Equilibrium Radionuclide Angiography for Evaluating the Effect of Facilitated Percutaneous Coronary Intervention on Ventricular Synchrony in Patients With Acute Myocardial Infarction

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Background: It is unclear whether facilitated percutaneous coronary intervention (PCI) via a transradial approach therapy is preferable to primary PCI, with improved ventricular synchrony performance (VS), in Chinese patients.

Methods and Results: The 152 patients with their first anterior acute myocardial infarction (AMI) were randomized to a primary PCI group or facilitated PCI group. In the 1st week and 6th month after AMI onset, the parameters of VS were measured by equilibrium radionuclide angiography with ventricular phase analysis. The rate of TIMI grade-3 flow in the infarct-related artery pre-PCI in the facilitated PCI group was higher than that in the primary PCI group (30.56% vs. 8.45%, P=0.001). At the 6th month post-AMI, the parameters of time to peak ejection rate, phase shift and peak phase standard deviation were lower than in the primary PCI group (P<0.05, respectively). The incidence of recurrent ischemia and new or worsening congestive heart failure post-AMI in the facilitated PCI group was significantly lower than that in the primary PCI group (2.78% vs. 9.86%, P=0.043; 2.78% vs. 12.68%, P=0.028).

Conclusions: Facilitated PCI via a transradial approach might significantly inhibit left ventricular remodeling and improve left ventricular function because of the complete, persistent patency of the infarct-related artery with few complications of vessel access and bleeding. (Circ J 2012; 76: 928–935)

Key Words: Acute myocardial infarction; Percutaneous coronary intervention; Synchrony; Thrombolysis; Ventricular remodeling

Left ventricular (LV) remodeling after acute myocardial infarction (AMI) is a pathophysiologic process caused by contractive stretching between normal and necrotic/ischemic myocardium around the infarcted area. As a result, the ventricle loses mechanical synchronization, which causes further deterioration in the hemodynamic abnormality. Therefore, LV remodeling is considered to be the main determinant factor for cardiac accident and long-term poor outcomes after AMI.

The key management technique to protect ventricular function and synchrony is to reperfuse the ischemic myocardium as soon as possible by recanalizing the infarct-related artery (IRA).2-5 Although intravenous thrombolytic therapy is simple, convenient and economic, the rate of patency of the IRA with TIMI grade II flow is only 50–70% in only half of these patients.6 Conversely, ischemic recurrence and IRA reocclusion may occur in 15–30% of them. Although primary percutaneous coronary intervention (PCI) can completely and persistently reopen the IRA, reperfusion is delayed up to 40–60 min as compared with thrombolytic treatment. Although facilitated PCI, which combines thrombolytic therapy and primary PCI, was once expected to preserve ventricular function and improve prognosis, the ASSENT-4 trial evaluating facilitated PCI after standard-dose thrombolytic infusion failed to find benefit at 90 days,7 and primary PCI was claimed to be superior to pre-intervention thrombolysis for long-term prognosis through 5 years of follow-up.8 However, it is unclear whether reduced-dose reteplase, combined with primary PCI, is preferable to either of them in opening the IRA, and in improving ventricular function. In the present study, we evaluated the influence of primary PCI and facilitated PCI (half-dose reteplase) on the cardiac function and synchronization, with the aim of providing reliable data on the strategy for protecting ventricular performance.
Methods

Study Population

A total of 152 consecutive patients with first anterior AMI were enrolled in this study from September 2006 to September 2009. Patient eligibility criteria included: (1) onset within 6h; (2) age <70 years; (3) ST elevation on contiguous 2-lead ECG; (4) transfer to the PCI center within 90 min; as well as (5) suitability for percutaneous revascularization; (6) no prior use of t-PA (tissue-type plasminogen activator); and (7) provision of informed consent.

This study was reviewed and approved by the ethics committee of the hospital. All patients gave informed written consent before any intervention procedures based on a randomized consent method. The treating physician informed study participants that this study was an investigated protocol, that selection of reperfusion therapy was randomized, and that refusal to participate in this study would not affect treatment. The treating physician described and discussed the content of the informed consent prior to participation in the present study.

Exclusion criteria were: (1) cardiogenic shock or severe heart failure (HF); (2) bleeding diathesis or recent stroke within 4 weeks; (3) recent surgery; (4) previous intracranial or spinal surgery; (5) neoplasms; (6) severe hypertension; (7) acute aortic dissection; (8) contraindication for reperfusion therapy; or (9) serious arrhythmia or bundle branch block.

Protocol

Of the enrolled 152 patients, 76 were randomized to a primary PCI group and 76 to a facilitated PCI group (reteplase 50 mg+ PCI). Five patients were excluded in the primary PCI group because of ST resolution before PCI (n=3) and PCI not being performed because the IRA was too small (n=2). Four patients were excluded in the facilitated PCI group because of ST resolution before t-PA administration (n=2), complicated cerebrovascular infarction (n=1), and requiring cardiopulmonary resuscitation (n=1).

Each patient received aspirin 300 mg and clopidogrel 300 mg as they were enrolled. The facilitated PCI group was pretreated with 50 mg reteplase (ACTILYSE, Boehringer Ingelheim Shanghai Pharmaceuticals Co Ltd). Heparin was given as an initial bolus of 100 U/kg (<10,000 U in total) before PCI. If necessary, additional boluses were administered to achieve an activated clotting time of 250s. Other medications, including β-blockers, nitrates and morphine, were administered at the discretion of the attending physician.

Catheterization Procedures and Angiographic Analysis

Diagnostic coronary angiography (CAG) were performed immediately after admission to our center in the primary PCI group or after reteplase administration in the facilitated PCI group. PCI were carried out under the standard procedure via the radial artery. PCI was performed when persistent occlusion or substantial stenosis of the IRA (either stenosis of ≥70% of the diameter of the artery or stenosis of 50–70% with thrombus, ulceration, or spontaneous dissection) was present.

If intracoronary stents were placed, clopidogrel (75 mg/day) and aspirin (300 mg/day) were prescribed. Glycoprotein IIb/IIIa inhibitors were administered at the discretion of the attending physician. In all cases the coronary perfusion status of the IRA was classified according to the system used in the Thrombolysis In Myocardial Infarction (TIMI) trial. Access and systemic bleeding complications were observed and recorded according to TIMI definitions of minor and major bleeding.

Laboratory Analyses

Total creatine kinase (CK) levels were measured at admission and every 6h. ECG was recorded at least daily.

LV Function and Synchrony Analysis

At 1 week and 6 months after the onset of AMI, equilibrium radionuclide angiography (ERNA) and ventricular phase analysis were carried out (Sopha DST, France) by 2 blinded, independent observers. Based on an in vivo red blood cell labeling technique, 740 MBq 99mTc was intravenously injected. The labeling efficiency was greater than 90%. The patients were required to fast for 4h prior to the study, and refrained from caffeine for 24h. They were injected with 20mg of stannous pyrophosphate in 1.5 ml saline while supine and 30min later, a rapid bolus of 740 MBq 99mTc pertechnetate was given intravenously. After time for equilibration in the blood, a standard gated cardiac blood pool study was acquired in the left anterolateral oblique projection that best displayed the intraventricular septum (ie, ~45° with 10° caudal angulation). The R–R interval was divided into 32 frames, and multigated acquisition was recorded for 900s in a 64×64 matrix with a total of 8 million counts. Processing and measurements were made according to the American Society of Nuclear Cardiology Society guidelines.

The LV ejection fraction (LVEF) was calculated from ERNA using the SOPHY processing system, which automatically drew regions of interest around the LV cavity for each frame of the cardiac cycle and derived the LVEF from end-diastolic and end-systolic counts inside the regions of interest. Other ventricular systolic and diastolic parameters could also be generated. The peak ejection rate (PER) and time to PER (TPER) were used to measure LV systolic function, and peak filling rate (PFR) and time to PFR (TPFRR) were used for diastolic function.

ERNA phase analysis provided a quantitative parametric display of the magnitude of regional contraction by means of amplitude images and additional information about the time sequence of regional contractions by means of phase images. The amplitude image, phase image and phase histogram were obtained with a SOPHY phase analysis processing system. Phase analysis was performed on images generated from a pixel-by-pixel fit of the first harmonic analysis of the blood pool data. The phase shift (PS) was defined as the difference between the earliest phase angle and the latest phase angle in the LV. The PS represented the temporal distribution of ventricular contractions, a greater PS demonstrating less synchronous ventricular contractions. Phase image can reflect the systolic and diastolic phases by pictures and the phase histogram reflects the compliance and balance of every part of the LV by quantitative parameters such as the PS, full width at half maximum (FWHM) and peak phase standard deviation (PSD); that is, the synchronism of the LV. FWHM and PSD show the centralization and average dispersion of myocardial contraction. A decrease in PSD, PS and FWHM indicates enhanced ventricular synchrony.

Medical Treatment and Follow-up

All the patients were given standard medicines such as angiotensin-converting enzyme inhibitor, β-blocker, aspirin and clopidogrel. Clinical follow-up was carried out by telephone or office visit throughout the 6-month follow-up. Major adverse cardiac events such as recurrent ischemia, re-infarction, new or worsening HF, urgent revascularization, bleeding complications and death were recorded.
Continuous variables are expressed as mean±standard deviation and categorical variables as percentages. Continuous variables were compared by Student’s t-test for normally distributed values; otherwise, the Mann-Whitney U test was used. Proportions were compared by Fisher’s exact test when the expected frequency was <5; otherwise, the chi-square test was applied. ANOVA was used for changes in continuous variables among the 3 groups. A P value <0.05 (2-tailed) was considered statistically significant. Analysis was performed with SPSS 10.0 software (Chicago, IL, USA).
Results

Baseline Clinical Characteristics and Interventions Course
There was no significant difference between the 2 groups in their clinical characteristics (Table 1). Time to emergency CAG in the facilitated PCI group was significantly longer than that in the primary PCI group. The TIMI grade-3 rate of the IRA pre-PCI in the facilitated PCI group was higher than in the primary PCI group (30.56% vs. 8.45%, P=0.001). The peak CK in the facilitated PCI group was lower than that in the primary PCI group (Table 2).

Changes in LV Ventricular Function
At the 6th month post-AMI, the parameters of LVEF and PER in the facilitated PCI group were increased by 18.01% and 22.94%, respectively (all P<0.05), while TPER, PS and PSD were decreased by 10.12%, 9.42% and 15.13%, respectively, as compared with the primary PCI group (all P<0.05) (Table 3). At the 6th month post-AMI, the improvements in the phase picture and phase histogram in the facilitated PCI group were much better than those in the primary PCI group (Figures 1–4).

Complications and Outcome
No statistical difference was noted between the 2 groups with regard to bleeding complications (Table 4). Blood transfusion was required in 1 patient in the facilitated PCI group, but in none of the primary PCI group. The incidence of recurrent ischemia and new or worsening congestive HF post-AMI in the facilitated PCI group was significantly lower than that in the primary PCI group (2.78% vs. 9.86%, P=0.043; 2.78% vs. 12.68%, P=0.028).

Table 3. ERNA Parameters of the 2 PCI Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Primary PCI (n=71)</th>
<th>Facilitated PCI (n=72)</th>
</tr>
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<tbody>
<tr>
<td>Systolic function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>34.0±3.26</td>
<td>42.75±3.47</td>
</tr>
<tr>
<td>PER (EDV/s)</td>
<td>1.59±0.10</td>
<td>2.18±0.08</td>
</tr>
<tr>
<td>TPER (ms)</td>
<td>184±11</td>
<td>168±15</td>
</tr>
<tr>
<td>Diastolic function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFR (EDV/s)</td>
<td>1.71±0.43</td>
<td>2.36±0.15</td>
</tr>
<tr>
<td>TPFR (ms)</td>
<td>209±28</td>
<td>170±22</td>
</tr>
<tr>
<td>Ventricular synchrony</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS (°)</td>
<td>53.16±18.64</td>
<td>46.28±12.33</td>
</tr>
<tr>
<td>FWHM (°)</td>
<td>30.15±9.27</td>
<td>20.78±3.85</td>
</tr>
<tr>
<td>PSD (°)</td>
<td>14.26±2.83</td>
<td>10.77±4.26</td>
</tr>
</tbody>
</table>

*Compared with the same time in the primary PCI group: <0.05; compared with 1 week within the same group, P<0.05.

ERNA, equilibrium radionuclide angiography; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; PER, peak ejection rate; TPER, time to peak ejection rate; PFR, peak filling rate; TPFR, time to peak filling rate; PS, phase shift; FWHM, full width at half maximum; PSD, peak phase standard deviation.

Figure 1. Representative ventricular phase image (A) and ventricular phase histogram (B) of ERNA in the 1st week post-AMI in a primary PCI group patient. The color maps have 256 levels, with the earliest phase angle corresponding to white and the latest phase angle corresponding to orange. A synchronous contraction pattern is reflected by homogeneous phase angle distribution of the phase image. (A) Significant phase delay (red region) at the anterior and apical wall. (B) The x-axis represents the timing of 1 cardiac cycle (R–R interval) in 360 degrees. The y-axis represents the frequency of distribution. Normalized phase distributions are relatively uniform and the corresponding phase histograms are highly peaked, narrow distributions. There are widely spread distributions with 79° PS, 16° PSD and 39° FWHM. ERNA, equilibrium radionuclide angiography; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; PS, phase shift; FWHM, full width at half maximum; PSD, peak phase standard deviation.
Discussion

Early and complete reperfusion in the setting of AMI is effective in both limiting LV damage and improving clinical outcome. Both thrombolysis and primary PCI are validated therapies in the treatment of AMI, which could improve the outcomes and reduce mortality. Intravenous thrombolytic therapy is an established, simple, widely available and cost-effective treatment option for AMI. Nevertheless, the utility of fibrinolytic drugs is limited by the risk of bleeding, suboptimal rates of reperfusion, particularly in the presence of “older” thrombi, and a significant rate of reocclusion, which has a powerful detrimental impact on survival. Primary angioplasty is considered the gold standard of myocardial reperfusion when promptly performed by a skilled team. However, as the efficacy of this therapy is time-dependent, logistical barriers and other constraints limit its use to no more than 20% of AMI patients worldwide. The no-reflow phenomenon in PCI may lead to failure of myocardial reperfusion. This study was designed to investigate the effects of facilitated PCI on myocardial reperfusion, infarct size limitation and LV remodeling.
Facilitated vs. Primary PCI in STEMI

The microthrombi and desquamation of atheromatous plaques caused by mechanical intervention often lead to distal microcirculatory embolism, platelet activation and release of vascular active factors, which result in the microvascular slow reflow (or no-reflow) phenomenon and decreased myocardial reperfusion. Some studies have demonstrated that both reperfusion of ischemia myocardium and residual stenosis in the IRA are important factors in the ventricular volume and ventricular remodeling after MI. Emergency CAG in this study resulted in a better rate of TIMI 3 flow in the IRA before PCI in facilitated PCI group compared with the primary PCI group, with lower peak values of CK-MB, which indicated that the therapies administered in the facilitated PCI group had better effects on reperfusion of the IRA and limiting of the size of the infarct. Some meta-analyses have found that facilitated PCI results in a higher percentage of enhanced early reperfusion when compared with primary PCI. According to our 6-month follow-up, the incidence of recurrent ischemia and of new or worsening congestive HF post-AMI was lower in the facilitated PCI group. These results strongly indicate that intravenous administration of reteplase played a role in loosening intracoronary thrombus and then improving myocardial reperfusion. The lowered CK-MB level and improved LV function in our study were in accordance with a reduction in both the size of the myocardial infarct and the incidence of major adverse cardiac events. Facilitated PCI was beneficial for early improvement in myocardial reperfusion and early protection of cardiac performance. ERNA is established as the gold standard for non-invasive cardiac function tests. However, these days gated single-photon emission computed tomography (SPECT) is widely used and may replace ERNA because it has a definite advantage in being able to simultaneously evaluate myocardial perfusion. However, gated SPECT has significantly underestimated LVEF and some other ventricular synchrony parameters in some studies, especially in a population of patients with large MI and LV dysfunction. On the other hand, another merit of the ERNA phase image is that the right ventricular phase can be simultaneously viewed, which is impossible with gated SPECT. Therefore, ventricular function was compared between the 2 groups by ERNA in this study, and the radionuclide phase analysis method was used to quantitatively analyze the changes in ventricular synchrony. Phase imaging objectively displayed the sequence of ventricular contraction, confirmed the conduction sequence and served as an indicator of ventricular synchrony. In recent years, phase analysis in ERNA has received increasing attention because it provides robust and re-

Table 4. Complications and Outcomes of the 2 PCI Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Primary PCI</th>
<th>Facilitated PCI</th>
<th>P value</th>
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<tbody>
<tr>
<td>New or worsening CHF</td>
<td>9 (12.68)</td>
<td>2 (2.78)</td>
<td>0.028</td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>7 (9.86)</td>
<td>2 (2.78)</td>
<td>0.043</td>
</tr>
<tr>
<td>Re-infarction</td>
<td>3 (4.23)</td>
<td>1 (1.39)</td>
<td>0.679</td>
</tr>
<tr>
<td>Urgent TVR</td>
<td>3 (4.23)</td>
<td>1 (1.39)</td>
<td>0.679</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>4 (5.63)</td>
<td>1 (1.39)</td>
<td>0.161</td>
</tr>
<tr>
<td>Noncardiac death</td>
<td>2 (2.82)</td>
<td>0 (0)</td>
<td>0.416</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>TIMI-defined bleeding Minor</td>
<td>7 (9.86)</td>
<td>8 (11.11)</td>
<td>0.813</td>
</tr>
<tr>
<td>Major</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Access bleeding</td>
<td>1 (1.41)</td>
<td>1 (1.39)</td>
<td>1.000</td>
</tr>
<tr>
<td>Transfusion</td>
<td>0 (0)</td>
<td>1 (1.39)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Data are n (%). PCI, percutaneous coronary intervention; CHF, congestive heart failure; TVR, target vessel revascularization; TIMI, Thrombolysis In Myocardial Infarction.
produces indices of mechanical dyssynchrony. Several studies have shown its feasibility for assessing LV systolic dysynchrony in patients with HF. In this study, ERNA showed that the parameters of ventricular systolic function and synchrony in the facilitated PCI group were much better than those in the primary PCI group at the 6-month follow-up. Because of myocardial necrosis accompanied by akinesia, even the paradox movement, ventricular compliance is damaged and causes phase deviation at the location of the infarction, so movement synchronism of the LV will be obviously limited. Some studies showed that early reperfusion treatment (within 3 h) can reduce myocardial necrosis and MI size, and also prevent LV remodeling and improve left heart function. Therefore, the advantages of facilitated PCI for ventricular synchrony are associated with time-dependent and complete reopening of the IRA.

Facilitated PCI via a transfemoral approach might increase the bleeding complications, particularly local access bleeding complications, which would offset the benefit of early myocardial reperfusion. The ASSENT-4 trial found more frequent bleeding and ischemic complications in the facilitated PCI group than in the primary PCI group. The FINNESE study indicated the effectiveness of pre-PCI administration of thrombolytic agents within 4 h from onset in patients with AMI. The FINNESE trial, however, found a higher incidence of bleeding complications in the facilitated PCI group (t-PA combined with abciximab) than in the primary PCI group. Recently, transradial access has been increasingly used in patients with AMI. In the present study, all patients underwent facilitated PCI via transradial artery access without any difference in bleeding complications among the 3 groups. Another reason for the differences between previous reports and the present results is the reduced-dose reteplase protocol used in the present study, which causes less bleeding complications than other standard-dose thrombolytic agents. All the above indicated that facilitated PCI had a good effect on early reperfusion and improving reperfusion of the microcirculation, and that the radial artery approach can reduce bleeding events and vessel complications.

Study Limitations

First, the total number of patients in the study was small. Second, the study was underpowered to detect differences in mortality because of the limited observation time. Third, fewer study patients presented within 3 h from onset, when they would be more likely to respond to thrombolysis. Further large-scale prospective randomized trials with broader inclusion criteria need to be designed with the main goal of identifying the optimal timing for early PCI after fibrinolysis and the subgroups most likely to benefit.

In conclusion, facilitated PCI via a transfemoral approach might significantly inhibit LV remodeling and improve LV ventricular function by complete and persistent patency of the IRA with few complications of vessel access and bleeding.

Acknowledgments

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References


