

# Risk Factors of Reperfusion Failure following Primary Angioplasty for ST-Segment Elevation Myocardial Infarction (STEMI)

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## Abstract

**Background:** Although percutaneous coronary intervention (PCI) improves outcomes compared to thrombolysis, a substantial number of ST-elevation myocardial infarction (STEMI) patients do not achieve optimal myocardial reperfusion. This study was designed to evaluate factors related to suboptimal myocardial reperfusion after primary PCI in patients with STEMI.

**Methods:** Totally, 155 patients (124 men; mean age =  $56.6 \pm 11.03$  years, range = 31- 85 years) with STEMI undergoing primary PCI were retrospectively studied. Additionally, the relationships between the occurrence of reperfusion failure and variables such as age, sex, cardiac risk factors, family history, Body Mass Index, time of symptom onset, ejection fraction, previous PCI, coronary artery bypass graft surgery or previous myocardial infarction, and angiographic data were analyzed.

**Results:** Procedural success was 97.1% and complete ST resolution occurred in 43.2%. Age; cardiac risk factors; family history; body mass index; previous MI, coronary artery bypass graft surgery, or PCI; and use of thrombectomy device and GPIIb/IIIa inhibitor were not the determining factors ( $p$  value > 0.05). According to our multivariate analysis, time of symptom onset (OR [95% CI]: 0.45 [0.2 to 0.98];  $p$  value = 0.044) and ejection fraction (OR [95% CI]: 0.37 [0.26 to .091];  $p$  value = 0.050) had reverse and male gender had direct significant associations with failed reperfusion (OR [95% CI]: 0.34 [0.11 to 1.08];  $p$  value = 0.068). More degrees of ST resolution occurred when the right coronary artery was the culprit vessel ( $p$  value = 0.001). The presence of more than three cardiac risk factors was associated with failed reperfusion ( $p$  value = 0.050).

**Conclusion:** Considering the initial risk profile of patients with acute STEMI, including time of symptom onset and ejection fraction, as well as the accumulation of cardiac risk factors in a given patient, we could predict failed myocardial reperfusion to design a more aggressive therapeutic strategy.

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## Introduction

As the preferred treatment strategy, the use of percutaneous coronary intervention (PCI) for patients with acute ST-segment elevation myocardial infarction (STEMI) is increasing.<sup>1-3</sup> Based on many studies, including a recent analysis from the GRACE (Global Registry of Acute Coronary Events), primary PCI has to be considered as the standard of care in many patients with STEMI.<sup>4</sup> Nevertheless, there are some limitations regarding primary PCI, which have rendered it an undesirable therapy for many operators and even for many PCI-capable centers. Despite high success rates in terms of epicardial artery patency, a large number of patients experience insufficient myocardial reperfusion mainly at the level of microvascular circulation. Angiographically, failure of reperfusion can be assessed using thrombolysis in myocardial infarction (TIMI) flow grade, TIMI frame count (TFC), and myocardial blush score. Moreover, reperfusion failure is associated with a poor prognosis and has been shown to be an independent predictor of death, MI, and impaired left ventricular function.<sup>5-7</sup> In clinical practice, ST-segment resolution is deemed a good indicator for the evaluation of reperfusion failure. Several studies have reported a relationship between different degrees of ST-segment resolution and clinical outcomes.<sup>8-10</sup> A large number of pathophysiological processes, usually in combination, are thought to be responsible for suboptimal myocardial reperfusion during primary PCI. Distal embolization of atherosclerotic debris, thrombus formation, and endothelial dysfunction of the distal arteriolar and capillary bed - including endothelial desquamation and microvascular spasm - are of possible causes.<sup>11</sup> Many preventive approaches have been tailored to improve myocardial perfusion in this setting. Several, but not all, have shown promising results in patients with STEMI. Patients who seem high risk for the occurrence of reperfusion failure might benefit from a more aggressive approach - including prompt transfer to the catheterization unit, use of new potent oral and parenteral antiplatelet drugs, thrombectomy devices, distal embolic protection, and - if possible - pre- and post-conditioning strategies. It is extremely difficult to completely treat reperfusion failure once it has occurred; therefore, recognition and adjustment of the related factors might decrease the prevalence or at least the severity of this phenomenon.

This retrospective study sought to analyze the rate of myocardial reperfusion following primary PCI and related clinical and angiographic factors associated with suboptimal myocardial reperfusion with a view to contributing to better treatment decisions in certain subgroups of STEMI patients.

## Methods

One-hundred fifty-five patients, who presented with acute STEMI to the Emergency Department between 2007 and 2009, were selected. The inclusion criteria were comprised of patients candidated for primary PCI with ST-segment elevation of more than 1 mm in two contiguous leads or 2-mm ST depression in V1 to V4 (true posterior MI)<sup>12</sup> and one of the following: 1) typical anginal pain and 2) elevated cardiac enzymes (CK-MB, troponin).

Patients with electrocardiographic (ECG) evidence of bundle branch or fascicular block and paced rhythm or those with initial cardiogenic shock were excluded. A guided medical history was taken, physical examination was performed, essential drugs were administered, and transthoracic echocardiography was conducted in all the patients. If eligible, the patients were transferred promptly to the Catheterization Unit, where they underwent coronary angiography. PCI was only done on the culprit artery, which was defined by the operator. The choice of opting for medications or thrombectomy devices was left at the discretion of the attending physician. Procedural success was defined as angiographic success without the occurrence of complications (death, MI, or bypass graft surgery) within 30 days of the procedure.<sup>13</sup> A 12-lead ECG was obtained 180 minutes after the procedure, and the clinical status of the patients was recorded. The percentage of ST-segment resolution in the leads with maximal initial ST-segment elevation was calculated. Based on the percentage of post-PCI ST-segment resolution, the patients were divided into three distinctive groups:<sup>14-17</sup> 1) patients with ST-segment resolution greater than 70% from baseline (complete); 2) patients with ST-segment resolution equal to or between 30 and 70% (partial); and 3) patients with less than 30% ST-segment resolution (failed).

The data are described as mean  $\pm$  standard deviation for the interval and count (%) for the categorical variables. Median (inter-quartile range [IQR]) was used for the interval, non-normally distributed variables. Fitness of interval data to normal distribution was assessed using the one-sample Kolmogorov-Smirnov test. Subgroup analysis was performed via the chi square, Mann Whitney U, and Kruskal Wallis tests. A p value smaller than 0.05 was considered statistically significant. SPSS 15 for Windows (SPSS Inc. Chicago, Illinois) was employed for the statistical analyses. Multivariable analysis was performed using an ordinal logistic regression model to determine the adjusted associations between ST-segment resolution and other determinants. STATA SE11 for Windows (STATA Corp. Texas, USA) was applied for statistical modeling.

## Results

One-hundred fifty-five patients (124 men; mean age = 56.6 ± 11.03 years, range = 31-85 years) were recruited in the present study. Dyslipidemia (43.9%) and smoking (40.6%) were the most common risk factors, and a relatively large number of the study patients (25%) suffered from diabetes mellitus. The demographic characteristics of the study population are depicted in Table 1.

Table 1. Demographic characteristics of the study patients

Age (y)	
Mean±SD	56.6±11.03 years
Range	31 to 85
Sex (M/F)	124 (80%) / 31 (20%)
Risk factors	
Smoking	63 (40.6%)
Hypertension	58 (37.4%)
Dyslipidemia	68 (43.9%)
Diabetes	39 (25.2%)
Family history	23 (10.9%)
Previous MI	27 (17.4%)
Previous PCI	16 (10.3%)
Previous surgical bypass graft	5 (3.2%)
Onset of symptoms	
< 6 hours	94 (60.6%)
≥ 6 hours	61 (39.45%)
BMI*	26 (24-29)
Initial EF*	40% (35% -45%)

\*Data are presented as median (IQR)

MI, Myocardial infarction; PCI, Percutaneous coronary intervention; BMI, Body mass index; EF, Ejection fraction

With respect to the culprit artery, the left anterior descending artery was involved in 59.4% of the cases, followed by the right coronary artery (31.6%) and the left circumflex artery (4.5%). The angiographic characteristics of the study population are outlined in Table 2. Procedural success was 97.1%, and the majority of the patients (98.7%) experienced complete relief of chest pain. A great number of the patients achieved TIMI-3 flow (88.4%) after the procedure, and slow-flow and no-reflow phenomena were seen in 10.3% and 1.3%, respectively. Despite the fact that the majority of the study patients achieved TIMI-3 flow (88.4%) and the fact that the patients with TIMI flow-3 accounted for 91% of the patients with complete ST resolution, TIMI-3 flow was also equally distributed between the patients with partial resolution and those with no resolution (p value = 0.55). Complete ST-segment resolution (> 70%) occurred in 43.2% and 63.2%, when the value of 50% was considered. Meanwhile, 23.2% of the patients experienced less than 30% ST-segment resolution. There was no association between

age or sex and the magnitude of ST-segment resolution (p value = 0.78 and 0.11, respectively). When considered separately, none of the cardiac risk factors was associated with ST change after revascularization (Table 3). When the analysis was conducted with the ST-segment resolution of 50%, significant relationships were observed with smoking (p value = 0.02), obesity (p value = 0.02), and positive family history (p value = 0.03). The presence of more than three cardiac risk factors was allied to failed reperfusion (p value = 0.05). A history of previous MI or revascularization, including PCI or surgical bypass graft, was not a good determinant (p value = 0.1).

Table 2. Angiographic and procedural characteristics of the study patients

Severity of CAD	
LM	1 (0.6%)
3VD	45 (29%)
2VD	42 (27%)
SVD	67 (43%)
Culprit artery	
LAD	92 (59.4%)
LCX	7 (4.5%)
RCA	49 (31.6%)
LM	1 (4.5%)
Others	6 (0.6%)
Post-PCI TIMI flow	
0, 1	2 (1.3%)
2	16 (10.3%)
3	137 (88.4%)

CAD, Coronary artery disease; LM, Left main; 3VD, Three-vessel disease; 2VD, Two-vessel disease; SVD, Single-vessel disease; LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery; TIMI, Thrombolysis in myocardial infarction

Time from symptom onset to initial puncture of the femoral artery in the catheterization laboratory was significantly related to the magnitude of ST-segment resolution (p value = 0.001). The median (IQR) of presentation time (hours) was 3 (1.5 - 5.5) in the patients with complete resolution, 5 (2 - 8) in those with partial resolution, and 5.5 (2 - 10) in the ones with no resolution. There was also a statistically significant association between initial ejection fraction, obtained at the time of presentation in the Emergency Department, and myocardial reperfusion, as is shown in Table 3. The analysis of the culprit artery associations threw up an interesting finding: whenever the right coronary artery was treated as the culprit artery, more degrees of ST-segment resolution were achieved, while the involvement of the left anterior descending artery was associated with poor myocardial reperfusion in spite of a successful procedure (p value = 0.001). Similarly, when the anterior wall of the left ventricle was not involved, higher levels of reperfusion were attained.



Neither the involvement of the septal or lateral wall, nor the right ventricle complicating inferior MI was significantly associated with the degree of ST-segment resolution. Thrombectomy catheters were used in 104 (64.5%) patients, but they were not correlated with better ST resolution in this study ( $p$  value = 0.4). In addition, GpIIb/IIIa inhibitors did not affect electrocardiographic reperfusion.

### Multivariate Analysis

Our multivariate analysis using an ordinal logistic regression model revealed a strong association between failed reperfusion and the variables of time of symptom onset (OR [95% CI]: 0.45 [0.2 to 0.98];  $p$  value = 0.044), ejection fraction (OR [95% CI]: 0.37 [0.26 to 0.91];  $p$  value = 0.05), and male gender (OR [95% CI]: 0.34 [0.11 to 1.08];  $p$  value = 0.068) (Table 4).

Table 3. Relation between the variables and amount of ST-segment resolution in the study patients

Evaluated factors	ST-resolution < 30% (n=36)	ST-resolution 30-70% (n=52)	ST-resolution > 70% (n=67)	P value
Age (y)				0.780
< 50	38.9%	17.3%	28.4%	
≥ 50	61.1%	82.7%	71.6%	
Sex				0.12
Male	33 (91.7%)	41 (78.8%)	50 (74.6%)	
Female	3 (8.3%)	11 (21.2%)	17 (25.4%)	
Smoking	18 (50.0%)	20 (38.5%)	25 (37.3%)	0.42
Diabetes	9 (25.0%)	13 (25.0%)	17 (25.4%)	0.990
Hypertension	16 (44.4%)	22 (42.3%)	20 (29.9%)	0.230
Dyslipidemia	14 (38.9%)	23 (44.2%)	31 (46.3%)	0.770
Obesity	3 (8.3%)	6 (11.5%)	15 (22.3%)	0.107
Family history	3 (8.3%)	7 (13.4%)	13 (19.4%)	0.303
Onset of symptoms (hr)*	5.5 (2.0 – 10.0)	5 (2.0 – 8.0)	3 (1.5 – 5.5)	0.001
Initial EF (%)*	35 (30.0 – 42.5)	40 (30.0 – 42.5)	45 (40.0 – 45.0)	0.001
Previous MI	6 (16.7%)	8 (15.4%)	13 (19.4%)	0.84
Culprit artery				0.001
LAD	28 (77.8%)	36 (69.2%)	28 (41.8%)	
LCX	1 (2.8%)	4 (7.7%)	7 (10.4%)	
RCA	6 (16.7%)	11 (21.2%)	32 (47.8%)	
Thrombectomy device	24 (66.6%)	33 (63.5%)	47 (70.1%)	0.74
GpIIb/IIIa inhibitor	10 (27.8%)	16 (30.7%)	20 (29.9%)	0.955

\*Data are presented as median (IQR)

EF, Ejection fraction; LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery; Glycoprotein IIb/IIIa inhibitor

Table 4. Multivariable analysis, providing adjusted associations between ST-segment resolution and the variables in the study patients

	Odds Ratio	95% Confidence Interval		P value
Gender	0.34	0.11	1.08	0.068
Smoking	0.58	0.26	1.30	0.189
Family history	1.85	0.63	5.43	0.265
Diabetes mellitus	0.91	0.33	2.50	0.860
Hypertension	0.53	0.22	1.26	0.151
Dyslipidemia	1.09	0.49	2.43	0.828
Age	1.02	0.42	2.48	0.966
Obesity	2.10	0.82	5.38	0.121
Myocardial infarction	0.74	0.25	2.17	0.587
Onset of symptoms	0.45	0.20	0.98	0.044
Ejection fraction	0.37	0.26	0.91	0.050

## Discussion

Approximately, one-third of acute coronary syndrome patients experience STEMI.<sup>18</sup> Rapid and complete restoration of the coronary blood flow using thrombolytics or transcatheter interventions is the mainstay of treatment.<sup>19</sup> Currently, primary PCI is the treatment of choice in many patients with acute MI inasmuch as not only can it confer more complete and protected reperfusion but also it can result in small infarct sizes and reduced mortality rates by comparison with fibrinolytic therapy.<sup>20</sup> Despite increased knowledge about the pathophysiological stream of STEMI and huge technological progress in the field of coronary interventions, there are still a small but significant number of patients who experience suboptimal results after primary PCI. If we regard STEMI as a risky and costly health problem even with maximal care, the impact of unsuccessful treatment would be clear. The most important cause of suboptimal results is reperfusion failure, which can lead to increased short- and long-term mortality. As was mentioned before, there are several measures to evaluate reperfusion failure post intervention. Of those, slow/no-reflow phenomena or prolonged TFC and impaired myocardial blush score have higher levels of association with insufficient epicardial flow, not merely failed reperfusion, at the levels below the large vessels. It seems that the amount of post-procedural ST-segment resolution is a better estimate for this purpose. Indeed, our study showed that TIMI flow might not yield a precise estimate of myocardial reperfusion.

The present study suggests that the status of the initial risk profile of patients might denote a rough estimate of the success rate of reperfusion as measured by ST-segment resolution. Even if the presence of every one of the usual cardiac risk factors is not strongly associated with poorer results, the accumulation of several of them in a patient could predict a lower chance for complete reperfusion. Time is the key element itself, and can potentiate the effects of the other factors. Although some of the previous studies have suggested that the association between time to treatment and final infarct size is weak if patients are treated with primary PCI,<sup>21</sup> our study demonstrated a linear relationship between time delay and the magnitude of reperfusion failure, which can be translated into the clinical outcome. This re-emphasizes the importance of the establishment of a general approach in health care systems to achieve lower ischemic times in patients with acute STEMI. We observed that the involvement of the right coronary artery, as the culprit lesion in acute MI, was strongly associated with higher degrees of ST-segment resolution; this can be due to the interesting ability of the right ventricle in handling the ischemic process or smaller sizes of infarcts in many patients with inferior MI. Despite our data, uncertainty persists because observational

data show that some patients with inferior MI are more prone to the development of early cardiogenic shock and have increased mortality possibly due to more extensive coronary artery disease and the involvement of the right ventricle.<sup>22-24</sup> Notably, patients with the acute occlusion of the left anterior descending artery are those who have the lowest levels of myocardial reperfusion and might benefit from a more aggressive therapy, including the routine use of thrombectomy devices and glycoprotein IIb/IIIa receptor antagonists as well as the possible adoption of a pre-PCI fibrinolytic therapy in case of prolonged transfer times.

## Conclusion

Considering the initial risk profile of patients with acute STEMI, including time of symptom onset and ejection fraction, as well as the accumulation of cardiac risk factors in a given patient, it is possible to predict failed myocardial reperfusion with a view to designing a more aggressive therapeutic strategy.

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