Mortality in patients with TIMI 3 flow after PCI in relation to time delay to reperfusion

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Background. Percutaneous coronary intervention (PCI) performed within 12 h from symptom onset enables complete blood flow restoration in infarct-related artery in 90% of patients. Nevertheless, even with complete restoration of epicardial blood flow in culprit vessel (postprocedural Thrombolysis in Myocardial Infarction (TIMI) flow grade 3), myocardial perfusion at tissue level may be insufficient. We hypothesized that the outcome of patients with STEMI/bundle branch block (BBB)-myocardial infarction and post-PCI TIMI 3 flow is related to the time to reperfusion.
Methods. Observational study based on a retrospective analysis of population of 635 consecutive patients with STEMI/BBB-MI and post-PCI TIMI 3 flow from January 2009 to December 2011 (mean age 63 years, 69.6% males). Mortality of patients was evaluated in relation to the time from symptom onset to reperfusion.
Results. A total of 83 patients (13.07%) with postprocedural TIMI 3 flow after PCI had died at 1-year follow-up. Median TD in patients who survived was 3.92 h (iqr 5.43), in patients who died 6.0 h (iqr 11.42), $P = 0.004$. Multiple logistic regression analysis identified time delay ≥ 9 h as significantly related to 1-year mortality of patients with STEMI/BBB-MI and post-PCI TIMI 3 flow (OR 1.958, $P = 0.026$). Other significant variables associated with mortality in multivariate regression analysis were: left ventricle ejection fraction < 30% ($P = 0.006$), age > 65 years ($P < 0.001$), Killip class >2 ($P < 0.001$), female gender ($P = 0.019$), and creatinine clearance < 30 mL/min ($P < 0.001$).
Conclusion. Time delay to reperfusion is significantly related to 1-year mortality of patients with STEMI/BBB-MI and complete restoration of epicardial blood flow in culprit vessel after PCI.

Key words: STE myocardial infarction, PCI, TIMI 3 flow, time-delay, mortality, microcirculation

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INTRODUCTION

Restoration of epicardial blood flow in the infarct-related artery (IRA) in patients with myocardial infarction is associated with greater myocardial salvage and increased survival[1,2]. The patency rate of the IRA in STEMI patients treated with fibrinolysis ranges between 60% and 80% and is strongly time-dependent[3-5]. PCI has been shown to improve epicardial vessel patency and myocardial salvage in comparison to fibrinolysis with higher rate of IRA patency - approximately 90%, within the extended time frame from symptom onset when compared to fibrinolysis[6-8]. Nevertheless, it has been shown that despite restoration of epicardial blood flow in IRA, myocardial perfusion at tissue level may be insufficient in up to 16-25% of patients[9-11]. Impaired microvascular perfusion is associated with poor left ventricular function and worse early and late prognosis[12].

Among factors that affect the success of epicardial and microvascular perfusion is the time to treatment[13]. Early reperfusion reduces the incidence of slow – flow and no – reflow phenomenon in the IRA (ref.[14]). Patients undergoing primary PCI in whom TIMI-3 (Thrombolysis In Myocardial Infarction) flow is present before angioplasty show greater clinical and angiographic evidence of myocardial salvage, are less likely to develop complications related to left ventricular failure, and have improved early and late survival[15]. Similarly, in GUSTO I, treatment with t-PA resulted in higher rates of TIMI grade 3 flow at 60 and 90 minutes compared with streptokinase, but by 180 minutes, rates were similar. Earlier achievement of TIMI 3 flow was associated with improved early left ventricular function and mortality[3].

The aim of this study was to assess the relationship between the time delay to reperfusion and the outcomes of patients in whom postprocedural TIMI 3 flow was achieved by PCI.

METHODS

Data from a registry of 735 consecutive patients hospitalized in a tertiary -care center with STEMI/BBB-MI and treated by PCI from January 2009 to December 2011 were retrospectively analyzed.

ECG criteria for entry included ST-segment elevation of >2 mm in at least two contiguous leads, left or right bundle branch block of new origin.

Clinical symptoms such as chest pain, dyspnea or syncope were assessed. In borderline cases, angiographic

findings or autopsy histology examination were retrospectively evaluated.

Medical history, demographic, angiographic and hemodynamic variables were assessed. Time to treatment was defined as the interval from symptom onset as stated by the patient to first balloon inflation. Patients with uncertain time delay to treatment were excluded from the study.

TIMI flow was assessed after PCI, residual stenosis was evaluated visually by an experienced interventional cardiologist. Optimal PCI outcome was defined as restoration of coronary blood flow with TIMI classification grade 3 and postprocedural diameter stenosis in the IRA of less than 30% by quantitative coronary angiography.

The institutional review board at University Hospital Kralovske Vinohrady, Prague, Czech Republic, approved the study and patients gave informed consent.

Statistical Analysis

The location and variability of continuous variables was expressed as arithmetic mean and standard deviation (SD) for normally distributed variables or as median and interquartile range for non-normally distributed variables. Two-sample t-test and Mann-Whitney test were used to test differences between groups. Categorical data were described using absolute and relative frequencies (expressed as percentages) and analyzed using Fisher's exact test.

Multiple logistic regression model and Cox's proportional hazards regression model were used to compare study subgroups and to identify predictors significantly related to the endpoint occurrence. The analyses were adjusted for confounding risk factors (age> 65 years, female gender, LVEF <30%, Killip >2, diabetes, hypertension, current smoking, history of ischemic heart disease,

Table 1. Baseline characteristics of the study population.

	All n=735	TIMI post <3 n=100	TIMI post=3 n=635	*P*
Age (mean, SD)	63.8 (12.6)	69.0 (13.5)	63.0 (12.3)	<0.001
Female gender	233 (31.7%)	40 (40.0%)	193 (30.4%)	0.064
Hypertension	402 (55.4%)	66 (66.7%)	336 (53.6%)	0.017
Diabetes mellitus	184 (25.3%)	38 (38.4%)	146 (23.2%)	0.002
Current smoker	371 (52.7%)	34 (38.6%)	337 (54.7%)	0.006
Hyperlipoproteinemia	136 (18.8%)	22 (22.2%)	114 (18.2%)	NS
Previous MI	116 (16.0%)	18 (18.2%)	98 (15.6%)	NS
Previous CABG, PCI	84 (11.6%)	15 (15.2%)	69 (11.0%)	NS
Previous stroke	58 (8.0%)	13 (13.1%)	45 (7.2%)	0.070
PAD	48 (6.6%)	9 (9.1%)	39 (6.2%)	NS
BMI	27.7 (4.5)	27.9 (5.2)	27.7 (4.4)	NS
BSA	1.97 (0.24)	1.94 (0.27)	1.97 (0.24)	NS
Creatinine clearance*	90.7 (55.0)	67.1 (63.0)	92.8 (53.9)	<0.001
Renal failure	106 (14.7%)	27 (28.4%)	79 (12.6%)	<0.001
LVEF <30%	46 (6.4 %)	16 (17.2%)	30 (4.8%)	<0.001
Killip >2	98 (13.4%)	21 (21.0%)	77 (12.2%)	0.026
Localization of MI:				NS
Anterior	329 (44.9%)	42 (42.0%)	287 (45.3%)	
Lateral	88 (12.0%)	7 (7.0%)	81 (12.8%)	
Inferior/Posterior	316 (43.1%)	51 (51.0%)	265 (41.9%)	
ECG at admission:				0.004
STElevations	647 (88.1%)	78 (78.8%)	569 (89.6%)	
BBB	87 (11.9%)	21 (21.2%)	66 (10.4%)	
Number of affected arteries				NS
1	249 (34.1%)	33 (33.3%)	216 (34.2%)	
2	222 (30.4%)	26 (26.3%)	196 (31.0%)	
3	222 (30.4%)	30 (30.3%)	192 (30.4%)	
4	38 (5.2%)	10 (10.1%)	28 (4.4%)	
TIMI preprocedural:				0.001
0	430 (58.5%)	75 (75.0%)	355 (55.9%)	
1	64 (8.7%)	9 (9.0%)	55 (8.7%)	
2	118 (16.1%)	9 (9.0%)	109 (17.2%)	
3	123 (16.7%)	7 (7.0%)	116 (18.3%)	

* median (interquartile range)

MI indicates myocardial infarction; CABG coronary artery bypass graft; PCI percutaneous coronary intervention; renal failure = creatinine clearance < 50 mL/min; LVEF left ventricular ejection fraction at admission; PAD peripheral arterial ischemic disease; BMI body mass index; BSA body surface area; BBB bundle branch block; affected arteries: 4 indicates left main disease.

peripheral artery disease, localization of MI, number of affected arteries, BBB on ECG).

The results are presented as the odds ratio or the hazard ratio, respectively, with the corresponding 95% confidence intervals. Kaplan-Meier estimators of survival curves were used to graphically illustrate the comparison.

The statistical analysis was performed by statistical software Stata, release 9.2 (Stata Corp LP, College Station, TX). All statistical tests were evaluated at a significance level of 0.05.

RESULTS

Baseline characteristics

Among 735 patients, 642 patients (87.4%) had postprocedural TIMI flow 3. Out of them, 635 (86.4%) patients with complete follow – up data were further analyzed.

Demographic, clinical, and angiographic characteristics in relation to postprocedural TIMI flow in IRA are reported in Table 1.

Patients with postprocedural TIMI 3 flow were significantly younger than patients with TIMI <3, less likely to be a woman and had less often comorbidities in their medical history (see Table 1). Bundle branch block (BBB) on admission ECG, preprocedural TIMI <3 flow in culprit lesion, left ventricular systolic dysfunction (LVEF <30%) and signs of heart failure at admission (Killip class >2) were less often present in patients with postprocedural TIMI 3 flow in comparison to patients with postprocedural TIMI <3.

Time delay in patients with postprocedural TIMI 3 flow

The median time delay to reperfusion in patients with postprocedural TIMI 3 flow was 4 h (iqr = 6.37), whereas the median TD in patients with postprocedural TIMI < 3 was almost twice as high - 7.59 h (iqr = 11.00; $P < 0.001$).

The distribution of patients with postprocedural TIMI 3 flow in relation to TD to reperfusion is shown in Fig. 1. 81.4% of patients from this group underwent PCI up to 12 h of TD, out of them 113 (17.8%) underwent PCI within TD up to 2 h, 109 (17.2 %) between 2 and 3 h, 187 (29.5 %) from 3 to 6 h, 71 (11.2 %) between 6 and 9 h, 37 (5.8 %) between 9 and 12 h. 118 patients (18.6 %) underwent PCI later than 12 h from symptom onset. Among demographic and clinical variables strongly associated with longer TD (≥ 9 h) are: female gender, hypertension, current smoking, renal failure (creatinine clearance < 50 mL/min) and the presence of BBB on ECG (Table 2).

Mortality of patients with postprocedural TIMI 3 flow

The all-cause 1-year mortality in patients with postprocedural TIMI 3 flow was 13.1%, 30-day mortality 7.1% (Table 3). Median TD in patients with postprocedural TIMI 3 who survived up to 1-year follow-up was 3.92 h (iqr 5.43), in patients who died 6.0 h (iqr 11.42), P = 0.004. Distribution of mortality in relation to time-delay is depicted in Fig. 2.

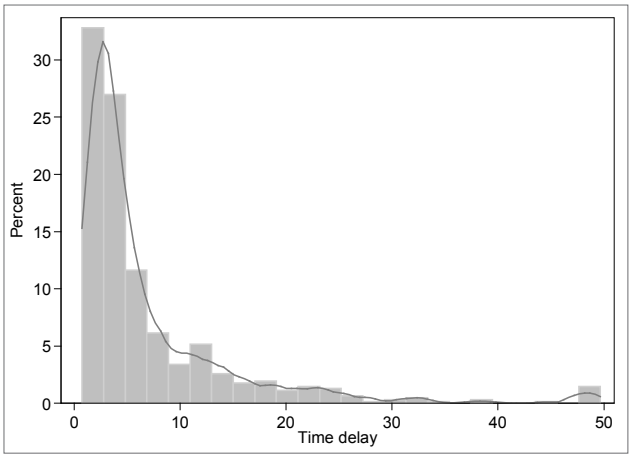

Fig. 1. Distribution of patients with AMI undergoing PCI in relation to time delay (h) to reperfusion.

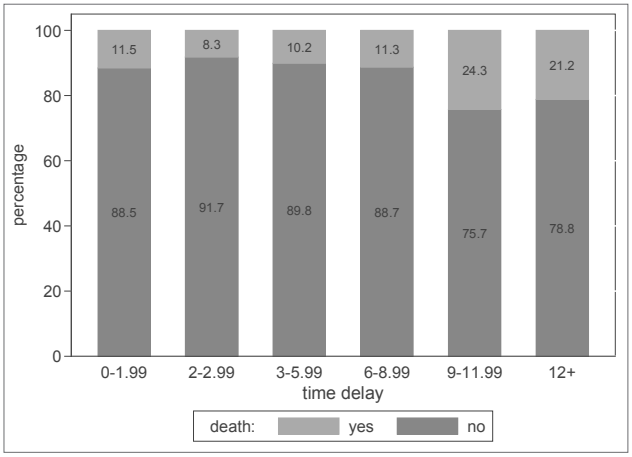

Fig. 2. Distribution of 1-year mortality of patients with postprocedural TIMI 3 flow in relation to time delay to reperfusion.

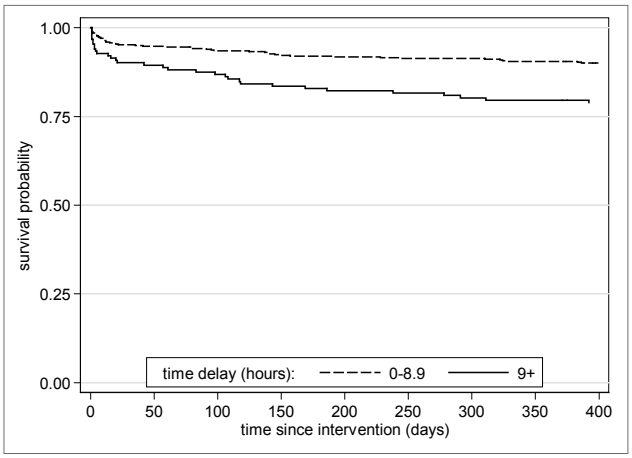

Fig. 3. Kaplan –Meier survival curves for patients with TD < 9 h and ≥ 9 h (P = 0.035).

Multiple stepwise logistic regression analysis demonstrated that TD longer than 9 h from symptom onset was significantly associated with higher mortality (OR 1.958, 95% CI 1.085 - 3.534, P = 0.026), compared to TD <9 h.

Table 2. Baseline characteristics related to time delay from symptom onset to reperfusion – patients with postprocedural TIMI flow grade 3.

	TD <9 h n=480	TD ≥ 9 h n=155	*P*
Age	62.1 (12.1)	65.5 (12.4)	0.003
Female gender	134 (27.9%)	59 (38.1%)	0.021
Hypertension	249 (52.6%)	87 (56.5%)	NS
Diabetes mellitus	104 (21.9%)	42 (27.3%)	NS
Current smoker	268 (58.5%)	69 (46.0%)	0.014
Hyperlipoproteinemia	92 (19.5%)	22 (14.3%)	NS
Previous MI	74 (15.6%)	24 (15.6%)	NS
Previous CABG, PCI	53 (11.3%)	16 (10.4%)	NS
Previous stroke	30 (6.4%)	15 (9.7%)	NS
PAD	24 (5.1%)	15 (9.7%)	0.053
BMI	27.9 (4.4)	27.1 (4.5)	0.062
BSA	1.99 (0.23)	1.92 (0.26)	0.003
Creatinine clearance*	94.8 (50.1)	82.7 (54.8)	<0.001
Renal failure	47 (9.9%)	32 (21.1%)	0.001
LVEF < 30%	20 (4.2%)	10 (6.5%)	NS
Killip >2	57 (11.9%)	20 (12.9%)	NS
Localization of MI:			NS
Anterior	210 (43.8%)	77 (50.3%)	
Lateral	63 (13.1%)	18 (11.8%)	
Inferior/Posterior	207 (43.1%)	58 (37.9%)	
ECG at admission:			0.048
STElevations	437 (91.0%)	132 (85.2%)	
BBB	43 (9.0%)	23 (14.8%)	
Number of affected arteries			NS
1	172 (35.8%)	44 (28.9%)	
2	151 (31.5%)	45 (29.6%)	
3	139 (29.0%)	53 (34.9%)	
4	18 (3.8%)	10 (6.6%)	
TIMI preprocedural:			0.035
0	264 (55.0%)	91 (58.7%)	
1	36 (7.5%)	19 (12.3%)	
2	82 (17.1%)	27 (17.4%)	
3	98 (20.4%)	18 (11.6%)	

* median (interquartile range)
MI indicates myocardial infarction; CABG coronary artery bypass graft; PCI percutaneous coronary intervention; renal failure =creatinine clearance < 50 mL/min; LVEF left ventricular ejection fraction at admission; PAD peripheral arterial ischemic disease; BMI body mass index; BSA body surface area; BBB bundle branch block; affected arteries:4 indicates left main disease.

Table 3. 30-day and 1-year mortality of patients in relation to the postprocedural TIMI flow.

	All patients n = 735	TIMI post <3 n = 100	TIMI post=3 n = 635	TIMI post=3, TD < 9 h n = 480	TIMI post =3, TD ≥ 9 h n = 155	*P*
Mortality 30-day	79 (10.7%)	34 (34.0%)	45 (7.1%)			<0.001
				27 (5.6 %)	18 (11.6%)	0.018
Mortality 1-year	127 (17.3%)	44 (44.0%)	83 (13.1%)			<0.001
				49 (10.2%)	34 (21.9%)	<0.001

The subgroup with postprocedural TIMI 3 is further divided into two groups following the TD to reperfusion

In Cox proportional hazards model, the hazard ratio for one-year mortality in patients with TD ≥ 9 h was 1.67 (*P* = 0.035, 95% CI 1.0357- 2.697), (Fig. 3).

DISCUSSION

TIMI-3 flow as an outcome predictor

The clinical practice in PCI procedures focuses on restoration of epicardial blood flow, as patients with optimal blood flow in culprit vessel after PCI for acute myocardial

infarction (AMI) have less extensive necrosis and better regional and global contractile function, lower incidence of adverse events and mortality than patients with poor postprocedural blood flow in infarct-related artery[1,2].

The success rate of achieving the postprocedural TIMI 3 flow and related patient characteristics in the present study conform to other studies: patients with postprocedural TIMI <3 flow were older, more commonly women, diabetics, with more frequent initial hemodynamic instability (Table 1) (ref.[9,16]). Current smoking was associated with lower incidence of postprocedural TIMI <3 flow, which was observed previously in studies with thrombolysis in AMI (ref.[9,17,18]) and is explained by different thrombus characteristics in smokers.

However, postprocedural TIMI 3 flow alone as a sign of post-PCI epicardial vessel patency is not a sufficient predictor of patient outcome after AMI as it does not guarantee an optimal reperfusion at microcirculatory level[19,20]. Suboptimal myocardial perfusion is associated with impaired coronary microcirculation, increased infarct size and higher mortality rates[11,21]. As a consequence, the focus of treatment is shifting towards the assessment of myocardial reperfusion at microvascular level.

Various methods of microcirculatory evaluation related to risk stratification after AMI have been in use, among most common ST- segment resolution[19,22], myocardial blush grade[12,23], myocardial contrast echocardiography[24], myocardial scintigraphy[25] or cardiac magnetic resonance[26,27].

However, as effective as these methods are, they are not always accessible for routine evaluation, may be costly or time consuming.

Simple and mostly quickly accessible information about time delay to reperfusion may contribute to the prognostic stratification of patients with successful reperfusion at the epicardial level. The time delay correlates negatively with the postprocedural epicardial patency and determines the microvascular perfusion and the infarct size[13,25,28-30]. In the work of Kondo et al.[25], prolonged ischemia time increased the likelihood of microvascular no-reflow phenomenon. In the study of de Luca and colleagues[31], time to treatment affected the rate of TIMI 3 flow, myocardial blush grade 2-3, complete ST-resolution and distal embolization, even when corrected for early Gp IIb-IIIa inhibitors and postprocedural TIMI 3 flow.

These findings correlate with worse outcomes of patients with postprocedural TIMI 3 and prolonged time-delay to reperfusion in our study. The impact of time on tissue perfusion had been explained by experimental studies where the microvasculature shows loss of its anatomic integrity with the time due to capillary injury, endothelial swelling and changes in blood viscosity, oxidative injury, myocardial edema and thrombus embolization[32,33].

Lately, there have been some concerns regarding the suitability of measuring the time from symptom onset to PCI (the time delay to reperfusion in this study), due to its complexity and involvement of many factors. The patient recall bias or unstable angina prior to AMI may modify the onset time information. The hemodynamic status of patient, severity of coronary artery disease, age, gender, presence of other comorbidities or socio-demographic factors affect the time from symptom onset to treatment and outcomes, hence may impose a selection bias[34-36]. For instance, patients with more severe disease and worse prognosis may present earlier, those presenting later are typically low- risk patients who have already survived the pre-hospital phase[36]. Therefore, some studies suggest that the first medical contact- to- PCI time may be a more objective measure of time to reperfusion[37,38].

Continuous efforts to reduce the patient, as well as system delays to reperfusion are crucial for the improvement of microvascular circulation following the AMI. In addition, new prevention and intervention possibilities such as pretreatment with new antithrombotic drugs[39-41], use of intracoronary thrombus aspiration[42,43], or administration of intracoronary GP IIb/IIIa antagonists during PCI (ref.[44]) in recent years have significantly improved microvascular reperfusion in patients with AMI undergoing PCI.

Limitations

The greatest limitation of this study lies in the retrospective analysis of angiographic and clinical data that could confound our results and conclusions. Furthermore, as in any study, potential residual confounding may have been present, such as inclusion of other baseline variables could have added prognostic information.

CONCLUSION

Our data show that time to reperfusion is significantly related to the prognosis of patients with STEMI/BBB in whom the epicardial circulation in IRA was successfully restored by PCI and may be used in the clinical practice as a simple prognostic stratification tool.

This study confirms that "time is myocardium and time is outcomes[45]" remains an important paradigm regardless of the improved antithrombotic drugs and advanced interventional methods for the treatment of AMI.

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