Clinical benefits of primary percutaneous coronary intervention for ST-elevation myocardial infarction patients with initial TIMI grade 3 flow in infarction-related artery

Jing Li¹, Yaowen Zhang², Yong Wang¹, Xianlun Li¹, Xiaofei Liu¹, Hu Zhang³, Wenhua Peng¹, Peng Yang¹, Shiyu Zhang¹, Nan Wang¹

¹Department of Cardiology, China-Japan Friendship Hospital, No. 2, Yinghua Road, Beijing 100029, China; ²Medieco Group Co. Ltd, B901 Building No. 20 Hepingxiyuan, Beijing 100029, China

Received July 13, 2017; Accepted March 28, 2018; Epub June 15, 2018; Published June 30, 2018

Abstract: Early spontaneous reperfusion (SR) before recanalization therapy can reduce the infarct size and preserve left ventricular function to provide a more favorable prognosis for patients with ST-elevation myocardial infarction (STEMI); however, whether SR patients should receive primary percutaneous coronary intervention (pPCI) remains unclear. This study aimed to evaluate whether pPCI is beneficial for patients with STEMI and SR. STEMI patients with SR (n=229; defined as achievement of initial TIMI grade 3 flow in the infarction-related artery (IRA) before reperfusion therapy) who received either pPCI or non-pPCI therapy were reviewed retrospectively. The average follow-up periods were 24±4 and 23±5 months for the pPCI and non-pPCI group. Compared with the non-pPCI group, the pPCI group showed shorter hospital stay (7±3 vs. 9±5 days; \(P=0.02\)), lower in-hospital reinfarction rate (0% vs. 3%, \(P=0.04\)), lower 1-year reinfarction rate (5% vs. 10%; \(P=0.02\)), lower 1-year unscheduled PCI rate (4% vs. 12%; \(P=0.02\)), and lower 1-year composite cardiac event rate (10% vs. 29%; \(P<0.01\)). In conclusion, pPCI is beneficial for STEMI patients with angiographic SR, leading to better short- and long-term major adverse cardiac events.

Keywords: ST-segment elevation myocardial infarction, spontaneous reperfusion, initial TIMI grade 3 flow, primary percutaneous coronary intervention, reinfarction, cardiac events

Introduction

Early and complete (TIMI grade 3 flow) infarct-related artery (IRA) patency and prompt myocardial salvage are of paramount importance to improve the clinical outcomes of patients with ST-segment elevation myocardial infarction (STEMI) [1]. According to the current guidelines, primary percutaneous coronary intervention (pPCI) for restoring epicardial coronary blood flow of the IRA is the mainstay therapy for STEMI patients [2]. With the increasing use of pPCI, early angiography has shown that some STEMI patients undergo spontaneous reperfusion (SR) with initial TIMI grade 3 flow in the IRA before reperfusion therapy (i.e., intravenous thrombolysis or PCI) [3, 4]. Moreover, compared with patients with initial TIMI grade 0-2 flow, patients with SR have smaller infarct size, better preserved left ventricular function, and more favorable prognosis after successful pPCI [5-7]. These observations suggest that the independent effect of initial TIMI grade 3 flow on survival persists even when corrected for post-procedural TIMI grade 3 flow and reveal the critical importance of early pre-PCI reperfusion [3]. Nevertheless, the long-term survival outcomes and optimal therapy for SR patients have not yet been evaluated in clinical trials, and the potential benefit of pPCI for these patients remains uncertain.

Materials and methods

Patient population

We retrospectively reviewed the medical records, electrocardiographic analysis, and cardiac catheterization films of patients presenting with acute STEMI, and who underwent emer-
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284 patients diagnosed with STEMI with angiographic SR between January 1, 2012 and January 1, 2015 (retrospective study)

Study cohort:
- pPCI group (n=156)
- non-pPCI group (n=73)

Excluded (total n=55)
- Incomplete data (n=11)
- Left bundle branch block (n=6)
- Thrombolytic therapy before arrival (n=8)
- Other cardiovascular causes (n=13)
- SR with ≤50% stenosis in IRA (n=5)
- Malignant tumor (n=3)
- Liver or renal failure (n=10)
- Acute stroke (n=3)

Figure 1. Study flowchart. IRA: infarct-related artery; SR: spontaneous reperfusion; STEMI: ST-elevation myocardial infarction.

Figure 2. Representative electrocardiograms (ECGs) before and after primary percutaneous coronary intervention (pPCI). A shows the elevated ST segments and peaked T waves in leads V1-V4, with preserved R-waves, in a 75-year-old female with STEMI and SR before pPCI. B shows normal ST segments, T waves and R waves in leads V1-V4 in the same patient 72 h after pPCI.

Figure 2. Representative electrocardiograms (ECGs) before and after primary percutaneous coronary intervention (pPCI). A shows the elevated ST segments and peaked T waves in leads V1-V4, with preserved R-waves, in a 75-year-old female with STEMI and SR before pPCI. B shows normal ST segments, T waves and R waves in leads V1-V4 in the same patient 72 h after pPCI.

gency coronary angiography on admission within 12 hours of symptom onset at the China-Japan Friendship Hospital (Beijing, China) between January 1, 2012 and January 1, 2015. Diagnosis of STEMI was based on the presence of symptoms of ischemia, increased serum biomarkers (cardiac-specific troponins and/or creatinine kinase-MB) and ST-segment elevation (≥1 mm in ≥2 contiguous leads) [8]. The study design is presented in Figure 1.

The study was conducted in accordance with The 1975 Declaration of Helsinki and was approved by the Ethics Committee of the China-Japan Friendship Hospital.

Inclusion and exclusion criteria

The inclusion criteria were: 18-75 years old, diagnosed with acute STEMI with angiographic SR, which was defined as achievement of TIMI grade 3 flow in the IRA before PCI (first contrast injection) [3]. The exclusion criteria were: left bundle branch block; thrombolytic therapy before arrival; final diagnosis other than STEMI, such as non-STEMI, unstable angina, takotsubo cardiomyopathy, and myocarditis; coronary spasm proved to be responsible for STEMI with angiographic SR; angiographic SR with ≤50% stenosis in IRA, which had no indication of stenting; malignant tumor; liver or renal failure; or acute stroke. Figure 2 presents a representative electrocar-
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diagram before and after pPCI in a STEMI patient with SR.

Therapeutic program

According to the European Society of Cardiology (ESC) guidelines (2012), pPCI was defined as PCI in patients with STEMI within 12 h of the onset of chest pain [9]. All patients in this study received emergency angiography. The decision of whether to perform pPCI for patients with patent IRA (TIMI grade 3 flow at initial angiography) was made by the interventional cardiology team.

Medication during hospital stay was as follow. All SR patients received a loading dose of 300 mg of aspirin and 300-600 mg of clopidogrel, as well as a single subcutaneous bolus of low molecular weight heparin (LMWH) in transit or on arrival in the emergency room. Intravenous heparin (3000 U) was routinely administered in the catheterization room before angiography. An additional dose of 6000 U and glycoprotein IIb/IIIa antagonist were used if pPCI was necessary. All patients were managed with standard administration of 100 mg of aspirin, 75 mg of clopidogrel, β-blockers, ACEI/ARB, and statins, according to the guidelines for STEMI.

Within 24 h of admission, left ventricular systolic function was assessed by echocardiography and laboratory data. If more than one assessment was performed, the results of first assessment were used in this study.

Outcomes and follow-up

Study outcomes included in-hospital and long-term mortality and major adverse cardiac event (MACE). The in-hospital MACE included death, malignant cardiac arrhythmia, heart failure, reinfarction, acute renal failure, and major bleeding, determined based on the medical records during hospitalization. The long-term MACE included 1-year reinfarction, unscheduled PCI (defined as unexpected PCI due to ischemic chest pain, not including PCI due to reinfarction), heart failure, death, and composite cardiac events, determined based on post-discharge data obtained from the clinic, hospital records, and telephone interviews during follow-up.

The cumulative ST (∑ST) segment elevation was calculated by adding the sum of the ST-segment elevations and depressions measured at the J-point with magnified calipers in electrocardiogram before angiography. ST-segment resolution was defined according to the Schroder’s method: ≥70% reduction of ∑ST elevation on consecutive electrocardiograms before angiography [10].

Patients were followed-up for 24 months (at 6-month intervals and started from 3 months after discharged first time). Echocardiography for assessment of left ventricular systolic function was performed 12 months post-discharge.

Statistical analysis

Statistical analyses were performed using SPSS for Windows Version 22.0 (IBM, Armonk, NY, USA). Type of IRA, number of diseased arteries, degree of IRA stenosis, and demographic and clinical categorical variables (e.g., sex, family history of myocardial infarction, previous myocardial infarction, hypertension, diabetes mellitus) were expressed as absolute numbers and percentages, and compared with the chi-square or Fisher exact test. Continuous variables, such as age, time from symptom onset to angiography, blood pressure, and heart rate, were expressed as mean±standard deviation (SD) and compared with the Student’s t-test. P<0.05 was considered to indicate statistical significance.

The main endpoint was composite cardiac events including 1-year reinfarction, unscheduled PCI, heart failure, and death. An observation was censored at the last follow-up if the patient was composite cardiac event-free or if the patient had died from a non-cardiac event-related cause. Follow-up analysis was performed using time-to-event data. Composite cardiac event rates for patients treated with pPCI or non-pPCI were estimated by the Kaplan-Meier method and compared using the log-rank test. P<0.05 was considered to indicate statistical significance.

The stepwise-Cox proportional hazards model with hazard ratios (HR) and 95% confidence intervals (95% CI) were used for multivariate analysis to estimate the simultaneous effects of prognostic factors on composite cardiac events, with an entry level of significance of 0.10. All P-values refer to two-tailed tests, and
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**Table 1. Baseline characteristics of patients with spontaneous reperfusion in the pPCI vs. non-pPCI groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>pPCI (n=156)</th>
<th>Non-pPCI (n=73)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63±15</td>
<td>62±14</td>
<td>0.82</td>
</tr>
<tr>
<td>Female sex</td>
<td>37 (24%)</td>
<td>19 (26%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Hypertension</td>
<td>86 (55%)</td>
<td>41 (56%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>38 (24%)</td>
<td>12 (17%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>87 (56%)</td>
<td>40 (55%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Current smoker</td>
<td>101 (64%)</td>
<td>42 (58%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Previous MI</td>
<td>8 (5%)</td>
<td>3 (4%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Previous revascularizationa</td>
<td>7 (4%)</td>
<td>3 (4%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Family history of MI</td>
<td>28 (18%)</td>
<td>12 (17%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Previous long-term aspirin</td>
<td>30 (19%)</td>
<td>17 (23%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Previous long-term statin</td>
<td>25 (16%)</td>
<td>8 (11%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Previous beta-blocker</td>
<td>22 (14%)</td>
<td>8 (11%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Previous RAS-inhibitorb</td>
<td>32 (21%)</td>
<td>13 (18%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Recurrent angina within 1 month before MI</td>
<td>105 (67%)</td>
<td>50 (68%)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Data represent mean±SD or number (percentage). pPCI, primary percutaneous coronary reperfusion; MI, myocardial infarction; aPCI or coronary artery bypass grafting; bAngiotensin converting enzyme inhibitor or angiotensin II receptor antagonist.

**Baseline characteristics**

The distribution of baseline characteristics in patients with and without pPCI (Table 1) were similar in terms of age, sex, family history of myocardial infarction, previous myocardial infarction, major cardiovascular risk factors (such as current smoker), hypertension, diabetes mellitus, dyslipidemia, chronic renal failure, and long-term (>1 y) therapy with aspirin and statins before myocardial infarction (MI).

**Clinical data**

The clinical features of the two groups are shown in Table 2. The time from onset of symptoms to angiography and the incidence of pre-MI angina were similar in the two groups. There were no significant differences between the two groups in terms of clinical manifestations, including blood pressure, heart rate, infarct location, infarction size (evaluated by peak troponin I), and cardiac function. Although the \( \Sigma \)ST-segment elevation in the two groups was similar, the incidence of pre-angiography ST-segment resolution was notably higher in the non-pPCI group than in the pPCI group (97% vs. 54%, \( P<0.01 \)).

**Results**

229 patients were eligible for this study; 156 patients received pPCI protocol.

\( P<0.05 \) was considered to indicate statistical significance.

**IRA conditions and PCI**

None of the patients received thrombolytic therapy before admission. All patients under-
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Table 3. Infarction-related artery conditions

<table>
<thead>
<tr>
<th>Variable</th>
<th>pPCI (n=156)</th>
<th>Non-pPCI (n=73)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct-related coronary artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>103 (66%)</td>
<td>45 (62%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>19 (12%)</td>
<td>11 (15%)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>33 (21%)</td>
<td>16 (22%)</td>
<td></td>
</tr>
<tr>
<td>Left main</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>The number of diseased artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>46 (29%)</td>
<td>23 (32%)</td>
<td>0.79</td>
</tr>
<tr>
<td>2</td>
<td>63 (40%)</td>
<td>26 (36%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>47 (31%)</td>
<td>24 (32%)</td>
<td></td>
</tr>
<tr>
<td>The degree of IRA stenosis</td>
<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>&lt;75%</td>
<td>6 (4%)</td>
<td>7 (10%)</td>
<td></td>
</tr>
<tr>
<td>75%-99%</td>
<td>151 (96%)</td>
<td>65 (90%)</td>
<td></td>
</tr>
</tbody>
</table>

*Diseased artery was defined as stenosis (≥50%) in at least one coronary artery.

went emergency angiography on admission, angiographic data are summarized in Table 3. The distribution of the IRA locations (left anterior descending, left circumflex, and right coronary arteries), the degree of IRA stenosis, and the numbers of diseased coronary arteries were similar in the pPCI and non-pPCI groups.

Among the 156 patients who received pPCI, 150 underwent the procedure as an emergency due to serious (≥75%) stenosis in the IRA; the other six patients with moderate (50-75%) stenosis and ruptured plaques and thrombi detected by angiography, also underwent emergency pPCI with thrombus aspiration and subsequent stent implantation.

Medication during hospital stay

The medication data of the two groups during hospital stay are shown in Table 4. All patients with SR received routine medication during hospital stay, as described before.

In-hospital and long-term outcomes

In-hospital outcomes: The In-hospital outcomes are shown in Table 5. Patients who underwent pPCI had a shorter hospitalization duration (7±3 d vs. 9±5 d, P=0.02), and showed superiority in short-term reinfarction rate over the non-pPCI group (0% vs. 3%; P=0.04). In the non-pPCI group, two patients suffered another STEMI in the original location on the 3rd and 5th day, respectively, received a second emergency angiography that both showed TIMI grade 0 flow in the original IRA, and received stent implantation.

The frequencies of heart failure, malignant arrhythmia, major bleeding, and death were similar in the two groups.

Long-term outcomes: The long-term outcomes are shown in Table 5. All 229 patients were followed-up at the clinic, none of the patients were lost to follow-up. The average follow-up duration was 24±4 months for the pPCI group and 23±5 months for the non-pPCI group. There were no significant differences for 1-year left ventricular systolic function between the two groups (60±13% vs. 58±12%; P=0.51), nor rates of heart failure (3% vs. 5%; P=0.26).

The rate of reinfarction was significantly lower in the pPCI group than in the non-pPCI group (5% vs. 10%; P=0.02). In the pPCI group, four patients suffered from reinfarction after discharge: two experienced another STEMI and one experienced NSTEMI, with IRAs different from the original ones. The fourth patient suffered from STEMI 8 months after stent implantation and discontinuation of dual anti-platelet therapy (DAPT). In the non-pPCI group, nine patients suffered reinfarction: four patients suffered from another STEMI in the original location after discharge (emergency angiography revealed total stenosis of the same IRAs as the original ones with TIMI grade 0 flow and PCI protocol was performed immediately); the remaining three reinfarctions occurred after discharge due to IRAs different from the one.

The rate of unscheduled PCI due to ischemic chest pain was significantly lower in the pPCI group than in the non-pPCI group (4% vs. 12%; P=0.02).

The pPCI group showed significant superiority over the non-pPCI group in terms of the composite cardiac events of reinfarction, unscheduled PCI, heart failure, and death (15% vs. 29%, P<0.01). Kaplan-Meier curves for composite cardiac event rates with a median of 18 months of follow-up are shown in Figure 3 (log-rank P<0.01).
Variables of ST-segment resolution before angiography and pPCI were introduced into a stepwise-Cox regression analysis to determine their association with composite cardiac events. The Cox regression analysis indicated that pPCI (HR=0.14, 95% CI: 0.06-0.33) and ST-segment resolution (HR=0.31, 95% CI: 0.13-0.74) were independent risk factors for composite cardiac events (Figure 3, Table 6). The relative risk of composite cardiac events for pPCI vs. non-pPCI was 0.14:1 (95% CI: 0.06-0.33).

**Discussion**

To our knowledge, this is the first study comparing the outcomes of pPCI and non-pPCI intervention in STEMI patients with initial patent IRA and early angiographic SR. In the present study, angiographic SR was defined as achievement of initial TIMI grade 3 flow in the IRA before reperfusion therapy. Previous studies reported SR prevalence of 8% to 57% in Caucasian, Hispanic, Israeli and other populations [5-7, 10-12], depending on the assessment time and definition of SR. Currently, with the increasing use of early antiplatelet and anti-coagulation drugs prior to pPCI, the incidence of SR may be even higher [13, 14].

Although pPCI is the preferred therapy for STEMI, the benefits of this procedure in SR patients remains to be clarified. Post-hoc analysis of four primary angioplasty in myocardial infarction (PAMI) studies [4] showed fewer complications and improved early and late survival in patients undergoing pPCI with TIMI-3 flow before angiography compared with those with TIMI 0-2 flow. Nevertheless, a comparison of the effects of pPCI with conservative therapy in the TIMI-3 flow subset alone was not included in this analysis. Steg et al. [15] compared 47 SR patients who received conservative therapy with two matched non-SR groups in whom early patency was obtained by emergency percutaneous transluminal coronary angioplasty (PTCA) or by intravenous thrombolysis; this
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myocardial damage [16, 17]. On the other hand, the patency of IRA might be unreliable without the protection of a stent, and reocclusion could induce reinfarction. Therefore, pPCI may provide more robust and “safe” protection for the IRA, and avoid the risk of reocclusion by providing stable patency for the IRA. This approach may allow early hospital discharge, with its attendant savings [18].

In this observational study, we retrospectively separated the SR patients into the pPCI and non-pPCI groups, with the aim to evaluate whether there are benefits to perform pPCI for STEMI patients with early SR. The two groups had matched baseline characteristics, including infarct location, distribution of IRAs, degree of IRA stenosis, and number of diseased vessels. In the pPCI group, the rate of ST-segment resolution before angiography was significantly lower, which might suggest a poorer initial blood supply and more delayed myocardial salvage than in the non-pPCI group, because ST-segment resolution in STEMI patients signals both epicardial vessel recanalization and microvascular flow at the cellular level [19, 20]. Furthermore, ST-segment resolution has been shown to be a powerful clinical predictor of better prognosis [21]. Nevertheless, despite this “inferior initial condition”, the pPCI group still showed better in-hospital and long-term outcomes, with especially lower rate of reinfarction and unscheduled PCI. Following Cox regression analysis to eliminate the possibility of bias from the mismatch in the ST-segment resolution, the pPCI group retained a significantly higher event-free survival rate. This finding provides evidence to advocate the use of pPCI on IRA for patients with angiographic SR.

In fact, the benefits of pPCI in SR patients appear to be equivocal. On one hand, pPCI seems unnecessary in patients who have achieved IRA TIMI grade 3 flow spontaneously because of the possibility of coronary thrombus disappearance and regression of the coronary stenosis after a few days of antithrombotic therapy. Furthermore, no reflow following ballooning or stenting may occur and lead to more evaluation revealed excellent in-hospital outcomes following conservative therapy without pPCI. Nevertheless, a comparison of the outcomes of initial conservative therapy and pPCI in SR patients was not included in this analysis and the benefits of pPCI in this cohort remained unclear.

Table 6. Multivariate analysis of prognostic factors for composite cardiac events in patients with spontaneous reperfusion

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-segment resolution</td>
<td>0.31</td>
<td>0.13-0.74</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>pPCI (yes vs. no)</td>
<td>0.14</td>
<td>0.06-0.33</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

pPCI, primary percutaneous coronary reperfusion; HR, hazard ratio; 95% CI, 95% confidence intervals; IRA, infarct-related artery.

The major threat to SR patients without pPCI is reinfarction due to the reocclusion of the IRA, because persistent residual stenosis in the vessel might be the source of plaque rupture/thrombosis. For such patients, pPCI would be expected to provide more reliable IRA reperfusion and long-term patency. In our study, the in-hospital and long-term rate of reinfarction were
both significantly lower in the pPCI group, providing evidence to support the strategy of performing pPCI protocol in the early SR patients with >50% degree of IRA stenosis.

Study limitations

This study is based on a retrospective analysis and 1-year follow-up of a cohort of 229 SR patients. The retrospective study design and relative small case number constitute the main limitations of this study. Furthermore, all cases in this study were collected in a single center. The unique opinion and operative technique of the interventional cardiologist team might be another important factor influencing the effectiveness of pPCI intervention for SR patients. A multi-center prospective study with larger cohort and longer follow-up is needed for further research.

Currently, despite of lower incidence of ST-segment resolution before angiography in the subset of STEMI patients with angiographic SR, those receiving pPCI were associated with a shorter hospitalization and lower rates of in-hospital and long-term reinfarction, long-term unscheduled PCI, and composite cardiac events.

Disclosure of conflict of interest

None.

Address correspondence to: Jing Li, Department of Cardiology, China-Japan Friendship Hospital, No. 2, Yinghua Road, Beijing 100029, China. Tel: +86-13910843524; Fax: +86-010-84205022; E-mail: nami2003@163.com

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