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Factors influencing no-reflow phenomenon in patients with ST-segment myocardial infarction treated with primary percutaneous coronary intervention

Faktori koji utiču na „no reflow“ fenomen kod bolesnika sa infarktom miokarda sa elevacijom ST-segmenta lečenih primarnom perkutanom koronarnom intervencijom

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Abstract

Background/Aim. It is not know which factors influence no-reflow phenomenon after successful primary percutaneous intervention (pPCI) in patients with myocardial infarction with ST elevation (STEMI). The aim of this study was to estimate predictive value of some admission characteristics of patients with STEMI, who underwent pPCI, for the development of no-reflow phenomenon. Worse clinical outcome in patients with no-reflow points to importance of selection and aggressive treatment in a group at high risk. **Methods.** This was retrospective and partly prospective study which included 491 consecutive patients with STEMI, admitted to a single centre, during the period from 2000 to September 2015, who underwent pPCI. Descriptive characteristics of the patients, presence of classical risk factors for cardiovascular disease, total ischemic time and clinical features at admission were all estimated as predictors for the development of no-reflow phenomenon. No-reflow phenomenon is defined as the presence of thrombolysis in myocardial infarction (TIMI) < 3 coronary flow at the end of the pPCI procedure, or ST-segment resolution by less than 50% in the first hours after the procedure. The significance of the predictive value of some parameters was evaluated by univariate and multivariate regression analysis. In univariate analysis, we used the χ^2 test and Mann Whitney and Student's *t*-tests. **Results.** No-reflow phenomenon was detected in 84 (17.1%) patients (criteria used: TIMI < 3 coronary flow) and in 144 (29.3%) patients (criteria used: ST-sement resolution < 50%). Patients older than 75 years [odds ratio (OR) = 2.53; 95% confidence interval (CI) 1.48–4.33; $p = 0.001$] and those who had Killip class at admission higher than 1 had increased risk to achieve TIMI-3 flow after pPCI. Killip class higher than 1 (OR 1.59; 95% CI 1.23–2.04; $p < 0.001$), left anterior descendent artery (LAD) as infarct related artery (IRA) and total ischemic time higher than 4 hour were associated with increased risk to failure of rapid ST segment resolution after pPCI. **Conclusion.** Older age and Killip class were main predictors of TIMI < 3 flow, and Killip class, LAD as IRA and longer total ischemic time were predictors for the failure of rapid ST segment resolution after pPCI.

Key words:
myocardial infarction; percutaneous coronary intervention; no-reflow phenomenon; risk factors.

Apstrakt

Uvod/Cilj. Nedovoljno je poznato koji faktori utiču na nastanak “no-reflow” fenomena nakon uspešne primarne perkutane intervencije (pPCI) kod bolesnika sa infarktom miokarda sa ST elevacijom (STEMI). Lošiji klinički tok i ishod lečenja kod bolesnika sa “no-reflow” ukazuje na značaj dobre selekcije i agresivnijeg lečenja u grupi sa visokim rizikom. Cilj studije bio je da se proceni prediktivna vrednost određenih karakteristika na prijemu kod bolesnika sa STEMI koji su lečeni PPCI za razvoj “no-reflow” fenomena. **Metode.** Radi se o retrospektivnoj i delom prospektivnoj studiji koja je obuhvatila 491 bolesnika sa STEMI, lečenih na Klinici za uregentnu internu medicinu Vojnomedicinske akademije u Beogradu, u periodu od 2000. godine do septembra 2015. godine pomoću pPCI. Deskriptivne karakteri-

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stike bolesnika, postojanje klasičnih faktora rizika za kardiovaskularne bolesti, vreme od početka bola do pPCI, kao i klinički status na prijemu procenjivani su kao mogući prediktori za razvoj fenomena "no-reflow". "No-reflow" fenomen definisan je kao tromboliza kod infarkta miokarda (TIMI) < 3 na kraju pPCI procedure ili rezolucija ST-segmenta za manje od 50% u prvih nekoliko sati nakon procedure. Značaj prisustva i prediktivne vrednosti ovih parametara, procenjivan je univarijantnom i multivarijantnom regresionom analizom. U univarijantnoj analizi, korišćen je χ^2, Mann Whitney i Studentov *t*-test. **Rezultati.** "No-reflow" fenomen nađen je kod 84 (17,1%) bolesnika (prema kriterijumu TIMI < 3 koronarnog protoka) i kod 144 (29,3%) bolesnika (prema kriteriumu ST – sement rezolucija < 50%). U grupi bolesnika starijih od 75 godina (*odds ratio* – OR = 2.53; 95% CI 1.48–4.33; $p = 0.001$), kao i kod onih koji su imali srčanu slabost definisanu kao Killip > 1 [(OR), 1.59; 95% *confidence interval* (CI) 1.23–2.04; $p < 0.001$], postojao je statitistički značajno veći rizik za razvoj "no-reflow" fenomena. Takođe, leva prednja descendentna arterija – *left anterior descending* (LAD), kao infarktna arterija (IRA) i ukupno ishemijsko vreme duže od četiri sata bili su povezani sa povećanim rizikom za razvoj "no-reflow" fenomena, praćeno preko parametra izostanak rezolucije ST segmenta za > 50% nakon PPCI. **Zaključak.** Starije osobe i srčana slabost i Killip > 1 bili su glavni prediktori TIMI < 3 protoka, a Killlip, LAD kao infarktna arterija i duže trajanje ishemije bili su prediktori za sporiju rezoluciju ST-segmenta nakon pPCI.

Ključne reči:
infarkt miokarda; perkutana koronarna intervencija; no-reflow fenomen; faktori rizika.

Introduction

There are several definitions of no-reflow phenomenon. Some authors defined it as an inadequate flow through the infarct related artery (IRA) after successful primary percutaneous intervention (pPCI), without mechanical obstruction [1].

Patients who develop this phenomenon have significantly worse short-term but also long-term prognosis. Therefore, identifying predictors of no-reflow phenomenon has a great clinical and prognostic significance.

It is known that many factors influence the development of no-reflow, such as demographic data, ischemic time, IRA, distal embolisation, microvascular obstruction or reperfusion injury [2].

Parameters that indicate existence of no-reflow phenomenon are flow through the infarct artery thrombolysis in myocardial infarction (TIMI) < 3 after successful pPCI, or resolution of ST-segment in electrocardiogram (ECG) that is less than 50% in the first hours after pPCI.

The main objective in this study was to estimate predictive value of several admission characteristics in patients with ST-segment elevation myocardial infarction (STEMI), who underwent pPCI, for development of no-reflow phenomenon.

Methods

This is a retrospective and partly prospective study which included 491 consecutive patients with STEMI admitted to the Clinic for Emergency Internal Medicine at the Military Medical Academy in Belgrade, Serbia, during the period from 2000 to September 2015. All patients included in the study were treated with pPCI with subsequent treatment in the cardiac intensive care unit (CICU), following current recommendations for the treatment of patients with STEMI in CICU [3]. Descriptive characteristics of the patients, presence of classical risk factors for cardiovascular disease, total ischemic time and clinical features at admission were all estimated as predictors for the development of no-reflow phenomenon. No -reflow phenomenon is defined as the presence of TIMI < 3 coronary flow at the end of adequate implantation of stent(s) after pPCI (no significant residual stenosis in the infarction related artery), or ST-segment resolution by less than 50% in ECG that was done one hour after the procedure. These two criteria were estimated independently on the same cohort of consecutive STEMI patients.

Numeric variables were described by the mean and standard deviation as measures of descriptive statistics for variables with normal distribution. For variables with non-normal distribution median and interquartile range were performed as a descriptive parameters. Categorical variables were described by number of cases and percentages. The Student's *t*-test was used for comparison of two groups for numerical variables with normal distribution. Mann Whitney U test was used for comparison of two groups for variables with non-normal distribution. The Pearson's χ^2 test was used for testing differences in categorical variables among groups.

To identify predictors, univariate and multivariate binary logistic regression was used. The variables that showed a statistically significant effect on the dependent variable in univariate logistic regression entered the model of multivariate binary logistic regression. The results are presented as the odds ratio (OR) with 95% confidence interval (CI) and *p* value.

Normality distribution was tested by Kolmogorov-Smirnov test.

The differences were considered significant if probability of null hypothesis was less or equal than 0.05 ($p \leq 0.05$). All calculations were performed by the SPSS, Version 20 (Statistical Package for the Social Sciences).

Results

No-reflow phenomenon was detected in 84 (17.1%) patients (criteria used: TIMI < 3 coronary flow) and in 144 (29.3%) patients (criteria used: ST-segment resolution < 50%).

Table 1

Basic demographic characteristics at admission of patients with STEMI treated with primary PCI in relation to TIMI flow at the end of the procedure and resolution of ST-segment in ECG in the first hour after the procedure

Demographic characteristics	TIMI 3 407 (82.9 %)	TIMI < 3 84 (17.1 %)	*p*	ST-segment resolution ≥ 50% 347 (70.7 %)	ST-segment resolution < 50% 144 (29.3 %)	*p*
Age (years), mean ± SD	61 ± 12	66 ± 13	0.002[a]	62 ± 12	64 ± 12	0.148[a]
Age intervals (years), n (%)						
< 59	188 (46.2)	26 (31.0)	0.011[b]	150 (43.4)	58 (40.4)	0.606[b]
59–74	149 (36.5)	30 (35.7)	1.000[b]	130 (37.5)	51 (35.3)	0.673[b]
> 74	70 (17.3)	28 (33.3)	0.002[b]	66 (19.1)	35 (24.3)	0.210[b]
Women, n (%)	107 (26.4)	21 (25.0)	0.892[b]	93 (26.8)	38 (26.5)	1.000[b]

TIMI – Thrombolysis In Myocardial Infarction; n – number in group; SD – standard deviation; *p* – statistical significance; [a]Student's *t*-test; [b]χ^2 – chi-square test; STEMI – ST elevation myocardial infaraction; PCI – percutaneous intervention; ECG – electrocardiogram.

Table 2

Basic characteristics at admission of patients with STEMI treated with primary PCI in relation to TIMI flow at the end of the procedure and resolution of ST-segment in ECG in the first hour after the procedure

Clinical characteristics	TIMI 3 407 (82.9 %)	TIMI < 3 84 (17.1 %)	*p*	ST-segment resolution ≥ 50% 347 (70.7 %)	ST-segment resolution < 50% 144 (29.3 %)	*p*
Risk factors, n (%)						
smoking	216 (53.0)	35 (42.5)	0.111[b]	189 (54.4)	65 (45.5)	0.099[b]
hypertension	277 (68.1)	63 (75.3)	0.235[b]	242 (69.8)	103 (71.6)	0.737[b]
hypercholesterolemia	256 (63.0)	52 (61.8)	0.892[b]	210 (60.4)	96 (66.7)	0.270[b]
diabetes	109 (26.7)	24 (29.3)	0.683[b]	87 (25.0)	45 (31.3)	0.166[b]
BMI (kg/m^2), mean± SD	26.4 ± 3.5	26.7 ± 3.8	0.685[a]	26.5 ± 3.5	26.2 ± 3.6	0.611[a]
Infarct related artery, n (%)						
LAD (left anterior descending)	165 (40.5)	36 (42.9)	0.717[b]	124 (35.7)	65 (45.1)	0.038[b]
ACX (circumflex artery)	74 (18.2)	13 (15.5)	0.639[b]	60 (17.3)	18 (12.5)	0.220[b]
RCA (right coronary artery)	157 (38.6)	34 (40.5)	0.806[b]	134 (38.6)	50 (34.7)	0.405[b]
Multivessel disease, n (%)	272 (66.9)	66 (79.0)	0.035[b]	240 (69.3)	99 (68.9)	1.000[b]
Kilip class > 1, n (%)	57 (14.1)	34 (40.5)	< 0.001[b]	45 (13.0)	40 (27.9)	< 0.001[b]
Ischemic time (hrs), median (IQR)	3.5 (2.5–6.0)	4.0 (3.0–6.5)	0.508[c]	3.0 (2.0–5.0)	5.0 (3.0–8.8)	< 0.001[c]
Overall stent length in IA, median (IQR)	23.0 (18.0–33.0)	24.5 (18.0–46.5)	0.114[c]	23.0 (18.0–32.0)	25.0 (19.0–36.5)	0.055[c]

TIMI – Thrombolysis In Myocardial Infarction; n – number in group; mean ± SD – mean ± standard deviation; IQR- Interquartile range; *p* – statistical significance; IA – infarct artery; [a]Student's *t*-test; [b]χ^2 – chi-square test; [c]Mann Whitney U test.

For abbreviations see under Table 1.

Patients with TIMI < 3 flow at the end of the procedure were significantly older than patients with TIMI 3 flow, in particular older than 74 years ($p = 0.002$). They have also had more often multivessel coronary disease ($p = 0.035$) and were more often admitted with signs of acute heart failure ($p < 0.001$). On the other side, patients with resolution of ST-segment less than 50% had more often LAD as IRA compared to patients with significant resolution of ST-segment in the ECG ($p = 0.035$). They have also had more often signs of acute heart failure at admission ($p < 0.001$), and borderline significance was achieved in comparison of the median overall stent lengths in infarction artery with longer overall stent length in this patients with absence of ST-segment resolution ($p = 0.055$). Other demographic and basic characteristics at admission are presented in Tables 1 and 2.

According to univariate binary regression analysis for TIMI flow criteria used, the best predictors of occurrence of flow TIMI < 3 at the end of the procedure were Killip class > 1 at admission (unadjusted OR = 4.14; 95% CI 2.74–6.95; $p < 0.001$), age over 74 years (unadjusted OR = 2.39; 95% CI 1.42–4.03; $p = 0.002$) and presence of multivessel disease (unadjusted OR = 1.86; 95% CI 1.05–3.30; $p = 0.035$). In multivariate binary regression ("stepwise" method) analysis, as the best independent predictor of flow TIMI < 3 was Killip class >1 (OR = 1.93; 95% CI 1.49–2.52; $p < 0.001$). Age > 74 was detected as the second most important predictor of TIMI < 3 (OR = 2.12; 95% CI 1.22–3.68; $p = 0.007$) (Table 3).

According to univariate binary regression analysis for ST-segment resolution criteria used, the best predictors of ST-segment resolution by less than 50% were: Killip class > 1 (unadjusted OR = 2.60; 95% CI 1.59–4.27; $p < 0.001$), ischemic time (unadjusted OR = 1.11; 95% CI 1.06–1.16; $p < 0.001$), overall stent length in infarction artery (unadjusted OR = 1.01; 95% CI 0.99–1.03; $p = 0.055$) and LAD as IRA (unadjusted OR = 1.55; 95% CI 1.03–2.32; $p = 0.038$) (Table 4). However, the best independent predictors of no-reflow according to this criteria, using the stepwise multivariate binary regression analysis, were ischemic time (OR = 1.15; 95% CI 1.08–1.22; $p < 0.001$) and Killip class > 1 (OR = 1.59; 95% CI 1.17–2.77; $p = 0.003$).

Discussion

The rate of no-reflow in our study is in the range of available literature data. Independent predictors of no-reflow in our group of consecutive STEMI patients were presence of acute heart failure at admission and total ischemic time. Older age and multivessel disease showed to be good predictors, as well.

These data are consistent with literature where percentage of no-reflow is between 11–40% [4].

Univariate and multivariate binary regression analysis for the best predictors of no-reflow (resolution of ST-segment less than 50% and TIMI < 3 flow) have shown that the Killip > 1 on admission is the best predictor of no reflow-phenomenon. This data correlates with the fact that the most difficult patients develop no-reflow [5].

Table 3

Unadjusted odds ratio (OR) and adjusted in univariate and multivariate analysis for the best predictors of TIMI flow less than 3

Parameters	Univariate binary regression analysis		Multivariate binary regression analysis		Multivariate binary regression analysis („stepwise" method)	
	unadjusted OR (95% CI)	*p*	adjusted OR (95% CI)	*p*	OR (95% CI)	*p*
Killip > 1	4.14 (2.47–6.95)	< 0.001	1.95 (1.49–2.54)*	< 0.001	1.93 (1.49–2.52)	< 0.001
Age 74 years	2.39 (1.42–4.03)	0.002	2.53 (1.48–4.33)**	0.001	2.12 (1.22–3.68)	0.007
Multivessel disease	1.86 (1.05–3.30)	0.035	1.67 (0.93–3.00)*	0.085	/	/

TIMI – Thrombolysis in Myocardial Infarction; OR – odds ratio; CI – confidence interval;*gender, age; ** gender; *p* – statistical significance.

Table 4

Unadjusted odds ratio (OR) and adjusted in univariate and multivariate analysis for the best predictors of resolution of ST-segment less than 50%

Parameters	Univariate binary regression analysis		Multivariate binary regression analysis		Multivariate binary regression analysis („stepwise" method)	
	unadjusted OR (95% CI)	*p*	adjusted OR (95% CI)*	*p*	OR (95% CI)	*p*
Killip > 1	2.60 (1.59–4.27)	< 0.001	1.59 (1.23–2.04)	< 0.001	1.59 (1.17–2.77)	0.003
Ischemic time	1.11 (1.06–1.16)	< 0.001	1.11 (1.06–1.17)	< 0.001	1.15 (1.08–1.22)	< 0.001
Overall stent length in IA	1.01 (0.99–1.03)	0.055	1.01 (0.99–1.03)	0.126	/	/
LAD as infarct artery	1.55 (1.03–2.32)	0.038	1.55 (1.03–2.33)	0.034	/	/

IA – infarct artery; LAD – left anterior descending; OR – odds ratio; CI – confidence interval;*gender, age; ** gender; *p* – statistical significance.*gender, age; *p* – statistical significance.

These data are particularly important in the case of elderly patients. According to the TIMI < 3 flow, elderly patients have a high risk to develop no-reflow.

Ischemic time greater than 4 hours, also represents an independent predictor of no-reflow phenomenon. This data is correlated with the data available in literature [6]. Additionally, data from literature, where ischemia-reperfusion period is listed as an essential parameter, visualization of thrombus mass in the IRA and target lesion length over 13.5 cm can also be considered as independent predictors of no-reflow phenomenon.

In the largest data reported (CathPCI registry), most obtained data coincided with our testing. Cardiogenic shock and time to PCI were also the most important parameters of no- reflow ($p < 0.001$). Angiographic criteria such as total length of the lesion, complexity of the lesions – type C and bifurcation lesions are also independent predictive factors. Adequately performed procedures are another important factors in the prevention of no-reflow phenomenon [7].

Consequently, we can conclude that elderly patients with anterior wall infarction, especially those with prolonged time of ischemia, are at the highest risk of no-reflow development. Patients with TIMI flow 0 or 1 before the pPCI intervention represent the high risk group. These factors are targeted for maximum therapeutic approach and special attention, due to a risk of no-reflow phenomenon. This is especially important because of the fact that this group of patients may have significantly worse prognosis.

Study limitation

This study was done in one sigle center, and we accept the limitations of the therapy which we use during the study. There is not fully systematized use of pharmacological therapy, and the effects are still unclear. Thus, the treatment strategy is not definied totally; we used standard therapy for all patients with no-reflow (glycoprotein platelet inhibitors, nitroglycerin, adenosine, verapamil, heparin), but further investigation is necessary.

Conclusion

Elderly patients with anterior wall infarction, especially those with prolonged time of ischemia, are at the highest risk of no-reflow development. Patients with TIMI flow 0 or 1 before the pPCI intervention represent the high risk group. These factors are targeted for maximum therapeutic approach and special attention because of the risk of no-reflow phenomenon. This is especially important due to fact that this group of patients may have significantly worse prognosis.

Signs of acute heart failure at admission and total ischemic time as well as older age above 74 years, and multivessel disease were significant predictors of the occurrence of no reflow phenomenon in patients with first STEMI who underwent primary PCI.

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