Optimal Time for Predicting Left Ventricular Remodeling After Successful Primary Coronary Angioplasty in Acute Myocardial Infarction Using Serial Myocardial Contrast Echocardiography and Magnetic Resonance Imaging

Tadamichi Sakuma, MD; Takenori Okada, MD; Yasuhiro Hayashi, MD; Masaya Otsuka, MD; Yuukou Hirai, MD

The objective of this study was to determine the optimal time to assess microvascular integrity within the risk area for myocardial infarction in order to predict unfavorable left ventricular remodeling (LVR) after successful primary coronary angioplasty. Fifty-three patients who underwent myocardial contrast echocardiography (MCE) just before recanalization, shortly after and 1 day (Day 2) and 3 weeks after recanalization were studied. The no- and low-reflow ratio (LR ratio) was analyzed at each stage. The wall-thinning ratio within the risk area was determined using magnetic resonance imaging performed 3–4 weeks after the recanalization. Thirteen of the 53 patients showed LVR 3–8 months after recanalization. The optimal time to predict LVR was found to be Day 2 based on the receiver operating characteristic curves. The LR ratio on Day 2 ($\rho^2=7.39$, $p=0.007$) and the collateral circulation before recanalization ($\rho^2=4.57$, $p=0.03$) were chosen as independent variables for predicting LVR. Patients with greater than 0.43 in the LR ratio on Day 2 showed a lower wall-thinning ratio (58±19% vs 72±20%, $p=0.05$). This study shows that the optimal time to estimate the microvascular integrity for predicting LVR is 1 day after recanalization, which is neither shortly after recanalization nor during the convalescent stage. (*Circ J* 2002; 66: 685–690)

**Key Words:** Contrast echocardiography; Left ventricular remodeling; Magnetic resonance imaging; Myocardial infarction

Early study has nicely shown that the detection of the no-reflow phenomenon on myocardial contrast echocardiography (MCE) can predict unfavorable left ventricular remodeling (LVR) in patients with a successfully recanalized myocardial infarction (MI). However, the optimal time to assess microvascular integrity in order to predict LVR has not been fully elucidated. Therefore, this study was designed to elucidate the optimal time for performing MCE for estimating LVR, and to clarify the left ventricular structural outcome using magnetic resonance imaging (MRI) in patients with or without preserved microvascular integrity within the risk area of a MI.

**Methods**

**Patient Selection**

The study population consisted of 53 consecutive patients (42 men, 11 women) ranging from 44 to 86 years of age (mean, 62 years) who underwent serial MCE with the diagnosis of a first acute anterior MI. They were prospectively selected if they met the following criteria: (1) Killip classification I–III; (2) collateral circulation grade 0–II to the infarct-related coronary artery; (3) culprit lesion located in the 6th or 7th segment; (4) single vessel coronary artery disease; (5) Thrombolysis in MI trial grade 0 or I flow on initial coronary angiography after selective infusion of 5 mg isosorbide dinitrate; (6) Thrombolysis in MI trial grade II or III flow with <50% diameter residual stenosis on coronary angiography after recanalization within 24 h of the onset of symptoms; (7) technically adequate 2-dimensional (2-D) echocardiographic images; and (8) high grade stenotic lesion (>70% diameter stenosis) in the 6th or 7th segment not observed in the remote stage after recanalization. The Institutional Review Board approved the study protocol. The registered patients and/or the family received written information concerning the study and each gave informed consent for participation. Diagnosis of acute MI was made based on the following criteria: chest pain lasting for more than 30 min, ST-segment elevation in at least 2 consecutive precordial leads on electrocardiogram (ECG); regional wall motion abnormalities in the territory of the left anterior descending (LAD) coronary artery on 2-D echocardiograms; and a typical pattern of increase and decrease with time in total serum creatine kinase.

**MCE and Interventional Procedures**

Emergency coronary angiography was performed following hospital admission, and providing the patients did not have severe congestive heart failure, left ventriculograms...
in the 30-degree right anterior oblique plane were also obtained prior to recanalization. After confirming occlusion of the proximal LAD coronary artery, MCE was performed prior to recanalization as follows. The procedure began with selective intracoronary injection of 2 mL sonicated ioxaglic acid (Hexabrix-320, Tanabe, Osaka, Japan) at 1 mL/s with a 5F diagnostic catheter. Echocardiographic images in the long axis apical view were recorded on super-VHS video cassette and a phased-array system (Model SSD 870 or SSD2200 Ultrasound Systems, Aloka, Tokyo, Japan) with a 3.5-MHz transducer. Images were aligned in order to correspond to a left ventriculogram obtained in the right anterior oblique projection. The gain settings and the contrast controls were held constant after we had determined the optimal settings for each patient. Risk area was defined in the end-diastolic phase before opening the infarct related coronary artery, after which primary percutaneous transluminal coronary angioplasty (PTCA) was performed. MCE was repeated shortly after successful recanalization. Care was taken to depict the same outline as that in the initial examination. Because residual stenosis decreases the coronary flow reserve and affects the maximum opacification in the risk area, we excluded patients with high-grade residual stenosis (>50% diameter stenosis). Angiotensin-converting enzyme inhibitors, diuretics, calcium antagonists, anti-arrhythmic agents and/or nicorandil (a potassium channel opener) were orally administered if required based on the cardiac condition. On the second hospital day, MCE was repeated and the arterial sheath was removed. In both the convalescent (2–4 weeks after recanalization) and remote stages (3–8 months after recanalization), whenever feasible, coronary angiograms, MCE and left ventriculography were repeated in a similar manner.

Assessment of Wall-Thinning in Risk Area Using MRI

Gadolinium-diethylenetriamine penta-acetic acid (DTPA) enhanced MRI using a 0.5-tesla system that was ECG gated was carried out 3–4 weeks after recanalization. Several contiguous axial sections and longitudinal sections were obtained by spin echo sequence with an echo time of 30 ms and a repetition time equivalent to the R-R interval on the ECG. The obtained images were 256×256 matrix images. T1-weighed MRI was done 10 min after intravenous administration of 0.1 mmol/kg of gadolinium-DTPA. The wall thickness within the risk area was assessed from 10 mm thick slices along the long axis plane. On the images, 100 chords were drawn perpendicularly from the pericardial contour to the endocardial contour and were measured using customized software. The average lengths of the chords in the territories of the risk area and those of the posterior walls were calculated. The wall-thinning ratio in the risk area was calculated by dividing the average lengths of the chords in the 2 regions. The signal intensity in the risk area using gadolinium-DTPA enhanced MRI was defined as the ratio of the gray scale in the risk area to that in the remote controls bed.

Quantitative Angiography, Left Ventriculography and Assessment of Microvascular Integrity

Coronary angiograms were analyzed using quantitative software to determine the minimal lumen diameter, reference coronary artery dimensions and % diameter stenosis at the site of most severe stenosis. Planimetry was used to measure the size of the initial risk area. Left ventricular end-diastolic volume, as well as the global left ventricular ejection fraction, was evaluated using the area–length method at baseline and in the remote stage. Left ventricular regional wall motion was assessed in each case using the centerline method. For serial measurements of MCE, image analysis was performed using the same outline as the pre-reflow examination, with the apical long axis view carefully delineated in each stage using the off-line computer system. We defined the ratio of the relative size of the initial risk area as follows:

\[
\text{risk area ratio} = \frac{\text{risk area in the territory of LAD}}{\text{total longitudinal cross-sectional area in the apical long axial view of the left ventricle}}.
\]

We defined the no- and low-reflow ratio (LR ratio) as follows:

\[
\text{LR ratio} = \frac{\text{Contrast deficit area at baseline}}{\text{Contrast defecit area after recanalization}}.
\]

For serial measurements of MCE, image analysis was performed using the same outline as the pre-reflow examination, with the apical long axis view carefully delineated in each stage using the off-line computer system. We defined the ratio of the relative size of the initial risk area as follows:

\[
\text{risk area ratio} = \frac{\text{risk area in the territory of LAD}}{\text{total longitudinal cross-sectional area in the apical long axial view of the left ventricle}}.
\]

We defined the no- and low-reflow ratio (LR ratio) as follows:

\[
\text{LR ratio} = \frac{\text{Contrast deficit area at baseline}}{\text{Contrast defecit area after recanalization}}.
\]
defined as the no reflow area. The transmural homogeneous but extremely low-opacified area and the patchily opacified area were defined as the low reflow area. The visually well and/or moderately homogeneously opacified region was defined as a good opacified area. Then, the LR ratio was defined as the ratio of endocardial length within the no- and low-reflow areas to endocardial length from the proximal edge of the basal septum to the distal edge of the initial risk area.

Statistical Analysis
Results are expressed as mean value ± standard deviation or as proportions. Continuous variables were compared using the unpaired t-test or using the Mann-Whitney U test if necessary. Statistical analysis of discrete variables was performed with the chi-square test, and the Fisher exact test was used when appropriate. Receiver operating characteristics (ROC) curve analysis was used to determine the optimal time for predicting LVR using LR ratios. In this process, the sensitivity and the specificity that corresponded to the value of LR ratios was calculated. Thereafter, the relationship between sensitivity (%) and 100-specificity (%) was delineated. The area under curve (AUC) in 3 different stages was compared in order to determine the optimal time for predicting LVR. The best cut-off for the LR ratio was determined as the value corresponding with the highest accuracy (minimal false negative and false positive results).

In the multivariate analysis, the independent factors for LVR were selected by logistic regression analysis. Findings of p<0.05 (2-sided) were considered significant.

Results
MCE was performed 33 min (range: 7–66) before opening the infarct-related coronary artery and again 51 min (range: 9–90) and 21 h (range: 10–38) after recanalization. The MCE was repeated 22 days (range: 16–32) after recanalization. The unfavorable LVR in the remote stage was defined as present when the ratio of the left ventricular end-diastolic volume in the remote stage to the left ventricular end-diastolic volume in the remote stage became greater than 1.2.

Table 2 Patient Clinical Characteristics

<table>
<thead>
<tr>
<th>Unfavorable LVR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present (n=13)</td>
</tr>
<tr>
<td>Collateral circulation</td>
<td>0.02</td>
</tr>
<tr>
<td>Grade 0</td>
<td>8 (62%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>4 (30%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 ( 8%)</td>
</tr>
<tr>
<td>Risk area ratio (%)</td>
<td>41±9</td>
</tr>
<tr>
<td>Time from onset to recanalization (min)</td>
<td>38±22</td>
</tr>
<tr>
<td>Q wave myocardial infarction</td>
<td>12 (92%)</td>
</tr>
<tr>
<td>TIMI grade of flow (Day 1)</td>
<td>0.25</td>
</tr>
<tr>
<td>Grade 2</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>10 (77%)</td>
</tr>
<tr>
<td>Percent diameter stenosis (Day 1)</td>
<td>27±15</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (Day 1)</td>
<td>43±12</td>
</tr>
<tr>
<td>Left ventricular regional wall motion (Day 1)</td>
<td>–2.9±0.43</td>
</tr>
<tr>
<td>Low- and no-reflow ratio (Day 2) (%)</td>
<td>56±28</td>
</tr>
<tr>
<td>Wall-thinnning ratio in risk area (%)</td>
<td>55±18 (n=8)</td>
</tr>
<tr>
<td>Left ventricular enddiastolic volume (Day 1) (ml)</td>
<td>132±34</td>
</tr>
<tr>
<td>Left ventricular enddiastolic volume (remote) (ml)</td>
<td>165±56</td>
</tr>
</tbody>
</table>

Medications
- Angiotensin-converting enzyme inhibitor | 3 (23%) | 7 (18%) | 0.47 |
- ß-blocker | 0 ( 0%) | 2 ( 5%) | 0.57 |
- Calcium antagonist | 9 (69%) | 26 (65%) | 0.53 |
- Potassium channel opener | 9 (69%) | 20 (50%) | 0.19 |
- Nitrate | 10 (76%) | 28 (70%) | 0.46 |

Table 3 Sensitivity and Specificity for Predicting Unfavorable Left Ventricular Remodeling

<table>
<thead>
<tr>
<th>Cut-off in LR ratio</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>67%</td>
<td>70%</td>
<td>83%</td>
</tr>
<tr>
<td>Specificity</td>
<td>61%</td>
<td>75%</td>
<td>56%</td>
</tr>
</tbody>
</table>

LR ratio, no- and low-reflow ratio.

Table 4 Independent Variables for Unfavorable Left Ventricular Remodeling

<table>
<thead>
<tr>
<th>LR ratio on Day 2</th>
<th>Coefficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collateral circulation grade</td>
<td>–0.98</td>
<td>4.57</td>
</tr>
</tbody>
</table>

LR ratio, no- and low-reflow ratio.
Diastolic volume on Day 1 was greater than 1.2. Left ventriculography was performed in 5.8±1.6 months after recanalization for LVR-positive patients and in 5.9±1.7 months for LVR-negative patients (p=0.42).

There were no significant differences in the patients' baseline characteristics between the patients with or without unfavorable LVR (Table 1). ROC curve analysis was used to determine the optimal time for predicting LVR. The AUC were 0.61, 0.72, and 0.66 on Days 1, 2, and 22, respectively (Fig 1). Best cut-off values for the LR ratios were determined as 0.51, 0.43, and 0.25 on Day 1, Day 2 and Day 22, respectively. Sensitivities for predicting LVR were calculated as 67%, 70% and 83%, respectively. Specificities were 61%, 75% and 56%, respectively (Tables 2, 3). Among the patients' clinical factors, the grades of collateral circulation prior to recanalization and the LR ratio on Day 2 were significantly different between the 2 groups (Table 2).

For the logistic regression analysis, the factors obtained by Day 2 showing a value of p<0.10 in univariate analysis (Tables 1, 2) were selected and the grade of collateral circulation and LR ratio on Day 2 were chosen. Both factors were determined as independent for predicting LVR (Table 4).

MRI was performed in 27 consecutive patients. The wall-thinning ratios in the risk area measured by MRI during the convalescent stage were also significantly lower in the patients with LVR (Table 2, Figs 2, 3). Obvious signal intensity in the risk area using enhanced MRI was observed in all patients. There were no significant differences in the signal intensity between patients with and without LVR (1.7±0.5 vs 1.6±0.4, p=0.42). Patients with LR ratio greater than 0.43 (best cut-off for predicting LVR) on Day 2 had a lower wall-thinning ratio (58±19% (n=10) vs 72±20% (n=17), p=0.05). However, no significant differences were found in the signal intensity using enhanced MRI between these 2 groups (1.8±0.6 vs 1.6±0.4, p=0.58).

**Discussion**

**Optimal Time to Assess Microvascular Integrity for Predicting LVR**

The no-reflow phenomenon detected by intracoronary MCE has been clearly demonstrated as reliable for predicting unfavorable LVR in the convalescent stage.1 MCE performed shortly after recanalization is regarded as a most useful clinical tool, but recent studies have shown instability of microvascular integrity immediately after reperfusion because of reactive hyperemia as well as microvascular impairment.6–8 In our previous study using intracoronary MCE with papaverine,5 the optimal time for predicting myocardial viability was 1 day after recanalization. Kamp et al have also shown that microvascular integrity assessed with intravenous MCE 12–24 h after successful recanalization is an independent predictor of viable myocardial tissue.8 In our present study, the optimal time for predicting LVR seems to be 1 day after recanalization based on ROC curve analysis. Microvascular circulation tended to converge to the best during the subacute stage, and scatter again toward the convalescent stage. Recovery from microvascular stunning, as well as neovascularature within the infarct region, did not seem to necessarily improve the statistical power for predicting LVR after successful PTCA.

**Structural Outcome and Signal Intensity in Risk Area Using MRI**

The thinning ratio within the initial risk area was significantly lower in patients with LVR. A previous study using serial conventional echocardiography has also shown significant wall thinning in the early convalescent stage (until 7 days after recanalization) in patients with LVR.9

In an early study using gadolinium-DTPA enhanced MRI, the infarct region was evident in the convalescent stage.10 In our present study, we also found high signal intensity within the risk area in all patients, but there were no significant differences in signal intensity between patients...
with and without LVR or between patients with and without broad low perfused region on Day 2. Previous experimental data have shown that gadolinium-DTPA enhanced MRI significantly shortened T1 in myocardial regions with irreversible injury, but no differences in signal intensity or relaxation time are seen in reversibly injured myocardium. In a clinical study, however, no differences were found in T1 values between patients with and without perfusion. Because the alterations in T1 are complex, it might not reflect specific histological findings. More accurate MRI measurements of the risk area may distinguish perfused and non-perfused myocardium.

Left Ventricular Remodeling and Collateral Circulation

The acute MI patients, whom we found had poor collateral blood flow to the infarct-related coronary artery, frequently had LVR, and in our study, the grade of collateral blood flow was an independent factor for predicting LVR. However, Sabia et al reported that there was no significant correlation between the grade of collateral flow on coronary angiography and improvement in wall motion after recanalization. The myocardial perfusion from collateral circulation detected by MCE is a more useful predictor of myocardial viability and these findings have been tested in patients in the acute as well as the subacute stage. Residual myocardial perfusion via collateral vessels from the non-infarct related coronary artery has been evaluated and the patients with significant residual flow showed better improvement in wall motion; similar findings can be demonstrated using intravenous MCE. Coggins et al performed an experimental study using MCE with high mechanical index intermittent harmonic imaging at pulsing intervals of <1 to 50 cardiac cycles, during an intravenous infusion of microbubbles. Perfusion defect size using shorter pulsing intervals of cardiac cycles corresponded to the risk area for MI, and defect size using longer pulsing intervals corresponded to the final infarct size. Combined assessment of reflow using MCE and the collateral blood flow using coronary angiography can precisely predict myocardial viability after acute MI and may help increase the sensitivity and the specificity for predicting LVR.

Study Limitations

First, we had to repeatedly perform coronary angiography as well as MCE, both of which are invasive techniques. Furthermore, sonicated ioxaglic acid is not a physiologic tracer. Second, we measured microvascular intensities on Day 1, Day 2 and Day 22 only. There are several limitations using invasive methods to definitively conclude when is the best time for predicting LVR. Lastly, we could not infuse the sonicated contrast media via the right coronary artery in several patients. The myocardial enhancement via the right coronary artery should have been estimated to evaluate the residual blood flow prior to recanalization.

Future Prospects

Recently it has been demonstrated that (1) MCE with Levovist reliably identifies the no reflow phenomenon after successful reperfusion in acute MI (2) intravenous MCE using Sonazoid immediately prior to primary PTCA seems safe and capable of detecting a perfusion defect and its subsequent dynamic changes in patients with a first acute MI and (3) harmonic power Doppler imaging using PESDA is a sensitive and specific method for the identification of myocardial reperfusion early after acute MI. It yields prognostic information for the late recovery of ventricular function, differentiating stunning from necrotic myocardium. Serial observation using invasive MCE enables us to estimate the risk of future events in patients who undergo primary PTCA. Therefore, intravenous noninvasive MCE might also be able to determine the optimal time for predicting LVR as well as the risk of future events.

Conclusion

The optimal time to assess microvascular integrity for the risk of unfavorable LVR appears to be 1 day after PTCA in patients with successfully recanalized MI. In patients with a broad region of low perfusion within the area at risk even on Day 2, significant wall-thinning is detected using MRI performed in the convalescent stage. The status of microvascular integrity 1 day after recanalization as well as collateral circulation prior to recanalization are independent variables for LVR.

Acknowledgments

We thank Amy Ozeki, BA and Hana Ozeki, BS for their assistance with the manuscript.

References