Evaluating Microvascular Obstruction After Acute Myocardial Infarction Using Cardiac Magnetic Resonance Imaging and 201-Thallium and 99m-Tc Pyrophosphate Scintigraphy

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Background: Few studies have compared the ability of cardiac magnetic resonance (CMR) with that of scintigraphy using 201-thallium (201-Tl) and 99m-technetium pyrophosphate (99m-Tc PYP) to evaluate microvascular obstructions (MOs). In the present study the relationship between the scintigraphic and CMR characteristics of MOs after acute myocardial infarction (MI) was examined.

Methods and Results: The 14 patients (age 69±8 years, 11 males) underwent 201-Tl/99m-Tc PYP SPECT 7±3 days, initial CMR 16±12 days, and follow-up CMR 193±20 days after a reperfused first acute MI. Each image was analyzed using a 17-segment model. Segmental extent of delayed enhancement (DE), wall motion (WM) and degree of 201-Tl uptake were scored in 238 segments. Of 91 MI segments, MO was recognized in 22 (25%) segments. WM was significantly better in proportion to 201-Tl uptake (P=0.01) in MO segments. All 8 MO segments with WM improvement at follow-up had 99m-Tc PYP uptake, although only 3 (21%) of 14 MO segments that did not show WM improvement at follow-up had 99m-Tc PYP uptake (P=0.001).

Conclusions: 99m-Tc PYP and 201-Tl scintigraphy have the potential to predict WM status and improvement of the MO region after reperfused acute MI. (Circ J 2010; 74: 2633–2640)

Key Words: Acute myocardial infarction; Cardiac magnetic resonance imaging; Microvascular obstruction; Scintigraphy

Poor preservation of wall motion (WM) after acute myocardial infarction (MI), even with adequate mechanical reperfusion therapy, is not uncommon, even within the golden time. In such cases, the restored epicardial blood flow is insufficient to protect the myocardium, because necrosis of myocytes and capillaries in the infarcted area and the occlusion of capillaries by dying blood cells and debris prevents the infarct core from promptly reperfusing. This microvascular obstruction (MO) is called the “no-reflow” phenomenon.

Contrast-enhanced magnetic resonance imaging (MRI) allows us to visualize in vivo regions of MO in patients who have suffered an acute MI. These MO regions appear as hypoenhanced areas surrounded by hyperenhanced myocardium and correspond to experimentally produced no-reflow regions. With the availability of excellent visualization of the MO region by cardiac MRI (CMR), many studies have been conducted to elucidate the prognosis of MO after acute MI. The extent of MO determines the magnitude of myocardial damage and thus the short-term prognosis. Additionally, with regard to the long-term prognosis, the presence of MO is an important predictor of remodeling and unfavorable outcome in patients with a successfully reperfused MI.

Studies that have aimed at analyzing the characteristics of MO regions have also been performed using CMR. Experimental data have shown the accuracy of first-pass enhancement MRI in determining the extent of MO. Delayed enhancement (DE) images of hypoenhanced regions that are surrounded by hyperenhancement have been described and could relate to persistent MO (PMO) in the core of infarcted myocardium. However, few studies have evaluate MO regions after acute MI using CMR in combination with other modalities such as scintigraphy.

Lesions that result in myocardial cell death, such as isch-
CMR and 201-Tl/99m-Tc PYP dual SPECT and investigate the predictive value of scintigraphy on the functional recovery of CMR-detected MO regions, using follow-up CMR imaging as the reference standard in patients with a reperfused acute MI.

### Methods

**Patient Population**

We enrolled consecutive patients presenting with a first ST-segment elevation acute MI, as diagnosed with standard electrocardiographic and enzymatic criteria. All patients had undergone primary percutaneous coronary intervention with stent implantation and were evaluated with initial and follow-up CMR, as well as 201-Tl/99m-Tc PYP dual SPECT during hospitalization. Exclusion criteria were unsuccessful angiographic reperfusion (Thrombolysis In Myocardial Infarction [TIMI] flow grade <2), hemodynamic or other clinical instability, failure to give written informed consent, or contraindications for CMR. We treated all patients with aspirin, clopidogrel or ticlopidine, heparin, statins, angiotensin-converting enzyme inhibitors, and beta-blockers according to the American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines.

The study was approved by the local ethics committee. The study population comprised 14 consecutive patients who completed the initial and follow-up CMR, as well as the 201-Tl/99m-Tc PYP dual SPECT, between January 2007 and December 2008.

### CMR Protocol

CMR was performed on a 1.5-T clinical scanner (Magnetom Symphony, Siemens, Erlangen, Germany) using a body-array coil. The ECG-gated images were acquired during repeated breath-holds of varying duration depending on heart rate. The initial study was performed at a median (25th, 75th percentiles) of 15.5 (4.8, 28.5) days after admission, with follow-up at 184.0 (180.5, 204.0) days. We performed cine imaging to determine left ventricular WM, using a steady-state gradient echo sequence (TrueFISP; Siemens). The imaging parameters were: repetition time/echo time, 3.6 ms/1.5 ms; slice thick-
ness, 5.5 mm; field of view, 380×285 mm; matrix, 192×127; pixel size, 2.0×2.2 mm; flip angle, 74°. The sequence lasted approximately 18–24 s depending on the heart rate. Nine contiguous short-axis sections were acquired from the left ventricle, from apex to base. DE images were obtained 10–15 min after intravenous bolus injection of 0.2 mmol/kg gadolinium-based contrast agent (Magnevist, Schering AG, Berlin, Germany) using a steady-state gradient echo sequence (TrueFISP; Siemens) with the phase-sensitive inversion recovery (PSIR) method and slice position identical to the cine images. The imaging parameters were: repetition time/echo time, 4.3 ms/1.9 ms; slice thickness, 5.5 mm; field of view, 380×285 ms; matrix, 256×154; pixel size, 1.5×1.9 mm; flip angle, 50°. The sequence lasted approximately 18–24 s.

**SPECT Protocol**

SPECT imaging was performed after intravenous injection of 740 MBq 99m-Tc PYP, followed by an injection of 74 MBq 201-Tl 2 h later, using a dual-head gamma camera with a low-energy, high-resolution, parallel-hole collimator (ECAM, Siemens). All patients underwent SPECT a mean ± standard deviation of 6.5±3.5 days after MI. A total of 37 projection images were obtained over a 180° arc, from 45° right anterior oblique to 45° left anterior oblique, for 20 s per image. Projection images were recorded as 64×64 matrices and analyzed with a dedicated nuclear medicine image processor (ICONP, Siemens) to generate short- and long-axis views. Energy discriminations were set at 70 keV with a 20% window for 201-Tl and 140 keV with a 15% window for 99m-Tc PYP images.

**Figure 1.** (A) Follow-up wall motion score of MO segments according to 201-Tl perfusion status. MO segments with better 201-Tl uptake had significantly better wall motion on follow-up CMR (P=0.01). Wall motion, 1=severe, 2=moderate, and 3=mild hypokinesis; 201-Tl, 1=mildly, 2=moderately, and 3=severely reduced uptake. Circle plots show the mean with standard deviation bars. (B) Follow-up transmural extent of DE of MO segments according to the degree of 201-Tl uptake. MO segments with better 201-Tl uptake had significantly less transmural extent of DE at follow-up CMR (P=0.01). DE extent, 1=1–25%, 2=26–50%, 3=51–75%, and 4=76–100%; 201-Tl, 1=mildly, 2=moderately, 3=severely reduced uptake. Box plots show the mean and 25th and 75th percentiles with standard deviation bars. DE, delayed enhancement; MO, microvascular obstruction; CMR, cardiac magnetic resonance; 201-Tl, 201-thallium.
Table 3. Comparison of MO Segments With and Without WM Improvement

<table>
<thead>
<tr>
<th>No. of segments</th>
<th>Initial CMR</th>
<th>Follow-up CMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM score &gt;1</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>WM score &lt;1</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>DE extent</td>
<td>3.4±0.9</td>
<td>2.9±0.8</td>
</tr>
<tr>
<td>DE extent</td>
<td>2.3±0.4</td>
<td>2.7±1.1</td>
</tr>
<tr>
<td>∆DE extent</td>
<td>−1.1±0.6</td>
<td>−0.2±1.0</td>
</tr>
</tbody>
</table>

Values are number (%) or mean±standard deviation. *Significant value.
Abbreviations seen in Table 2.

Image Analysis

Both CMR and SPECT images were compared using a 17-segment model as previously recommended by the AHA. Representative short-axis slices of the basal (6 segments), mid-ventricular (6 segments), and apical (4 segments) regions of the left ventricle were analyzed. The apex was evaluated from long-axis slices. A total of 238 segments were assessed for both CMR and SPECT, with semiquantitative scores. All images were assessed independently by 2 observers.

For CMR, the transmural extent of DE (DE extent) within each segment was scored visually and subjectively as follows: 0=no enhancement, 1=1–25%, 2=26–50%, 3=51–75% and 4=76–100%. We defined the difference in DE extent between initial and follow-up CMR as follows: ∆DE extent = DE extent_{follow-up} – DE extent_{initial}.

Segmental WM was also scored visually and subjectively according to the following scale: 0=akinesis, 1=severe, 2=mildly reduced, 3=mild hypokinesia, and 4=normal. We defined the difference in WM score at follow-up as follows: ∆WM score = WM score_{follow-up} – WM score_{initial}.

A recent report by Cochet et al suggested that the prognostic impact of PMO may be superior to MO in acute MI patients after successful reperfusion; thus, in this study we used the PMO finding, namely a persistent hypoenhanced area surrounded by hyperenhancement in DE-CMR, as an index of MO.

For SPECT, 201-Tl uptake was evaluated from 0 to 4: 0=normal perfusion, 1=mildly reduced, 2=moderately reduced, 3=severely reduced, and 4=absent tracer activity, and 99m-Tc PYP uptake was scored as either present, 1 or absent, 0. Segments with uptake of 201-Tl and 99m-Tc PYP in the same segment were classified as overlap positive.

Statistical Analysis

Continuous data are expressed as the mean±SD, and dichotomous data are expressed as numbers (percentage). For continuous variables, the normality of the distribution was tested by the Shapiro-Wilk test. Comparison between 2 groups was made using either Student’s t-test or the Mann-Whitney test for continuous variables as appropriate and according to the normality of the distribution. When we compared continuous variables among 3 groups, we used 1-way analysis of variance or the Kruskal-Willis test as appropriate and depending on the normality of the distribution. Categorical data were compared with Fisher’s exact test. A value of P<0.05 was considered statistically significant. Receiver-operating characteristic (ROC) curves showing the predicting performance of 201-Tl uptake, 201-Tl/99m-Tc PYP overlap and initial DE extent on future WM improvement of MO lesions were constructed. Statistical analysis was performed with PASW Statistics 18.0 software (SPSS Inc, IBM, Chicago, IL, USA).

Results

Patient Characteristics

Baseline patient characteristics are shown in Table 1: 6 (43%) patients had an anterior MI, 4 (29%) had a postero-lateral MI, and the other 4 (29%) patients had an inferior MI. Ten (71%) patients had multivessel disease. Preprocedure TIMI flow grade was ≥1 in 78% (11) of the patients. Final TIMI flow grade after the procedure was grade 3 in 10 (71%) patients and 2 in 4 (29%) patients. The average time to reperfusion was 9±6 h.

MI Segment Analysis

A total of 238 segments were available for analysis and of these, 91 (38%) showed DE. Of the 91 MI segments detected with DE-CMR, MO was recognized in 22 (24%).

The DE segments were compared according to the presence of MO and are described in Table 2. Comparing MO-positive DE segments with MO-negative DE segments, the latter had a significantly better WM score (1.5±1.1 vs 2.2±1.2; P=0.03) and lesser extent of DE (3.1±0.9 vs 2.2±0.9; P=0.0001) on the initial CMR. The same results were also seen on follow-up CMR (1.9±1.1 vs 2.6±1.3; P=0.01, 2.5±1.1 vs 1.9±1.2; P=0.03, respectively). 201-Tl uptake was significantly better in MO-negative DE segments than in MO-positive DE seg-
MO Segment Analysis

MO segments had significantly better WM and less DE on follow-up CMR in proportion to 201-Tl uptake (P=0.01, P=0.01, respectively) (Figures 1A, B).

Of 22 MO segments, 8 (36%) showed WM improvement (ΔWM score ≥1) on follow-up CMR. Comparing these segments with the other 14 segments that showed no WM improvement on follow-up CMR, the former segments had a significantly larger decrease in DE extent than the latter group (−1.1±0.6 vs −0.2±1.0; P=0.03) (Table 3). All of the former segments had significantly better uptake of 99m-Tc PYP than the latter group (1.0±0.0 vs 0.2±0.4; P=0.001) (Table 3), and all of the former segments had overlap of 201-Tl and 99m-Tc PYP, whereas only 3 (21%) segments of the latter group showed overlap (P=0.001) (Table 3, Figure 2).

When MO segments were compared in terms of 99m-Tc PYP uptake, 11 (50%) MO segments with 99m-Tc PYP uptake had significantly better WM improvement (0.64±0.14 vs 0.00±0.14; P=0.003) (Figure 3A) and a larger decrease in the extent of DE than those without 99m-Tc PYP uptake (−1.18±0.22 vs 0.09±0.22; P=0.001) (Figure 3B).

Analyses with ROC curves comparing the predictive value of 201-Tl uptake, 201-Tl/99m-Tc PYP overlap and initial DE extent in predicting future WM improvement of MO lesions...
showed 201-Tl/99m-Tc PYP overlap to be better than the others (Figure 4). More specifically the area under the curve for 201-Tl/99m-Tc PYP overlap, 201-Tl uptake and initial DE extent was 0.893, 0.371 and 0.647, respectively.

**Discussion**

In the present study, we demonstrated the following: (1) MO segments have better WM and less DE on follow-up CMR in proportion to 201-Tl uptake; (2) MO segments with improved WM have a larger decrease in the extent of DE on follow-up CMR and have more 99m-Tc PYP uptake, expressing overlap with 201-Tl, compared with those without WM improvement; and (3) MO segments with 99m-Tc PYP uptake show better WM improvement and a greater decrease of DE on follow-up CMR compared with those without 99m-Tc PYP uptake.

The predictive value of the existence of MO after acute MI in determining a poor prognosis was based on comparisons between MO groups and non-MO groups but few studies have evaluated the MO regions themselves in detail. We believe that risk stratification of MO segments is important with regard to patient management after acute MI. Some studies that used a combination of CMR and SPECT reported the superiority of CMR for detecting specific lesions, such as small infarcts, subendocardial infarcts, and non-anterior infarctions. However, none have used both modalities to assess MO.

The results of the present study indicate that 201-Tl may predict WM status and that 99m-Tc PYP may estimate WM improvement in MO segments. A possible explanation for these findings is that MO lesions detected by CMR, which are thought to represent the no-reflow phenomenon at the microcirculation level, have a blood supply that is subtle enough to bring these isotopes to the damaged cardiomyocytes. 201-Tl is a perfusion tracer, and 99m-Tc PYP uptake not only needs calcium ions in the mitochondria within injured cardiomyocytes but also requires circulation to reach those cardiomyocytes. We speculate that these 2 tracers may represent residual microcirculation in MO regions. In addition, we speculate that 99m-Tc PYP may accumulate in stunned cardiomyocytes, as inferred from its association with WM improvement on follow-up images. Previous reports suggested that 99m-Tc localizes in severely injured but still viable myocardium early after reperfusion. Therefore, we assume that 99m-Tc PYP uptake represents calcium overload within severely ischemic cardiomyocytes after reperfusion therapy. We also found that a better WM status or an improvement of MO segments at follow-up is accompanied by a decrease in the DE extent. A possible explanation for this finding is that stunned peri-infarction areas around the core of infarction are edematous, with more interstitial fluid, and therefore overestimated by contrast enhancement. We speculate that in the chronic phase, this peri-infarction area shows recovered WM and the disappearance of the edema, resulting in decreased contrast enhancement. Previous studies have shown that infarct size decreases after acute MI.

Contrary to previous reports that found the existence of MO to be a poor prognostic factor, Nijveldt et al recently reported that the functional changes found in patients with MO were comparable to those in patients without MO. Based on our results, we consider it possible to use 201-Tl/99m-Tc PYP dual SPECT to stratify MO lesions and this offers an adequate explanation for this controversial phenomenon.

WM status and the improvement in the MO region improved in proportion to 201-Tl and 99m-Tc PYP uptake, and were accompanied by a decreased DE. These findings suggest that the residual microcirculation significantly contributes toward the preservation of myocardial function after acute MI. Reperfusion therapy should therefore be performed in patients with acute MI, primarily considering the microcirculation. The most important goal in the treatment of acute MI is to maximize the probability of achieving complete and sustained reperfusion at both the epicardial coronary artery and microcirculation levels. Abrupt reperfusion therapy itself can cause reperfusion injury. Many treatment strategies using drugs, such as human atrial natriuretic hormone,
nicorandil, and mechanical postconditioning methods pro-
tect reperfused myocardium in the setting of acute MI.31–33
However, globally we do not have a specific reperfusion strat-
 egy in daily clinical practice. Many researchers use CMR, an
excellent modality with high spatial resolution, as a tool for
evaluating reperfused myocardium in acute MI. During
reperfusion therapy with coronary intervention, the no-reflow
phenomenon is a major problem, underscoring the need for a
method of adequately assessing and stratifying no-reflow to
evaluate the MO regions with regard to reperfusion strategy.
The results of the present study show that 201-Tl/99m-Tc PYP SPECT
is a possible strategy for evaluating MO after acute MI.

Study Limitations
The main limitation of this study is the small sample size,
which makes the results very preliminary. In addition, the
time elapsed between the onset of acute MI and the initial
CMR was relatively long when compared with other pub-
lished studies, which might have influenced CMR parame-
ters such as DE and PMO. Also, the time lag between SPECT
imaging and initial CMR makes the comparison very com-
plicated. Furthermore, all the images were assessed by semi-
quantitative visual analysis. Therefore, further investigation
should include a larger sample size and a stricter imaging pro-
tocol, using analysis software to perform quantitative assess-
ment, to confirm the results of the present study.

Conclusions
Our study demonstrates the feasibility and potential of 201-Tl/
99m-Tc PYP SPECT in combination with CMR for evaluat-
ing MO regions in patients with reperfused acute MI.

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