A large, multicenter study reported that the incidence of unintentional failure to hospitalize patients presenting at the emergency department with acute myocardial infarction (AMI) or unstable angina pectoris (UA) was low, although possibly associated with a poor outcome, and it was suggested that the incidence of missed diagnoses of acute cardiac ischemia in the emergency department could be reduced by using a new imaging modality.

Recently, the clinical usefulness of a perfusion tracer in the diagnosis of acute coronary syndromes (ACS) was reported.\(^1\)–\(^4\) Rest myocardial perfusion imaging with \(^{99m}\)Tc-sestamibi had a high sensitivity for identifying patients with ACS\(^1\) and the sensitivity of \(^{99m}\)Tc perfusion tracer and \(^{201}\)TlCl imaging for detecting coronary artery lesions ranged from 82% to 95% and from 80% to 84%, respectively, with a specificity of 75–100% and 75–82%.\(^2\)–\(^4\) \(^{123}\)I-\(\beta\)-methyl-p-iodophenyl-pentadecanoic acid (BMIPP), \(^{201}\)TlCl scintigraphy (imaging) and T2-weighted inversion–recovery magnetic resonance imaging (MRI) for the detection of culprit lesion in patients with acute coronary syndromes (ACS) was compared.

**Background** The incidence of missed diagnoses of acute cardiac ischemia in the emergency department could be reduced by a new imaging modality. In the present study, the clinical significance of \(^{99m}\)Tc-pyrophosphate (PYP), \(^{123}\)I-\(\beta\)-methyl-p-iodophenyl-pentadecanoic acid (BMIPP), \(^{201}\)TlCl scintigraphy (imaging) and T2-weighted inversion–recovery magnetic resonance imaging (MRI) for the detection of culprit lesion in patients with acute coronary syndromes (ACS) was compared.

**Methods and Results** The study group comprised 18 patients with ACS: 12 patients with acute myocardial infarction (AMI) (11 males; mean age, 63±11 years) and 6 patients with unstable angina (UA) (3 males, mean age, 67±5 years). Of the 12 patients with AMI, 10 underwent \(^{201}\)TlCl and PYP single photon emission computed tomography (SPECT) studies as a dual-energy acquisition (\(^{201}\)TlCl/PYP) and 8 underwent \(^{201}\)TlCl SPECT within 1 week of the BMIPP study. All 18 patients underwent BMIPP SPECT and MRI. The MRI pulse sequence was black blood turbo short-inversion-time inversion recovery (STIR) (breath-hold T2-weighted studies). The T2-weighted inversion-recovery MRI showed higher sensitivity and negative predictive value than PYP and \(^{201}\)TlCl, and higher specificity and positive predictive value than BMIPP and \(^{201}\)TlCl. The area under the receiver-operating characteristic curve for PYP, BMIPP, \(^{201}\)TlCl and MRI was 0.787, 0.725, 0.731 and 0.878, respectively. The difference between the areas of MRI and BMIPP was significant (p<0.05).

**Conclusion** Accurate detection of culprit lesion is improved by using MRI rather than BMIPP, particularly for patients with ACS. (Circ J 2004; 68: 1023–1029)

**Key Words:** Acute coronary syndrome; \(^{123}\)I-BMIPP; MRI; \(^{99m}\)Tc-pyrophosphate; \(^{201}\)TlCl
Methods

Objectives

The study group comprised 18 patients (14 males, 4 females) with ACS (Table 1). All patients were admitted to the Yokohama City University School of Medicine, and gave informed consent before examination.

The stenosed artery was diagnosed using coronary arteriography (CAG) and serial electrograms. A diagnosis of AMI required a creatine kinase (CK) value 2-fold higher than the lower limit and a relative index ([CK-MB/total CK]) × 100 ≥ 4.0.1

The electrocardiographic variables designated as indicating ischemia or infarction when present in at least 2 anatomically contiguous leads were as follows: pathologic Q wave (≥1 mm in depth and 0.3 s in duration), ST-segment elevation or depression ≥1 mm, and elevated or inverted T waves. The ST-segment and T-wave abnormalities were not considered potentially indicative of ischemia when any of the following were present: left ventricular hypertrophy, left or right bundle-branch block, and early repolarization variant. The electrocardiogram (ECG) were considered to be normal or nondiagnostic if it showed less than 1 mm of ST-segment elevation or depression, no T-wave inversion, and no pathological Q waves in 2 contiguous leads.15

SPECT Image Acquisition

Of the 12 patients with AMI, 10 underwent 201TlCl and PYP studies as a dual-energy acquisition (201TlCl/PYP) 2–8 days post-onset. At 75 min after an intravenous (iv) injection of PYP (740 MBq), 201TlCl (111 MBq) was injected and acquisition of data was started 15 min later. Eight patients underwent 201TlCl SPECT within 1 week of the BMIPP study. The photopeak and windows used for the dual-energy acquisition were 70 keV and 20% for 201TlCl and 140 keV and 20% for 99mTc.

SPECT imaging was performed with a single-head gamma camera equipped with a low-energy general purpose collimator (Starcam 3000 XC/T, General Electric, Milwaukee, WI, USA). Data were acquired using 64×64 matrices throughout 180° of rotation, rotating in an anterior direction from 45° right anterior oblique to 45° left posterior oblique. The sampling angle was 6° allowing 30 s per projection. Using a standard filtered back-projection algorithm, transaxial, vertical long-axis and short-axis images were reconstructed. The SPECT studies were performed 11±4 days post-onset in all patients.

BMIPP (111 MBq iv) was injected while the patient was resting under fasting conditions and SPECT data acquisition began 15 min later. The photopeak was centered on 160 keV with a 20% window. The data acquisition and reconstruction were essentially the same as described earlier.

To avoid any overlap in tracer activity, the SPECT studies were performed at different times at least 2 days apart.

MRI

MRI was performed 12±4 days post-onset in all patients, using an Impact system (1.0 Tesla, Siemens, Erlangen, Germany). Exclusion criteria were hemodynamic instability and contraindications for MRI (eg, pacemaker or ferromagnetic vascular clips). There was a limitation to the MRI study in the patients with unstable AMI because the 12-lead ECG cannot be operated in the MRI room, and many infusion lines also limit the MRI study.

A standard body coil was used while the subjects were supine. All MRI studies used an acquisition matrix of 128×256 lines. The field of view in the phase-encoding direction was user definable and was chosen to maximize spatial resolution within a given breath-hold period. Patients were examined with ECG triggered and the breath-hold black blood turbo STIR sequence, which is a variation of the black-blood turbo SE sequence that applies a triple inversion–recovery (IR) pulse before turbo SE data acquisition. Please refer to the enclosed timing chart. The first and second IR pulses are used for nullifying the blood signal and third IR pulse nullifies the fat signal. Because the heart is surrounded by the air in the lungs, chemical shift selective fat nullifying pulses sometimes cause inhomogeneous fat suppression because of the susceptibility to changes.

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Table 1 Baseline Characteristics of the Patients With Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>CAG stenosis (*= culprit)</th>
<th>Intervention</th>
<th>Diagnosis</th>
<th>Max CK (U/L)</th>
<th>MRI (day from onset)</th>
<th>BMIPP (day from onset)</th>
<th>TI-201 (day from onset)</th>
<th>PYP (day from onset)</th>
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<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>M</td>
<td>LAD*, LCX</td>
<td>PTCA</td>
<td>AMI</td>
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<tr>
<td>2</td>
<td>68</td>
<td>M</td>
<td>RCA, LAD*</td>
<td>PTCA</td>
<td>AMI</td>
<td>3,299</td>
<td>17</td>
<td>13</td>
<td>3</td>
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<tr>
<td>3</td>
<td>56</td>
<td>M</td>
<td>LAD*</td>
<td>PTCA</td>
<td>AMI</td>
<td>3,033</td>
<td>16</td>
<td>16</td>
<td>2</td>
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<tr>
<td>4</td>
<td>61</td>
<td>M</td>
<td>RCA*, LA*D</td>
<td>PTCA + Stent</td>
<td>AMI</td>
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<td>16</td>
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<td>2</td>
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<tr>
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<td>57</td>
<td>M</td>
<td>RCA, LCX*</td>
<td>Not done</td>
<td>AMI</td>
<td>528</td>
<td>14</td>
<td>11</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
<td>M</td>
<td>RCA, LAD*</td>
<td>Not done</td>
<td>AMI</td>
<td>953</td>
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<td>11</td>
<td>8</td>
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<tr>
<td>7</td>
<td>63</td>
<td>M</td>
<td>LCX*</td>
<td>Not done</td>
<td>AMI</td>
<td>1,085</td>
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<td>10</td>
<td>3</td>
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<tr>
<td>8</td>
<td>32</td>
<td>M</td>
<td>RCA*</td>
<td>Not done</td>
<td>AMI</td>
<td>708</td>
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<td>18</td>
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<td>8</td>
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<td>AMI</td>
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<td>11</td>
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<td>8</td>
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<tr>
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<td>PTCA</td>
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<tr>
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<td>AMI</td>
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<td>LAD, LCX*</td>
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<td>UA</td>
<td>100</td>
<td>16</td>
<td>9</td>
<td>6</td>
<td>–</td>
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<tr>
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<td>M</td>
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<td>PTCA</td>
<td>UA</td>
<td>81</td>
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<td>6</td>
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<td>–</td>
</tr>
<tr>
<td>15</td>
<td>73</td>
<td>M</td>
<td>LAD*</td>
<td>Not done</td>
<td>UA</td>
<td>51</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>–</td>
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<tr>
<td>16</td>
<td>69</td>
<td>F</td>
<td>LCX*</td>
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<td>78</td>
<td>14</td>
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<td>2</td>
<td>–</td>
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<tr>
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<td>F</td>
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<td>Not done</td>
<td>UA</td>
<td>220</td>
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<td>5</td>
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<tr>
<td>18</td>
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<td>F</td>
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<td>Not done</td>
<td>UA</td>
<td>133</td>
<td>9</td>
<td>8</td>
<td>5</td>
<td>–</td>
</tr>
</tbody>
</table>

CAG, coronary arteriography; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; PTCA, percutaneous transluminal coronary angioplasty; AMI, acute coronary syndrome; UA, unstable angina.
between air and the myocardium. The IR pulse is more reliable because it is very robust against susceptibility.

For the present studies, the repetition time (TR) was set to twice the RR interval and the inversion time (TI) for blood signal suppression was set to the maximum allowed by the subject's RR interval. Data acquisition windows were adjusted patient by patient. If the RR interval is long, the effective TI is set long, and a shorter TI for shorter RR interval, a method that also achieves optimal TI for nullifying the blood signal. The echo time (TE) was set to 64 ms and the echo train length was 23. Typical section dimensions were an 8-mm thickness. A spin echo series was obtained after injection of 0.1 mmol/kg gadolinium-diethylenetriamine pentaacetic acid (DTPA). The whole of the left ventricle was scanned as slices of 8 mm thickness. The TR was equivalent to the RR interval and the TE was 32 ms and the echo train length was 9.

Six of the 12 patients with AMI underwent ECG-gated cine MRI with the images acquired at 8 base–apex short-axis locations during repeated breath-holds. The sequence was k-space segmented gradient echo with the following parameters: 8-mm slice section thickness, TR 60 ms, TE 6.1 ms, 8 frames per cardiac cycle and flip angle of 30°.

**Echocardiography**

Echocardiographic examinations were performed using a commercially available scanner (Sonos 2500, Hewlett Packard Medical Products, Andover, MA, USA) with 3.75 MHz phased-array cardiac probe. End-systolic and end-diastolic measurements were made from the M-mode tracing according to the American Society of Echocardiography recommendations. The left ventricular ejection fraction (LVEF) was calculated from each pair of diameter measurements using the Teichholz formula.16

**Data Analysis**

For interpretation and quantification of SPECT, 2 short-axis slices and a vertical long-axis slice were selected for semi-quantitative analysis (Fig 1). Two slices from near the cardiac base and mid-to-apical portion were used, and each slice was divided into 8 segments. The apex of the long-axis image was divided into 2 segments. Thus there were 18 segments for each myocardium. The reduction of each segment was evaluated using a 4 point scale (normal = 0, mild reduction = 1, moderate reduction = 2, severe reduc-
tion = 3). Regarding the territory of the coronary artery, the anteroseptal-to-apical region was considered to correspond to the left anterior descending artery (LAD) territory, the lateral region to the left circumflex artery (LCX) territory and the infero-posterior region to the right coronary artery (RCA) territory. The patient’s SPECT and MRI images of each region were visually interpreted by 2 clinicians, taking individual variation into consideration.

To evaluate the 201TlCl and BMIPP SPECT images, more than 2 segments with abnormal point scales (>1 on the 4-point scale) was considered abnormal in each coronary territory. For assessment of the PYP images, the lower cutoff level was 40% to avoid over-estimation of abnormal findings, and PYP accumulation with reduced 201TlCl uptake considered abnormal in the same coronary territory was also considered an abnormal finding.

To evaluate the MR images, increased intensity of the myocardium in more than 2 segments in the same coronary territory was considered abnormal. For the ECG-gated cine MR images, 2 short-axis locations matching the SPECT images were selected to evaluate regional wall motion with a 6-point scale (normal = 0, mild hypokinesis = 1, moderate hypokinesis = 2, severe hypokinesis = 3, akinesis = 4, dyskinesia = 5). A score over 1 is considered abnormal.

Receiver-operating characteristic (ROC) curves were generated for each of the methods using a commercial statistics software package (Medcalc, Belgium) and the area under each of the ROC curves was compared for statistically significant differences.

**Results**

**Clinical Features**

Of the 12 patients with AMI, 11 were males, and the mean age was 63 ± 11 years (mean ± SD). There were 10 cases of first infarction. The number of culprit lesions in the LAD, RCA and LCX was 5, 4 and 3, respectively. Six patients had 1-vessel disease, 5 patients had 2-vessel disease and 1 patient had 3-vessel disease. The mean LVEF was 54.7 ± 14.7 (%; mean ± SD).

Six patients had unstable angina (UA) and three of them were males; the mean age was 67 ± 5 years (mean ± SD). The number of culprit lesions in the LAD and LCX was 4 and 2, respectively. Five patients had 1-vessel disease, and 1 patient had 2-vessel disease. The LVEF was 66.2 ± 15.0 (%; mean ± SD).

Medical therapy was individualized, including nitrate, calcium antagonist and anti-platelet therapy, and continued during the nuclear study.

**Results of Scintigraphy and MRI**

The number of abnormal segments on PYP was 66, 127 on BMIPP, 110 on 201TlCl and 92 on MRI. In patients with AMI, the number of culprit lesions detected by PYP, BMIPP, 201TlCl and MRI was 8/10, 11/12, 10/12 and 11/12, respectively. In patients with UA, the number of...
culprit lesions detected by BMIPP, 201TlCl and MRI was 5/6, 4/6 and 3/6, respectively.

In patients with AMI, 70% of the abnormal MRI segments matched the PYP findings. In all patients, 74% and 83% of the abnormal MRI segments matched the 201TlCl and BMIPP findings, respectively.

Fig 2 shows a representative case of UA in which there is not a significant elevation of either CK or CKMB, but there is an inverted T wave recorded in the V1–4 leads on ECG. 201TlCl SPECT shows normal uptake and a mild BMIPP defect can be seen in the anteroseptal region. The T2-weighted inversion–recovery MRI and T1-weighted Gd-enhanced MRI show high signal intensity in the same region.

Fig 3 shows a case of AMI in which increased PYP uptake, a moderate 201TlCl defect and a severe BMIPP defect are apparent in the anteroseptal region, where there is also high signal intensity on both the T2-weighted inversion–recovery MRI and T1-weighted Gd-enhanced MRI.

The 6 patients with AMI and a culprit lesion detected by MRI showed abnormal regional wall motion on cine MRI. Fig 4 shows a representative case. T2-weighted inversion–recovery MRI shows high signal intensity in the septum and cine MRI shows reduced wall motion in the same region.

Among the 12 patients with AMI, the sensitivity, specificity, and positive and negative predictive values for culprit lesion assessment were 80%, 95%, 89% and 91%, respectively, for PYP; 92%, 79%, 69%, and 95% for BMIPP; 83%, 79%, 67%, and 90% for 201TlCl; and 92%, 88%, 79% and 95% for MRI. Among all patients, the sensitivity, specificity, and positive and negative predictive values were 89%, 83%, 73% and 94%, respectively, for BMIPP; 78%, 86%, 74% and 86% for 201TlCl; and 78%, 89%, 78% and 89% for MRI.

T2-weighted inversion-recovery MRI had a higher sensitivity and negative predictive value than PYP and 201TlCl, and higher specificity and positive predictive value than BMIPP and 201TlCl.

One patient with an anteroseptal AMI showed high signal intensity in the anteroseptal region on MRI without abnormal PYP SPECT findings. Two patients without abnormal PYP SPECT findings underwent PYP SPECT study at 8 days after onset, and the maximum CK value was <1,000 U/l. One patient with a small branch lesion of the LCX could not be diagnosed by CAG assessment only, but was diagnosed by combined assessment using MRI, perfusion SPECT and CAG. Three cases of AMI had an abnormal BMIPP defect in the inferior lesion that was not the culprit lesion; 2 were old myocardial lesions and one lesion supplied by the LAD run from the apex to the inferoapical region.

The area under the ROC curve for PYP, BMIPP, 201TlCl and MRI was 0.787, 0.725, 0.731 and 0.878, respectively, and the difference between the areas for MRI and BMIPP was significant (p<0.05) (Fig 5).

**Discussion**

In the evaluation of myocardial viability by contrast-enhanced (CE) MRI, it has been suggested that Gd-DTPA-enhanced MRI may be useful. Absence of delayed hyper-enhancement in AMI has good diagnostic accuracy in predicting functional improvement in dysfunctional segments. Preliminary clinical results show the potential advantages of the turbo STIR technique, which employs the strategies of breath holding, diastolic gating, and blood signal nullifying to suppress the effect of respiration, cardiac motion, and pulsatile blood flow. Combining a STIR preparation with the turbo SE technique suppresses the fat signal and enhances many types of focal lesions, while keeping imaging time to a reasonable breath-hold period.

In the present study, high image quality was achieved by combining several techniques (breath-hold scan to suppress
motion artifacts by breathing, black blood sequence to suppress flow artifacts, setting of the acquisition window to end-diastole to reduce blurred images, and adjusting the RR interval patient by patient, using a phased array coil for higher signal to noise ratio). Focal high signal intensity consistent with edema was seen in 2 patients with AMI.

We evaluated the culprit lesions of 18 patients (14 males, 4 females) with ACS and compared the PYP, BMIPP and \(^{201}\)TICI SPECT findings. Non-flow-limiting stenoses are a common site of subsequent plaque rupture and thrombotic occlusion. Studies with myocardial perfusion SPECT have shown a correlation between the location of the perfusion defect and the site of the subsequent AMI\(^2\)–\(^3\). Myocardial perfusion scintigraphy and coronary angiography can indicate the need for revascularization procedures in patients with chronic coronary artery disease.\(^2\)–\(^4\)

Acute coronary syndrome is more likely to develop when occlusive thrombosis complicates a mildly obstructive plaque. For effective management of coronary patients, it is important to know the ability of anatomic and functional investigations to predict future events, and it is believed that myocardial SPECT can predict the site of subsequent AMI\(^2\)–\(^3\).

PYP uptake early after reperfusion occurred in experimental studies with dogs whose myocardial cells were viable but severely injured, possibly because of excess cytosolic calcium. Sarcolemmal Ca\(^{++}\) permeability is thus very likely to occur, resulting in increased uptake of PYP even after a short period of ischemia without infarction. Membrane phospholipid metabolic alterations in ischemic canine myocardium have been reported. Phospholipid depletion during ischemia creates a Ca\(^{++}\) permeability defect that results in increased intracellular Ca\(^{++}\) and subsequent accumulation of PYP.

PYP myocardial scintigraphy was reported as positive in 76% patients with unstable angina.\(^12\) However, another report suggested only 8% could be classified as having positive scan without CK-MB elevation,\(^15\) thus indicating that the clinical utility of PYP myocardial scintigraphy may be limited.

In an extension of the concept of ischemic memory imaging, BMIPP at rest has been used to identify ischemic myocardium.\(^2\)–\(^4\) In addition, decreases in BMIPP uptake are often associated with regional wall motion abnormalities in subjects without a history of AMI.\(^2\)–\(^3\) Among a group of patients with ACS, the results of using BMIPP and metaiodobenzylguanidine were compared, and the BMIPP study more accurately identified damaged myocardium in the territory of the culprit coronary artery.\(^3\)–\(^4\) Therefore, in such patients, BMIPP imaging is considered the better method for showing that regional abnormalities represent ischemic memory.\(^5\) In the patients with multivessel disease, not only acute or subacute phase ischemic events, but also chronic phase ischemic events, reveal decreased BMIPP uptake and in these cases, accurate diagnosis of the culprit lesion is difficult and it is very hard to determine therapeutic strategies.

In the present study, T2-weighted inversion–recovery MRI had a higher sensitivity and negative predictive value than PYP and \(^{201}\)TICI, and a higher specificity and positive predictive value than BMIPP and \(^{201}\)TICI. Therefore, MRI is more clinically useful than BMIPP for assessment of the culprit lesion in patients with ACS.

Conclusions
The T2-weighted inversion–recovery MRI showed higher sensitivity and negative predictive value than PYP and \(^{201}\)TICI, and higher specificity and positive predictive value than BMIPP and \(^{201}\)TICI. Therefore, MRI is more clinically useful than BMIPP for assessment of the culprit lesion in patients with ACS.

Study Limitations
Because the number of patients in this study was limited, similar comparative studies with follow-up are necessary. We did not quantitatively analyze the high signal intensity of T2-weighted inversion–recovery MRI.

References
Cardiol 1976; 37: 7–11.