and SPECT. Currently, multicomponent CMR is used in clinical practice, which combines LGE with MPI to detect myocardial ischemia more accurately.\textsuperscript{30} In SPECT, the combination of global and regional left ventricular function and perfusion can improve diagnostic performance compared to MPI alone. The post-stress acquisition of regional wall motion and thickening abnormalities,\textsuperscript{31} and transient ventricular dilatation\textsuperscript{32} caused by the persistence of post-ischemic stunning has been shown to be useful particularly in patients with MVD. The diagnostic performance of CMR and SPECT might be improved with these latest imaging techniques. Recently, automated quantitative scores obtained from SPECT-MPI have been reported to be closely correlated with visual analysis, the repeatability of such scores is excellent, and they are used in clinical practice.\textsuperscript{33} Visual analysis of SPECT-MPI, however, was used in many previous studies that evaluated diagnostic performance for the detection of myocardial ischemia and the prediction of cardiovascular events in patients with CAD.\textsuperscript{33,34} Therefore, we used only semi-quantitative scores obtained using visual analysis.

Fourth, although this study enrolled consecutive patients, it was difficult to obtain consent for all imaging tests, which might have induced selection bias. In addition, patients with unstable angina pectoris, old Q-wave myocardial infarction, prior coronary artery bypass grafting, contraindications to DSE, CMR or ATP infusion were excluded, which might also have produced a selection bias. Therefore, the present findings must be interpreted within this context.

Finally, the sample size was small. We could not obtain sufficient samples in each clinical and angiographic subgroup to determine statistically significant differences between 3 imaging modalities. A much larger data sample is needed to confirm the present results and identify significant differences in these subgroups.

Conclusions
CMR-MPI performed favorably in detecting functionally significant stenosis defined according to FFR, and had the highest diagnostic sensitivity in patients with CAD among the 3 modalities evaluated.

References


Supplementary Files

Supplementary File 1

Figure S1. Receiver operative characteristic (ROC) curves for diagnostic performance of regional summed stress score (SSSr) and regional summed difference score (SDSr) in detecting functionally significant coronary artery disease on a per-vessel basis (fractional flow reserve <0.8).