Delayed angioplasty is superior to an emergency strategy in ST-segment elevation myocardial infarction patients who present late and with infarct artery spontaneous reperfusion before intervention

Mingxing Li, Zidi Wu, Yong Yuan, Li Feng, Yi Lao, Zhigang Guo

Abstract

Objective: The best time to perform percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) patients presenting 12 to 72 hours after chest pain is unclear. The aim of this study was to explore whether delayed PCI was superior to emergency PCI in STEMI patients who presented 12 to 72 hours after onset of symptoms and with a spontaneous reperfusion infarct-related artery (IRA).

Methods: STEMI patients who presented 12 to 72 hours after symptom onset were enrolled and assigned to either the emergency PCI or delayed PCI group. We compared the rates of procedural success and in-hospital mortality as well as the main adverse cardiac events (MACE) during hospitalisation and after one year of follow up.

Results: We enrolled 159 patients in this retrospective study. Emergency PCI was performed in 73 patients and delayed PCI in 86 patients. A remarkably high rate of procedural success was achieved in the delayed PCI group compared with the emergency PCI group (97.7 vs 86.3%, \(p = 0.007\)) due to a lower rate of no re-flow or slow flow (2.3 vs 13.7%, \(p = 0.007\)). There was no significant difference in terms of MACE and in-hospital mortality rates (16.4 vs 9.3%, \(p = 0.133\); 1.4 vs 2.3%, \(p = 0.562\)). During one year of follow up, the left ventricular ejection fraction was similar in the two groups [median 58% (57–68) in the emergency PCI group vs median 56% (50–62) in the delayed PCI group, \(p = 0.666\)]. Although the emergency PCI group had a trend towards a higher rate of MACE, the difference was not statistically significant (12.2 vs 11.6%, HR = 1.067, 95% CI: 0.434–2.627, \(p = 0.887\)).

Conclusion: In STEMI patients who presented late (12–72 hours) after symptom onset and with a spontaneous reperfusion IRA, delayed PCI showed a higher rate of procedural success without increased rates of in-hospital and long-term MACE and mortality.

Keywords: ST-segment elevation myocardial infarction, angioplasty, TIMI flow, timing, spontaneous reperfusion

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Treatment of patients with ST-segment elevation myocardial infarction (STEMI) has substantially evolved over the past 10 years, due to improvement in pharmacological and mechanical reperfusion strategies.1 Current clinical practice, however, includes a high proportion of patients presenting late after onset of symptoms.2,4 STEMI patients who present late would be outside of the ‘golden time window’ for reperfusion and are expected to exhibit less myocardial salvage, an expansion of infarct size, as well as a higher mortality rate when compared with early comers.7,8 A growing body of evidence has shown that STEMI patients who present late but with a patent infarct-related artery (IRA) tend to have a better prognosis,11,12 and benefit from percutaneous coronary intervention (PCI).13,14 What remains unknown is the exact time window during which late reperfusion can still provide the best prognosis as well as the lowest related risk. The aim of this study was to explore whether delayed PCI (performed more than 24 hours after admission) was superior to emergency PCI (performed within two hours of admission) in STEMI patients who presented 12 to 72 hours after symptom onset and with a spontaneous reperfusion IRA (TIMI flow grade of 2 to 3).

Methods

The population consisted of STEMI patients treated with percutaneous coronary intervention at our institute from 1 January 2008 to 1 January 2015. The local ethics committee approved the study.
Inclusion criteria were: STEMI patients who were admitted after more than 12 but within 72 hours of the onset of symptoms; an IRA TIMI flow grade of 2 to 3 during initial angiography; and PCI performed during hospitalisation. The major exclusion criteria were: the time from the onset of symptoms to admission was 12 hours or less, or more than 72 hours; the IRA TIMI flow grade was 0 to 1; patients suffered from cardiogenic shock or electrical instability, or chest pain persisted when admitted; PCI was not performed during hospitalisation.

The emergency PCI group was defined as PCI performed within two hours of admission. The delayed PCI group was PCI performed more than 24 hours after admission. STEMI was defined as follows: ST-segment elevation consistent with a myocardial infarction (MI) of at least 2 mm in contiguous precordial leads and/or ST-segment elevation of at least 1 mm in two or more limb leads or new left bundle branch block; positive cardiac necrosis markers (CK-MB and/or troponin T).

The baseline and post-procedural blood flow in the IRA was quantified with the TIMI grading system. Slow flow was defined as a decrease in TIMI flow from 3 to 2 during the procedure; no re-flow was defined as decrease in TIMI flow from 3 or 2 to either 0 or 1 during the procedure.

After the diagnosis of STEMI was confirmed, all patients received clopidogrel (300 mg loading dose followed by 75 mg orally once daily) and aspirin (300 mg loading dose followed by 100 mg orally once daily). Statins, angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) and beta-blockers were routinely prescribed if no contra-indications existed. Low-molecular-weight heparin (LMWH) was instituted according to current guideline recommendations. A glycoprotein (GP) IIb/IIIa receptor antagonist was administered based on the decision of the operator.

At the time of diagnostic angiography, epicardial blood flow was assessed via the TIMI grading system. All angiograms were reviewed by two experienced operators who were blinded to all data apart from the coronary angiograms.

The primary endpoint was procedural success, defined as a final diameter stenosis of less than 30%, TIMI 3 flow, no occurrence of slow flow, and no re-flow or distal embolisation. The secondary objectives were in-hospital mortality and major adverse cardiac events (MACE), defined as heart failure, recurrent angina pectoris, target vessel revascularisation or arrhythmia.

It is routine in our hospital, after discharge, for out-patient nurses to record information of STEMI patients’ adherence to medication, tolerance of activity and well-being every three months. We collected all the information needed for one year of follow up, according to out-patient records. Re-hospitalisation due to heart failure, recurrent angina pectoris, target-vessel revascularisation or arrhythmia were regarded as MACE.

Statistical analysis
Statistical analysis was conducted with Statistical Package for the Social Sciences (SPSS) 17.0 software (SPSS Inc, Chicago, IL, USA). Numerical variables are represented as the mean ± standard deviation or median, and categorical variables as percentages or rates. To test differences between the groups, the Student’s t-test was used for numerical variables with a regular distribution, and the Mann-Whitney U-test was employed if there was an irregular distribution. Categorical variables were analysed with the chi-squared and Fisher’s exact tests. Kaplan–Meier survival analysis was used for the analysis of endpoints that occurred after the follow-up period, and a log rank test was performed to test the differences. A p-value of < 0.05 was regarded as statistically significant.

Results
From 1 January 2008 to 1 January 2015, a total of 729 STEMI patients who presented late after onset of symptoms were admitted to our department; 251 of the 729 patients presented with an IRA TIMI flow of grade 0 to 1, and 228 patients presented after 72 hours of symptom onset. Of the remaining 250 patients, PCI was not performed in 85 patients. Six were also excluded because they exhibited cardiac shock or electrical instability. Finally, 159 patients were included in the study.

Emergency PCI was performed in 73 patients and delayed PCI in 86 patients (Fig. 1). The average age was 63 years and 78% were male. There were no significant differences between the two groups in terms of baseline clinical characteristics except that patients in the delayed PCI group had higher high-sensitivity C-reactive protein (hs-CRP) and elevated fasting glucose levels. The time from symptom onset to admission or PCI was shorter in the emergency PCI group compared with the delayed PCI group (Table 1).
As shown in Table 2, there were more patients whose most recent chest pain occurred within 12 hours before admission in the emergency PCI group compared with the delayed PCI group (36.9 vs 18.6%, p = 0.012). Loading doses of aspirin and clopidogrel were given in both groups of patients, as described in the study protocol. Dual antiplatelet therapy (more than one day) and LMWH pre-PCI were administered more often in the delayed group compared with the emergency group (94.2 vs 10.8%, p < 0.001; 94.2 vs 0%, p < 0.001; 100 vs 8.5%, p < 0.001), and the emergency group had a higher rate of GPIIb/IIIa receptor antagonist use during the procedure (24.3%) compared with the delayed PCI group (4.7%, p = 0.015).

There was no significant difference between the two groups in terms of location, length or diameter of the target lesion, except that the emergency PCI group had a higher rate of thrombus-containing lesions (p = 0.028). The number of patients with an initial TIMI 3 flow was similar in the two groups (43.24 vs 58.14%, p = 0.493).

All patients underwent angiography and stent implantation. A significantly higher procedural success rate was achieved in the delayed PCI group, with a 97.7% success rate, compared to an 86.3% success rate in the emergency PCI group (p = 0.007). This higher procedural success rate was related to a remarkably lower rate of no re-flow or slow flow (2.3 vs 13.7%, p = 0.007) during PCI. Consequently, TIMI 3 flow was observed significantly more frequently at the end of the procedure in the delayed PCI group compared with the immediate PCI group (100 vs 86.3%, p < 0.001) (Table 3).

There was one death in the emergency PCI group due to cardiac rupture, and two other deaths in the delayed PCI group; one patient died of cardiac arrest and the other of cardiogenic shock. No difference was found in in-hospital mortality rates between the two groups (1.4 vs 2.3%, p = 0.562). There was no

### Table 1. Baseline clinical characteristics in the emergency PCI and the delayed PCI groups

<table>
<thead>
<tr>
<th></th>
<th>Emergency PCI</th>
<th>Delayed PCI</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Age (year)</td>
<td>62.31 ± 13.40</td>
<td>63.08 ± 12.85</td>
<td>0.714</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>60 (82.19)</td>
<td>65 (75.58)</td>
<td>0.338</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>40 (54.79)</td>
<td>41 (47.67)</td>
<td>0.427</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>17 (23.28)</td>
<td>26 (30.23)</td>
<td>0.37</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>10 (13.7)</td>
<td>5 (5.81)</td>
<td>0.11</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>38 (52.05)</td>
<td>44 (51.16)</td>
<td>1.00</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>141.31 ± 27.40</td>
<td>130 ± 23.16</td>
<td>0.052</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81.22 ± 16.59</td>
<td>74.44 ± 13.50</td>
<td>0.218</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>79.61 ± 15.27</td>
<td>81.41 ± 20.25</td>
<td>0.74</td>
</tr>
<tr>
<td>hs-CRP (median) (mmol/l)</td>
<td>6.58 (0.48–114.7)</td>
<td>9.87 (0.42–68.77)</td>
<td>0.022*</td>
</tr>
<tr>
<td>Peak CK-MB, n (median) (U/l)</td>
<td>63 (6–544)</td>
<td>37 (6–546)</td>
<td>0.10</td>
</tr>
<tr>
<td>Creatine, n (median) (mmol/l)</td>
<td>83 (36–188)</td>
<td>81 (46–378)</td>
<td>0.921</td>
</tr>
<tr>
<td>Uric acid (mmol/l)</td>
<td>372.49 ± 102.05</td>
<td>355.88 ± 118.06</td>
<td>0.293</td>
</tr>
<tr>
<td>LDLC-C, n (median) (mmol/l)</td>
<td>2.96 (0.99–6.05)</td>
<td>2.7 (1.23–6.46)</td>
<td>0.407</td>
</tr>
<tr>
<td>LDL-C, n (median) (mmol/l)</td>
<td>2.68 (0.99–6.05)</td>
<td>2.7 (1.23–6.46)</td>
<td>0.407</td>
</tr>
<tr>
<td>Fasting glucose, n (median) (mmol/l)</td>
<td>5.6 (3.86–17.56)</td>
<td>5.96 (3.81–23.11)</td>
<td>0.038*</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>3.88 ± 0.38</td>
<td>3.94 ± 0.46</td>
<td>0.386</td>
</tr>
<tr>
<td>Killip I, n (%)</td>
<td>58 (79.45%)</td>
<td>71 (82.56%)</td>
<td>0.686</td>
</tr>
<tr>
<td>Anterior wall infarction, n (%)</td>
<td>51 (69.86%)</td>
<td>65 (75.58%)</td>
<td>0.338</td>
</tr>
<tr>
<td>Time from onset to admission (h)</td>
<td>24 (12–72)</td>
<td>26 (12–72)</td>
<td>0.063</td>
</tr>
<tr>
<td>Time from onset to PCI (h)</td>
<td>24 (12–72)</td>
<td>192 (20–480)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>
| SBP, systolic blood pressure; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; *p < 0.05

### Table 2. Baseline angiographic and procedural data in the two groups

<table>
<thead>
<tr>
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<th>Emergency PCI</th>
<th>Delayed PCI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure success rate, n (%)</td>
<td>73 (100)</td>
<td>86 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>Final TIMI 3, n (%)</td>
<td>63 (86.3)</td>
<td>86 (100)</td>
<td>0.001</td>
</tr>
<tr>
<td>Slow flow/no re-flow, n (%)</td>
<td>10 (13.7)</td>
<td>2 (2.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Procedure success rate, n (%)</td>
<td>63 (86.3)</td>
<td>84 (97.7)</td>
<td>0.007</td>
</tr>
</tbody>
</table>
| *p<0.05

### Table 3. Final angiographic and procedural data after PCI

<table>
<thead>
<tr>
<th></th>
<th>Emergency PCI</th>
<th>Delayed PCI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial TIMI 3 flow, n (%)</td>
<td>32 (43.8)</td>
<td>50 (58.1)</td>
<td>0.081</td>
</tr>
</tbody>
</table>
significant difference in rate of MACE between patients who had received emergency PCI and those in whom PCI was delayed (16.4 vs 9.3\%, \( p = 0.133 \)). The left ventricular ejection fraction was similar in the two groups at the time of discharge, and was an average of 52\%.

Information on one year of follow up was collected for the remaining 156 patients. The left ventricular ejection fraction was similar in the two groups [median 58\% (57–68) in the emergency PCI group vs median 56\% (50–62) in the delayed PCI group, \( p = 0.666 \)]. Although the emergency PCI group had a trend towards a higher rate of MACE, the difference was not statistically significant [12.2 vs 11.6\%, hazard ratio (HR) = 1.067, 95\% CI: 0.434–2.627, \( p = 0.887 \)] (Fig. 2).

Discussion

For STEMI patients with an onset of symptoms of less than 12 hours, it has been clearly demonstrated that an early restoration of the patency of the infarcted artery is critical to improve clinical outcomes.\(^1\) Current clinical practice, however, includes a high proportion of patients with acute MI who present beyond this time limit. In the present study, we found that 22.8\% (729 of 3202) of STEMI patients presented late (more than 12 hours) without persistent symptoms, presenting 12 to 48 hours after symptom onset. Our results are similar to those of previous reports.\(^2,3\)

STEMI patients who present late would be outside of the ‘golden time window’ for reperfusion and are expected to exhibit less myocardial salvage, an expansion of infarct size as well as a higher mortality rate when compared with early comers.\(^4\) Therefore, it is of great valuable to explore an optimal therapy strategy for these patients, aiming to provide the best prognosis as well as the lowest related risk. Patients who presented at 12 to 72 hours after the onset of symptoms were defined as ‘early late-comers’.\(^5\) In the last few years, much attention has been paid to the controversy of whether these late-comers could benefit from PCI.\(^6,7\) Based on the different status of IRA patency, previous studies have shown conflicting results.\(^8,9\)

The BRAVE-2\(^{10}\) and Danish\(^{11}\) trials were the two most valuable studies concerning this issue. Data from BRAVE-2 showed that primary PCI with adjunctive use of abciximab reduced infarct size\(^12\) and four-year mortality rate\(^13\) in patients with acute STEMI without persistent symptoms, presenting 12 to 48 hours after symptom onset. The Danish study\(^14\) showed that myocardial salvage could still be achieved, even when primary angioplasty was performed in STEMI patients beyond the 12-hour limit.

Because of this powerful clinical evidence, routine primary PCI strategy was given a IIa recommendation for STEMI patients who present 12 to 48 hours after symptom onset by both 2014 and 2017 editions of the European Society of Cardiology (ESC) guidelines.\(^2,3\) Two issues must however be noted in these trials. First, in the Danish study, angioplasty in patients presenting 12 to 72 hours after the onset of symptoms shared the same salvage index (%) with patients who presented less than 12 hours after symptom onset (81 vs 71\%, \( p = 0.42 \)). This indicated that in STEMI patients who presented late and with a patent IRA, the time window in which PCI could be beneficial may exceed the 48-hour limit up to 72 hours or even later. Second, 43.4\% (79 of 182) of patients in the BRAVE-2 study and 43.6\% (24 of 55) in the Danish study who received primary PCI had a patent IRA, according to initial angiographic results. Previous studies have shown immediate PCI resulted in a higher rate of procedural failure compared with delayed PCI in patients who presented less than 12 hours after onset of symptoms with a patent IRA.\(^6\) Similar results were found in patients whose MI had occurred more than 12 hours to less than seven days earlier, and PCI before day 4 experienced a higher rate of failure,\(^15\) but the status of IRA patency was not taken into consideration in this study. Based on these results, we may speculate that if patients had been treated differently according to their initial status of IRA patency in the BRAVE-2 and Danish trials, the results may have been even better than published.

It seems that patency of the IRA plays an important role and patients with a patent IRA who present 48 to 72 hours post onset of symptoms still benefit from PCI. What remains unclear is when late reperfusion should be performed to provide the best clinical results, as well as the lowest related risk. This has not been well established since there are limited data available on this clinical condition.\(^6\)

We hypothesised that delayed PCI could be better than an emergency strategy among these patients. In our study, we found that in STEMI patients who presented 12 to 72 hours after symptom onset with IRA TIMI flow grades of 2 to 3, emergency PCI had a lower rate of procedural success due to higher rates of slow flow or no re-flow of IRA during the operation, compared with the delayed PCI strategy, whereas in-hospital MACE and mortality rates were similar in the two groups.

Several explanations may exist for our results. First, the thrombus becomes organised and firmer as time progresses during the acute phase of acute myocardial infarction (AMI).\(^16\) The organised thrombus is broken down into fragmented debris by mechanical devices such as balloons or stents during primary or elective PCI, and this debris causes embolisation of the branch or distal vessels and can completely plug the microvasculature, resulting in the slow flow or no re-flow phenomenon. Second, antithrombotic agents play an important role in preventing generation and expansion of the thrombosis.

Many studies have shown than an antithrombotic agent creates a safe environment for PCI by preventing re-occlusion.\(^17\) In our study, the use of dual antiplatelet therapy was common in both groups, but only loading doses of aspirin and clopidogrel were given before PCI in the emergency group, while the delayed PCI group of patients were maintained for at least one day on a routine dose of aspirin plus clopidogrel in addition to the loading dose. Platelet activation may be incompletely suppressed if clopidogrel is initiated only at the time of PCI.\(^18\) Moreover the delayed PCI group had a much higher rate of LMWH treatment compared with the emergency PCI group (8.46 vs 100\%, \( p < 0.001 \)). Sufficient duration of antithrombotic therapy maintained a stable haemodynamic state, allowing the drugs to take effect, and gave the lesion time to ‘cool off’.\(^19\) Furthermore, although our study showed that GPIIb/IIIa receptor antagonists were used more frequently in the emergency group (24.3 vs 4.7\%, \( p = 0.015 \)), they were primarily used only during the emergency PCI procedure, and late initiation may limit antithrombotic function.

In this study, PCI of a significantly stenosed infarcted artery was performed in all the late-coming STEMI patients enrolled. Our practice was based on the following evidence. First, the 12-hour time limit in primary angioplasty is based on two facts: (1) thrombolysis would not be efficacious in patients with AMI...
beyond 12 hours from symptom onset;[15,16] (2) late presenters were not included in the trials that showed the superiority of primary angioplasty over fibrinolysis.[17,18] This indicates that the 12-hour limit established for fibrinolysis may not be relevant in primary angioplasty.

Second, human AMI has a stuttering course with intermittent occlusion and re-canalisation. Previous studies showed the infarct-related artery was not totally occluded in up to one-third of patients.[19] Third, the attenuation of chest pain in patients with AMI may result from necrosis-related sympathetic denervation and adverse events, according to the GRACE scoring system.[20] In this study, we found 115 late-coming AMI patients who were asymptomatic but presented with a target lesion of 80 to 99% and a median of 95% stenosis, according to initial angiography data. It is clear that the lack of chest pain may not be used as an index to rule out the necessity of mechanical reperfusion in these patients.

We failed to find significant differences in terms of in-hospital mortality rate and MACE between the two groups in this study. Two reasons may explain this. First, all of the enrolled patients were haemodynamically and electrically stable and had patent IRAs, which means they had a relatively low risk for mortality and adverse events, according to the GRACE scoring system.[21] Second, only 159 patients were enrolled in the study, and the small sample may have reduced the power to draw a significant conclusion regarding mortality rate.

There were several potential limitations of this study. First, it is a single-centre, retrospective study with a small sample size. Second, most recent chest pain within 12 hours before admission was more likely in the emergency PCI group compared with the delayed PCI group (Table 2), which may have led to a bias towards an emergency decision by the operator. Third, we did not assess the TIMI thrombus grade of the IRA during the initial angiography since TIMI thrombus grade may have contributed to different angiography results. Finally, the blush grade was not evaluated as a more valuable indicator for normalised microvascular flow since this study was designed retrospectively.

**Conclusion**

In STEMI patients who presented late (12–72 hours) after symptom onset and with an IRA TIMI flow of grade 2 to 3, delayed PCI showed a higher rate of procedural success due to a lower rate of slow flow or no re-flow, without an increase in hospital or long-term MACE or mortality rates.

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**References**


