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Patency of infarct-related artery and platelet reactivity in patients with ST-segment elevation myocardial infarction

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ABSTRACT

Background: Outcome in ST-segment elevation myocardial infarction (STEMI) is affected by patency of the infarct-related artery (IRA) on the initial angiogram. There is a controversy if preloading with antiplatelet drugs affects initial IRA patency in case of shortening transportation time for primary percutaneous coronary intervention (PCI). The aim of the study was to assess the relation between IRA patency and platelet reactivity on admission after preloading with aspirin and clopidogrel within 2 h to primary PCI.

Methods: The study included 49 subjects who received 600 mg of clopidogrel and 300 mg of aspirin and underwent primary PCI within 120 min from loading. Platelet reactivity testing was performed on admission with means of impedance aggregometry after induction with arachidonic acid (ASPItest) and adenosine diphosphate with prostaglandin E₁ (ADPtest HS) to assess response to aspirin and clopidogrel, respectively. IRA patency was defined as TIMI flow 2 or 3 on the initial angiogram.

Results: Patent IRA on the initial angiogram was found in 20 patients (41%). Median time between preloading with antiplatelet drugs and primary PCI was 64 min (IQR 59–84 min). Patients who received clopidogrel earlier than 84 min before PCI (4th quartile) had more suppressed platelet reactivity than patients in the 1st quartile (< 59 min) as measured with ADPtest HS ($p = 0.04$). Nevertheless, there was no difference in platelet reactivity between patients with and without IRA patency on the initial angiogram.

Conclusions: In patients preloaded with aspirin and clopidogrel within 2 h to primary PCI, there was no association between the magnitude of platelet inhibition and IRA patency at the time of the initial coronary angiography.

SOUHRN

Kontext: Na výsledek infarktu myokardu s elevací segmentu ST (ST-segment elevation myocardial infarction – STEMI) má vliv průchodnost infarktové tepny (infarct-related artery – IRA) zjištěná na angiogramu okamžitě po hospitalizaci pacienta. Zatím nebylo dosaženo shody, zda zahájení protidestičkové léčby spolu se zkrácením doby do provedení primární perkutánní koronární intervence (PCI) ovlivňuje počáteční průchodnost IRA. Cílem naší studie bylo posoudit vztah mezi průchodností IRA a reaktivitou krevních destiček při příjmu pacienta po předchozím podání kyseliny acetylsalicylové a clopidogrelu během 2 h do provedení primární PCI.

Metody: Do studie bylo zařazeno 49 osob, u nichž byla do 120 min po podání clopidogrelu v dávce 600 mg a kyseliny acetylsalicylové v dávce 300 mg provedena primární PCI. Při příjmu byla pomocí impedanční agregometrie po indukci kyselinou arachidonovou (ASPItest) a adenosindifosfátu s prostaglandinem E₁

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Klíčová slova:

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Průchodnost koronární tepny
Reaktivita destiček

(ADPtest HS) vyšetřena reaktivita destiček ke stanovení odpovědi na kyselinu acetylsalicylovou, respektive clopidogrel. Průchodnost IRA byla hodnocena stupněm 2 nebo 3 TIMI na počátečním angiogramu.

Výsledky: Průchodná IRA byla na počátečním angiogramu zjištěna u 20 pacientů (41 %). Medián doby mezi předběžnou aplikací protideštičkových léků a primární PCI byl 64 min (IQR 59–84 min). Při použití ADPtestu HS byla u pacientů s podáním clopidogrelu do 84 min před PCI (4. kvartil) reaktivita destiček potlačena více než u nemocných v 1. kvartilu (< 59 min) ($p = 0,04$). Přesto nebyl shledán žádný rozdíl v reaktivitě destiček mezi pacienty s průchodnou IRA a bez průchodné IRA na počátečním angiogramu.

Závěry: U pacientů, jimž byly aplikovány kyselina acetylsalicylová a clopidogrel do 2 h před provedením primární PCI, nebyl na prvním koronarogramu pozorován žádný vztah mezi mírou inhibice krevních destiček a průchodností IRA.

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Introduction

Outcome in ST-segment elevation myocardial infarction (STEMI) is affected by patency of the infarct-related artery (IRA) on the initial angiogram [1–3]. It has been demonstrated that patients with initially patent IRA have better perfusion after primary percutaneous coronary intervention (PCI), smaller infarct size (IS) and better survival [1–3].

Since the introduction of the pre-hospital treatment with loading doses of aspirin and clopidogrel there has been a belief that this strategy influences initial IRA patency [4,5]. However, available reports show conflicting results [6–10]. The systematic review of the published data demonstrated that initial IRA patency and clinical outcome were improved in patients who received pre-treatment with clopidogrel [6]. On the contrary, recent results of the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) and of the randomized CIPAMI trial demonstrated lack of relation between preloading with clopidogrel and IRA patency at baseline [7,10]. Two other recent studies on platelet reactivity revealed that initial IRA patency may be associated with higher platelet inhibition by aspirin or clopidogrel, respectively [8,9].

It is hypothesized that the role of preloading with antiplatelet drugs on the initial IRA patency may depend on the duration of transportation to the hospital, as the onset of action of clopidogrel after high loading dose of 600 mg is generally observed no earlier than 2 h from administration of the drug [11].

Therefore the aim of the study was to assess the relation between initial IRA patency and platelet reactivity on admission after preloading with aspirin and clopidogrel within 2 h to primary PCI.

Materials and methods

Study population

The study group included 49 subjects treated with primary PCI. All patients received loading doses of 300 mg of aspirin and 600 mg of clopidogrel in the pre-hospital phase (in the referring hospital or in the ambulance), which generally reflected the transportation time to primary PCI. In any case the time between preloading and start of primary PCI did not exceed 120 min. Glycoprotein IIb/IIIa inhibitors were used at the discretion of the operator. They were administered in the catheterization laboratory

after initial angiogram and blood sampling for platelet reactivity testing, which did not influence the results.

STEMI was defined as (1) presence of continuous chest pain for at least 30 min, (2) ST-segment elevation in 2 or more contiguous ECG leads (≥ 1 mm for the arm leads and ≥ 2 mm for precordial leads), (3) presence of coronary artery occlusion or significant coronary artery stenosis on the initial angiogram in the territory corresponding with ECG changes. Each case of STEMI had to be eventually confirmed with the presence of an elevated troponin I (TnI). Patency of IRA was based on the TIMI flow classification and defined as TIMI flow 2 or 3 [12].

Informed consent was obtained from each participating patient. The local ethics committee approved the study.

Platelet aggregation

Platelet reactivity testing was performed with means of a previously validated multiple electrode impedance aggregometry (Multiplate analyzer, Roche, Basel, Switzerland) [13,14]. The instrument measures the change in impedance between two electrodes as platelets adhere and aggregate in response to a specific agonist. Platelet aggregation is recorded continuously. The increase of impedance is transformed to arbitrary aggregation units and plotted against time (AU*min).

Platelet reactivity testing was performed on admission from the blood drawn at the time of the initial angiogram. For that purpose peripheral blood was withdrawn into a polyethylene tube containing a stabilized direct thrombin inhibitor (TI blood). Specific agonists were used to detect platelet reactivity dependent on aspirin (arachidonic acid – ASPItest) and clopidogrel (adenosine diphosphate plus prostaglandin E_1 – ADPtest HS).

Statistical analysis

All results for categorical variables were expressed as number and percentage and for continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the normality of distribution assessed with the use of a Kolmogorov-Smirnov test. Platelet aggregation measured with multiple electrode impedance aggregometry and time between preloading with antiplatelet drugs and primary PCI were not normally distributed and were therefore presented as median and IQR. Chi-square test or Fisher exact test were used for comparison of categorical variables, when appropriate. Student t-test or Mann-Whitney test were

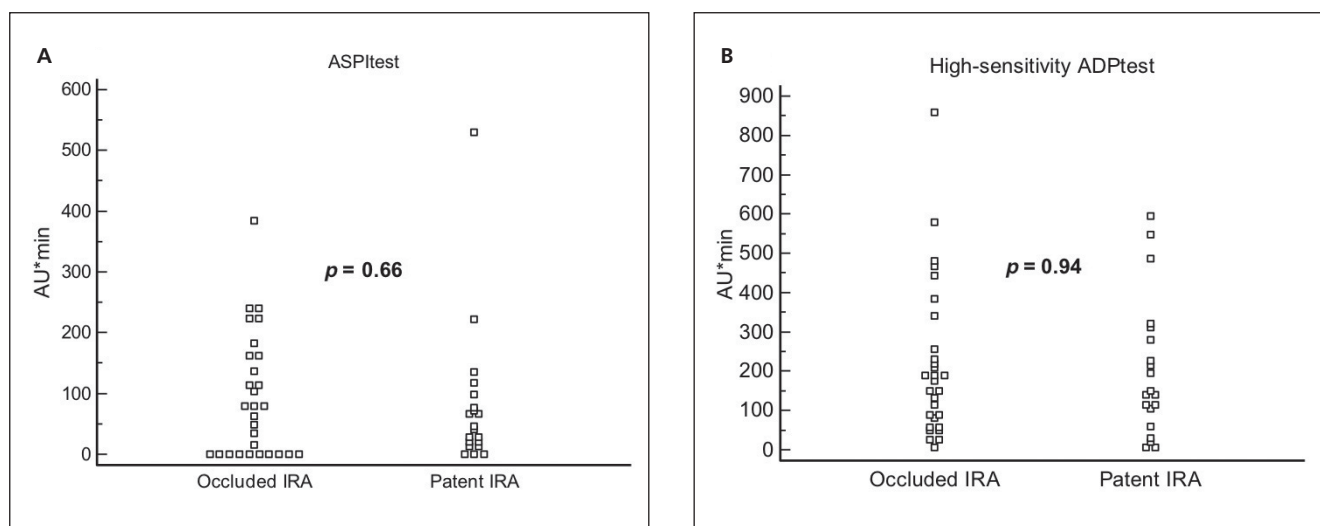


Fig. 1 – Data plot showing results of the platelet aggregation stimulated with arachidonic acid (ASPItest) (A) or adenosine diphosphate and prostaglandin E₁ (high-sensitivity ADPtest) (B) in a subgroup of patients with occluded (n = 20) and patent infarct-related artery (IRA) (n = 29).

applied to compare continuous variables depending on the normality of distribution. Correlation was assessed with means of the Spearman test. All tests were two-sided with the significance level of $p < 0.05$. Statistical analyses were performed with MedCalc statistical software 10.0.2.0 (MedCalc, Mariakerke, Belgium).

Results

Time of preloading and platelet reactivity

Median time between preloading with antiplatelet drugs and primary PCI was 64 min (IQR 59–84 min, range 13–118 min). There was no significant correlation between time of preloading and platelet reactivity – for ASPItest $\rho = -0.139$, $p = 0.34$ and for ADPtest HS $\rho = -0.214$, $p = 0.14$. However, patients who received antiplatelet drugs earlier than 84 min before PCI (4th quartile) had more suppressed platelet reactivity than patients in the 1st quartile (< 59 min) as measured with ADPtest HS (82 IQR 16–210 AU*min vs. 204 IQR 89–376 AU*min, $p = 0.04$), but not with ASPItest (35 IQR 0–126 AU*min vs. 59 IQR 11–209 AU*min, $p = 0.26$).

Patients with and without initial IRA patency

Patent IRA on the initial angiogram was found in 20 patients (41%). Patients with initially occluded IRA had larger infarct size measured with means of peak TnT concentration in comparison to those with initially patent IRA (81.0 ng/ml vs. 11.1 ng/ml, $p < 0.0001$) (Table 1). There was also a trend towards more frequent presence of proximal lesions in patients with occluded IRA (67% vs. 39%, $p = 0.05$) (Table 1). Median time between preloading with antiplatelet drugs and primary PCI was similar in both subgroups.

IRA patency and platelet reactivity at baseline

There was no difference in initial platelet reactivity between patients with and without IRA patency on the initial angiogram as measured with ASPItest (43.5 IQR 17.8–

88.6 AU*min vs. 79.0 IQR 0.0–137.3 AU*min, $p = 0.66$) and ADPtest HS (145.0 IQR 79.6–296.7 AU*min vs. 176.0 IQR 87.9–231.3 AU*min, $p = 0.94$). Data plot for both of the analyzed groups is presented in Figs. 1A and 1B.

According to producer's data (available at www.multiplate.net) ASPItest values below 5th percentile of the reference range in the untreated, normal population (< 745 AU*min) were observed in all of the studied patients. The same criterion for high-sensitivity ADPtest (< 311 AU*min) was not met by 12 patients (24%).

Discussion

Initially patent IRA (TIMI flow 2/3) was previously related to better post-procedural perfusion, smaller infarct size, higher left ventricular ejection fraction, less frequent progression to heart failure and lower mortality [1–3].

Results of the CLARITY-TIMI 28 trial demonstrated that pretreatment with clopidogrel leads to a relative 36% decrease of the IRA occlusion on the initial angiogram [4]. A significant 32% increase in the initial IRA patency in patients who received pretreatment with clopidogrel was also observed in the large systematic review performed by Vlaar et al. [6]. However, recent report from the randomized controlled CIPAMI trial comparing a loading dose of 600 mg of clopidogrel given in the pre-hospital phase versus clopidogrel administered only after the diagnostic angiogram in patients with STEMI demonstrated no increase in the pre-PCI patency of the infarct vessel [10]. Lack of the effect of clopidogrel on the IRA patency was also observed in the Swedish registry – SCAAR [7].

These contradictory results may be explained by differences in timing of clopidogrel pretreatment as suggested also by the authors of the CIPAMI trial [10]. In the CLARITY-TIMI 28 trial patients were undergoing angiography after 48–192 h from the start of clopidogrel treatment [4]. Currently used treatment schemes and improvement in transportation led to a situation when time between

aspirin/clopidogrel loading and PCI is usually shorter than 120 min. Such interval may be too short to achieve satisfactory effect of platelet inhibition, subsequent thrombus resolution and restoration of flow in the occluded artery leading to initial IRA patency [11]. However, none of the above studies analyzed platelet reactivity at baseline to verify this hypothesis.

Our results demonstrated that platelet reactivity stimulated with arachidonic acid for aspirin effect or adenosine diphosphate and prostaglandin E₁ for clopidogrel effect was similar in patients with and without patent IRA in case of preloading within 120 min to primary PCI. To our knowledge, there is only one study published recently which analyzed the relationship between platelet reactivity and IRA patency [9]. The authors of that study demonstrated lower platelet aggregation on clopidogrel in patients with patent IRA with means of two aggregation tests. However, only one of these tests (light transmittance aggregometry) is truly validated to assess platelet function on clopidogrel and results obtained with that test showed only borderline difference between studied groups [15]. In the same study [9], as in our there was no difference in platelet aggregation dependent on aspirin between patients with patent and occluded IRA.

We cannot exclude the possibility that other factors than platelet reactivity play a more pivotal role in the restoration of flow in the IRA. These may include the efficacy of antithrombotic/fibrinolytic mechanisms or location, size and structure of the thrombus or atherosclerotic plaque.

It should be noted that at the time of PCI around 25% of patients did not develop platelet inhibition below the 5th percentile of the reference ranges proposed for the clopidogrel by the manufacturer of the aggregometer. This fact supports the need for widespread introduction of new, more potent and faster acting P2Y₁₂ receptor inhibitors [16,17]. Further studies are needed to demonstrate whether pre-hospital administration of these new drugs in the setting of STEMI improves initial IRA patency in comparison to other antiplatelet dosing regimens. Nevertheless, pre-hospital administration of clopidogrel might reduce ischemic complications after primary PCI despite lack of influence on initial IRA patency and is now a common practice in Europe [10].

The results of this study might have been influenced by a small sample size. This excluded the possibility to perform further subgroup analyses. We were also unable to analyze the influence of different antiplatelet drug dosing regimens on platelet reactivity, which could have further supported the conclusion. Due to ethical reasons it was, however, impossible to include a control group of patients who did not receive preloading with antiplatelet drugs. This is justified by current STEMI guidelines stating that patients undergoing primary PCI should receive oral antiplatelet drugs as early as possible before angiography [18]. Finally, as activated clotting time (ACT) was not routinely measured in this group, we were unable to assess the role of antithrombotic treatment in the restoration of IRA patency.

Table 1 – Characteristics of patients with and without infarct-related artery (IRA) patency on the initial angiogram.

Parameter	Occluded IRA n = 29 (59%)	Patent IRA n = 20 (41%)	p
Age (y) (SD)	60.1 (11.2)	61.6 (9.4)	0.86
Male sex (no.) (%)	20 (69)	16 (80)	0.52
Hypertension (no.) (%)	18 (62)	11 (65)	0.84
Hyperlipidemia (no.) (%)	17 (57)	12 (60)	0.84
Diabetes mellitus (no.) (%)	5 (17)	3 (15)	1.00
Current cigarette smoking (no.) (%)	15 (52)	9 (45)	0.86
Time from the onset of pain to primary PCI			0.84
≤ 2 h	5 (17)	3 (15)	
> 2–6 h	20 (69)	13 (65)	
> 6–12 h	4 (15)	4 (20)	
Time between preloading with aspirin and clopidogrel and primary PCI (IQR)	65 (61–76)	63.5 (54–91)	0.97
Infarct-related artery (no.) (%)			0.35
LAD	13 (44)	12 (60)	
RCA	14 (48)	8 (40)	
Cx	3 (8)	0 (0)	
Lesion location in IRA (no.) (%)			0.04
Proximal	19 (67)	7 (35)	
Mid	7 (25)	12 (60)	
Distal	3 (8)	1 (5)	
Peak TnI (ng/ml) (IQR)	81.0 (55.8–106.9)	11.1 (3.9–21.9)	< 0.0001

Cx – circumflex artery; IRA – infarct-related artery; LAD – left anterior descending artery; PCI – percutaneous coronary intervention; peak TnI – peak concentration of troponin I; RCA – right coronary artery.

Conclusions

In patients preloaded with aspirin and clopidogrel within 2 h to primary PCI, there was no association between the magnitude of platelet inhibition and IRA patency at the time of the initial coronary angiography. Larger confirmatory studies as well as studies with new more potent P2Y₁₂ inhibitors are needed.

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