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Initial Patency of the Infarct-related Artery in Patients with Acute ST Elevation Myocardial Infarction is Related to Platelet Response to Aspirin

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Running title: Aspirin response and TIMI flow in AMI

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Abstract

Introduction: A proportion of patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary angiography (PCI) presents with patent infarct-related artery (IRA) on initial angiography. We tested the hypothesis that stronger platelet response to aspirin in these patients at admission might be associated with higher initial coronary flow in the IRA. Methods: Platelet response to aspirin was assessed with Multiplate® ASPI-test before coronary angiography in 70 patients on previous aspirin treatment admitted for acute STEMI. Coronary flow on initial angiogram was evaluated quantitatively according to the Thrombolysis In Myocardial Infarction (TIMI) grading system. Depending on the degree of arachidonic acid (AA) induced platelet aggregation in ASPI-test, patients were stratified into four quartiles and compared according to initial TIMI flow.

Results: When TIMI flow was compared according to quartiles of platelet aggregation in ASPI-test, we have found significantly higher frequency of TIMI-2 and TIMI-3 flow among patients with low values of ASPI-test, i.e. with stronger aspirin response (P=0.014). None of the patients in the highest quartile of ASPI-test had TIMI flow of 2 or 3.

Conclusions: Patients with stronger antiplatelet response to aspirin therapy in acute STEMI are more likely to present with spontaneous IRA recanalization.

Keywords: Infarct-related artery patency; aspirin response; platelets.

Introduction

Approximately 10-20% of patients with acute ST-segment elevation myocardial infarction STEMI present themselves with spontaneous coronary recanalization before angioplasty and the prognosis of these patients is significantly better in terms of smaller size of infarction, lower incidence of heart failure, and improved early as well as late survival when compared to patients with persistent occlusion [1]. Platelet-dependent thrombosis plays a crucial role in the occlusion of the infarct-related artery (IRA) in acute MI. It is possible that stronger platelet response to aspirin may influence the tendency to early spontaneous coronary reperfusion in a certain proportion of patients with acute STEMI. The aim of our study was to determine whether patients presenting with higher coronary flow in the IRA at the time of initial angiography differ from patients with persistent occlusion in terms of platelet response to aspirin.

Material and methods

Study population included 70 consecutive patients who underwent primary percutaneous coronary intervention (PCI) for acute STEMI. All patients were using 100 mg of aspirin daily for at least 7 days before admittance. The compliance to aspirin was assessed by interview. Blood samples were collected from antecubital vein before clopidogrel loading and angiography. Exclusion criteria were: previous treatment with clopidogrel, nonsteroidal anti-inflammatory drugs, heparin and GpIIbIIIa inhibitors, a history of bleeding disorders, platelet count $\leq 100 \times 10^9$/L, hematocrit ≤0.30 or renal failure (creatinine ≥140 μmol/L). All patients had given informed consent and the study protocol was approved by the local ethics committee.

Platelet function test was done using Multiplate® ASPI-test. This is the impedance-based «point-of-care» test, where a resistance change between two electrodes immersed into the whole blood is determined after the addition of AA with its final concentration of 0.5 mM [2]. Aggregation is expressed in arbitrary units (U). *Platelet reactivity* was expressed as interquartile range. *Aspirin resistance* was defined by an AUC of >31 U (75^{th} percentile of aggregation in ASPI-test from 110 control patients with stable coronary artery disease taking daily 100 mg of aspirin).

Coronary flow was evaluated quantitatively according to the Thrombolysis In Myocardial Infarction (TIMI) grading system by two independent interventional cardiologists at the core lab, blinded for aggregation measurements. TIMI-0 is related to complete occlusion of the IRA, TIMI-1 is related to some penetration of contrast beyond the point of obstruction but without perfusion of the distal coronary bed, TIMI-2 is related to perfusion of the entire IRA into the distal coronary bed but with delayed flow compared with a normal artery and TIMI-3 represents full perfusion of IRA with normal flow [3].

Statistical Analysis: Statistical analyses were performed using the MedCalc v.7.2.1.0 statistical software. Categorical data are presented as absolute and relative frequencies, continuous variables as median with range. Non-parametric tests (Wilcoxon's and Kruskal-Wallis as appropriate) tests were used for group comparisons of continuous variables; chi-squared test was used for comparisons of categorical variables. Spearman's correlation was used for correlation analysis. Statistical significance was set at $P<0.05$.

Results

Patients were stratified into 4 quartiles based on the results of aggregation in ASPI-test: 1st quartile (Q1): 13.6–35.6, 2nd quartile (Q2): 35.6-55.9, 3rd quartile (Q3): 55.9–95.9 and 4th quartile (Q4): 95.9-180.7. There were no differences between quartiles with respect to: age, gender, previous myocardial infarction, diabetes mellitus, hypertension, hypercholesterolemia, smoking status, previous medical therapy, platelet count and mean platelet volume. On the initial angiography, TIMI-3 flow was observed in 4 patients (6%), TIMI-2 flow in 6 patients (9%), TIMI-1 flow in 12 patients (17%) and TIMI-0 flow in 48 (68%). There was no association of patients' gender, age, diabetes mellitus, hypertension, hypercholesterolemia, smoking status, previous medical treatment, platelet count or mean platelet volume with initial TIMI flow.

When compared initial TIMI flow in patients according to quartiles of aggregation in ASPI-test, we have found significantly higher frequency of TIMI-2 and 3 flow among those with low values of ASPI-test (P=0.014). None of the patients in the highest quartile of ASPI-test had TIMI flow of grade 2 or 3 (Table 1). The result was similar if we compared TIMI flow in patients with ASPI values that equaled optimal for our control population (ASPI<31): patients with optimal ASPI-test had significantly higher proportion of TIMI-2 or 3 flow than the patients with suboptimal ASPI levels (P=0.004, Table 2).

Table 1. Distribution of TIMI flow before intervention according to quartiles of patients' ASPI test

	1st quartile	2nd quartile	3rd quartile	4th quartile	P value
TIMI 0	11 (61.1%)	14 (82.4%)	9 (52.9%)	14 (77.8%)	0.014
TIMI 1	1 (5.6%)	3 (17.6%)	4 (23.5%)	4 (22.2%)	
TIMI 2	5 (27.8%)	0 (0%)	1 (5.9%)	0 (0%)	
TIMI 3	1 (5.6%)	0 (0%)	3 (17.6%)	0 (0%)	
total patients	18 (100%)	17 (100%)	17 (100%)	18 (100%)	

TIMI = Thrombolysis In Myocardial Infarction score

Table 2. Difference of TIMI flow before intervention in patients with optimal and suboptimal ASPI test

	ASPI ≤ 31 (optimal)	**ASPI > 31 (suboptimal)**	
TIMI 0	7 (58.3%)	41 (70.2%)	**P=0.004**
TIMI 1	0 (0%)	12 (20.1%)	
TIMI 2	4 (33.3%)	2 (3.5%)	
TIMI 3	1 (8.3%)	3 (5.3%)	
total patients	**12 (100%)**	**58 (100%)**	

TIMI = Thrombolysis In Myocardial Infarction score

Discussion

The benefit from aspirin in patients with acute MI has already been ascertained. However it is not known whether this is due to a higher rate of early spontaneous IRA recanalisation. The influence of platelets physiology on early coronary patency has been previously reported. Soluble platelet glycoprotein V as a marker of stronger platelet activation was found to be higher in plasma of patients with acute STEMI and persistent occlusion at initial angiography when compared to those with spontaneous recanalization [4]. Maden et al found that lower admission mean platelet volume was an independent predictor of IRA patency in patients with acute STEMI [5], although we didn't confirm this in our study. Finally, aspirin effect is heterogeneous and a part of treated patients have suboptimal antiplatelet response, the so called aspirin resistance. There is a substantial body of evidence for its unfavorable role in the development of adverse clinical cardiovascular events [6].

Our study is the first to examine the relation of platelet aspirin response to the patency of IRA before primary angioplasty in acute STEMI. We had only 6% of patients with initial TIMI-3 flow which is much lower then 16% reported by Stone et al [1]. This can be explained by their definition of TIMI-3 flow, where "complete filling of the distal vessel by the third cardiac cycle" overestimates the proportion of these patients when compared to the original TIMI definition that was used in our study [7].

Our results indicate that patients with stronger response to aspirin as assessed by AA induced aggregation in ASPI-test have significantly higher initial coronary flow when compared to those with suboptimal platelet response. The limitations of our study are the small size of the study

population and lack of objective method, other than patient interview, to ascertain previous usage of aspirin.

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