

Clinical Predictors of No-Reflow in Percutaneous Coronary Intervention for Acute Myocardial Infarction

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ABSTRACT

Background

The no-reflow phenomenon in the setting of primary coronary intervention for acute myocardial infarction (AMI) is relatively common and is associated with adverse outcomes. The detection of clinical variables associated with this phenomenon before the procedure might help to adopt preventive measures and thus improve the results.

Objective

The aim of this study was to identify clinical predictors of the no-reflow phenomenon in the setting of percutaneous coronary intervention for ST-segment elevation acute myocardial infarction, prior to the procedure.

Methods

A total of 742 patients with AMI < 12 hours since onset of symptoms treated with primary percutaneous coronary intervention were analyzed. Patients with epicardial TIMI grade 0 flow after the procedure were excluded. No-reflow was considered as the presence of TIMI grade 1-2 flow immediately after the procedure in the absence of residual stenosis. Demographic variables, coronary risk factors, family history and delay to reperfusion were analyzed. Multivariate logistic regression was used to determine the independent prognostic value of the variables associated with no-reflow.

Results

A total of 675 patients were included. The no-reflow phenomenon was present in 119 patients (17.6%). Patients with no-reflow were older (60.8 ± 12 vs. 57.0 ± 11 years; $p = 0.0001$) and had less prevalence of current smoking (58.8% vs. 67.8%, $p = 0.03$) and of previous history (22.7% vs. 37.8%, $p = 0.0007$), with no significant differences in the rest of coronary risk factors and history of cardiovascular disease. Anterior AMI (58.8% vs. 43.7%, $p = 0.002$), heart failure at admission (17.6% vs. 10.1%, $p = 0.01$) and delay to reperfusion (240 [151-360] vs. 195 [120-302] minutes, $p = 0.02$) were more frequent in the no-reflow group. Multivariate analysis identified age > 60 years, anterior infarction and delay to reperfusion > 3 hours as independent predictors of no-reflow.

Conclusion

Advanced age, anterior infarction and delay to reperfusion were independent clinical predictors of no-reflow. The confirmation of these findings in prospective studies might allow the implementation of strategies to prevent this phenomenon and eventually improve the long-term clinical outcomes.

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Key words > Myocardial infarction – No-reflow - Percutaneous coronary intervention - reperfusion

Abbreviations >	AMI	Acute myocardial infarction	IVUS	Intravascular ultrasound
	STEMI	ST-segment elevation myocardial infarction	LBBB	Left bundle branch block

INTRODUCTION

Since the introduction of percutaneous coronary angioplasty in 1978, (1) percutaneous coronary interventions have been replacing fibrinolytic therapy as an early reperfusion strategy in the setting of acute ST-segment elevation myocardial infarction (STEMI), with better angiographic reperfusion rates at 90 minutes than those achieved with pharmacological reperfusion. (2)

The progress in medical technology and drug therapy has improved the clinical outcomes; however, a significant percentage of patients do not achieve adequate microvascular reperfusion despite the restoration of epicardial flow in the treated vessel.

The no-reflow phenomenon in the setting of primary coronary interventions for acute myocardial infarction (AMI) is the absence of myocardial perfusion restitution after adequate recanalization of the infarct-related artery. (3) The incidence of this phenomenon is present in 10% to 54% of the procedures depending on the characteristics of the population studied and on the method used for its diagnosis, and it is associated with an adverse clinical outcome with greater short and long term progression to heart failure and increased mortality.(4-8)

Several authors have established a significant association between this phenomenon and plasma levels of different markers (9-15) or with certain features of atherosclerotic plaque visualized by IVUS. (16-18) However, the usefulness of these diagnostic techniques is limited as these complex methods are not always available in the emergency setting of AMI. Other studies have shown that the combination of clinical variables with procedural findings is useful to identify this group of patients. (7, 19)

The goal of the present study was to identify clinical predictors of the no-reflow phenomenon before performing a percutaneous coronary intervention in STEMI patients.

METHODS

The study included 742 patients referred to the cath lab for primary percutaneous coronary intervention due to STEMI within 12 hours since onset of symptoms.

STEMI was defined as prolonged ischemic chest pain unresponsive to nitrates associated with ST-segment elevation ≥ 1 mm in at least two contiguous precordial leads or showing new or presumably new left bundle branch block (LBBB).

Percutaneous coronary intervention was performed following the usual standards. All the patients received aspirin 200 mg and clopidogrel 300 mg in the cath lab. An introducer was inserted and intraarterial heparin (70-100 U/Kg) was injected in bolus. Pretreatment with glycoprotein IIb/IIIa inhibitors was not systematically used.

Demographic variables, coronary risk factors, previous and family history, delay to treatment and the presence of clinical signs of heart failure at admission (Killip and Kimball class B, C or D) were analyzed.

Angiographic analysis and definition of no-reflow:

The angiographic evaluation of epicardial flow was made by two independent and experienced operators using the semi-

quantitative TIMI (Thrombolysis In Myocardial Infarction) grading scale (20). Discrepancies were solved by consensus.

After excluding patients with absence of epicardial flow (TIMI grade 0 flow after the procedure), 675 patients were included in the analysis. No-reflow after reperfusion was defined as postprocedural TIMI grade 1- 2 flow in the absence of residual stenosis $\geq 30\%$, coronary dissection, vasospasm or visible thrombus. (21)

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation (SD), or median and interquartile range, as applicable, and categorical variables as frequencies and percentages. Qualitative variables were analyzed with the chi-square test or Fisher's exact test, as applicable. The Kruskal-Wallis test was used to analyze non-parametric variables. Within-group variability of continuous variables was analyzed using Student's t test for paired samples. The t-test and the Kruskal-Wallis test for unpaired samples, or the analysis of variance (ANOVA), were used for variability between groups, with previous verification of normal distribution and homogeneity of variance employing Bartlett's test. Clinical variables associated with no-reflow with a p value < 0.10 at univariate analysis were included in a multivariate logistic regression model to determine their independent prognostic value and were expressed as odds ratio (OR) and 95% confidence interval (95% CI). A p value < 0.05 was considered statistically significant.

RESULTS

Between October 2001 and May 2011, 742 patients underwent primary percutaneous coronary intervention due to STEMI within 12 hours since onset of symptoms. Sixty seven patients (9.0%) with TIMI grade 0 flow immediately after the procedure were excluded from the study. Of the 675 patients analyzed, 119 (17.6%) presented no-reflow phenomenon. The rest of the patients presented TIMI grade 3 flow immediately after the procedure.

Mean age was 57.8 ± 11.5 years and 83.1% were men. The baseline characteristics of both groups are shown in Table 1. Patients in the no-reflow group were older (60.8 ± 12.6 vs. 57.0 ± 11.2 years; $p=0.0001$) and most patients were > 60 years (47.1% vs. 33.6%; $p=0.005$). The no-reflow group had lower proportion of current smokers (58.85% vs. 67.8%; $p=0.03$) and of family history of cardiovascular disease (22.7% vs. 37.8%; $p=0.0007$). They also evidenced a trend towards higher dyslipidemia without significant differences in the prevalence of other coronary risk factors, previous angina or AMI. Anterior infarction and heart failure at admission were significantly more common in patients with no-reflow (58.8% vs. 43.7%, $p=0.002$ and 17.6% vs.10.1%; $p=0.01$, respectively).

The angiographic characteristics of both groups are described in Table 2. The no-reflow phenomenon was associated with TIMI grade 0-1 flow before percutaneous coronary intervention (95.0% vs. 82%; $p=0.0001$) and with the left anterior descending as the infarct-related artery (58.8% vs. 43.3%; $p=0.0001$). There was no association with the extent of coronary artery disease.

Table 1. Clinical characteristics of the population

	NO-REFLOW n (%)	TIMI GRADE 3 FLOW n (%)	OR (95% CI)	p
N	119 (17.6)	556 (82.4)		
Male gender	97 (81.5)	464 (83.5)		0.30
Age	60.8 ± 12.6	57.0 ± 11.2		0.0001
Age > 60 years	56 (47.1)	187 (33.6)	1.75 (1.17 - 2.62)	0.005
Hypertension	62 (52.1)	257 (46.2)		0.12
Diabetes	18 (15.1)	74 (13.3)		0.29
Current smoking	70 (58.8)	377 (67.8)	0.68 (0.45 - 1.00)	0.03
Dyslipidemia	60 (50.4)	236 (42.4)	1.38 (0.92 - 2.05)	0.057
Obesity	57 (47.9)	219 (39.4)		0.08
Family history	27 (22.7)	210 (37.8)	0.48 (0.30 - 0.76)	0.0007
Previous angina	51 (42.9)	247 (44.4)		0.37
Previous AMI	23 (19.3)	89 (16.0)		0.19
Anterior infarction	70 (58.8)	243 (43.7)	1.84 (1.23 - 2.75)	0.002
Severe heart failure at admission	21 (17.6)	56 (10.1)	1.91 (1.11 - 3.30)	0.01

AMI: Acute myocardial infarction

Table 2. Angiographic variables

	NO-REFLOW n (%)	TIMI GRADE 3 FLOW n (%)	OR (95% CI)	p
Delay to reperfusion (minutes)	240 (151 - 360)	195 (120 - 302)		0.02
Delay to reperfusion >180 minutes	69 (57.9)	258 (46.4)	1.59 (1.05 - 2.43)	0.02
Infarct-related artery				
Left anterior descending coronary artery	70 (58.8)	241 (43.3)		0.0004
Right coronary artery	28 (23.5)	238 (42.8)		
Left circumflex coronary artery	21 (17.6)	75 (13.5)		
Left main coronary artery	0	2 (0.4)		
Extent of coronary artery disease				
One-vessel disease	50 (42.0)	246 (44.2)		0.06
Two-vessel disease	37 (31.1)	174 (31.3)		
Three-vessel disease	32 (26.9)	136 (24.5)		
Baseline TIMI grade 0-1 flow	113 (95.0)	461 (82.9)	0.26 (0.11 - 0.60)	0.0001
Use of IIb-IIIa	24 (20.2)	65 (11.7)	1.90 (1.53 - 3.20)	0.009
Use of stent	100 (84.0)	514 (92.4)	0.43 (0.24 - 0.77)	0.003

Delay to treatment was significantly higher in the no-reflow group [240 minutes (151-360) vs. 195 minutes (120-302); $p=0.02$]. The use of stent was lower in this group (84.0% vs. 92.4%; $p=0.003$). The use of glycoprotein IIb-IIIa inhibitors was low in both groups, but significantly higher in the no-reflow group (20.2% vs. 11.7%; $p=0.009$), as indication of these agents was left to the discretion of the physician in charge of the procedure.

Multivariate analysis also included the presence

of heart failure at admission, family history, obesity, smoking habits and dyslipidemia. Age > 60 years (OR: 1.83; 95% CI: 1.19 to 2.81), anterior infarction (OR: 1.65; 95% CI: 1.07-2.54) and delay to treatment > 180 minutes (OR: 1.55; 95% CI: 1.01 to 2.42) were the only independent predictors of the no-reflow phenomenon (Table 3).

DISCUSSION

Since its initial description in a canine model in 1974,

Table 3. Multivariate analysis

	OR (95% CI)	p
Age > 60 years	1.83 (1.19 - 2.81)	0.006
Anterior infarction	1.65 (1.07 - 2.54)	0.02
Delay to reperfusion >180 minutes	1.55 (1.01 - 2.42)	0.05

(3) numerous studies have associated the no-reflow phenomenon with major cardiovascular events, with short and long-term increased risk of mortality, reinfarction and ventricular dysfunction. (4-8)

Many tools as the use of glycoprotein IIb-IIIa inhibitors, intracoronary administration of diverse agents or mechanical methods such as thrombus aspiration have been evaluated in this setting with variable and not definitive clinical results, at the expense of increased development of severe adverse events. (22) The appropriate use of these therapies requires adequate risk stratification to enhance their benefits avoiding complications.

Many laboratory tests, as C-reactive protein, atrial natriuretic peptide, thromboxane A2, intraplatelet melatonin or plasma glucose level at admission, (9-15) and complex imaging studies as intracoronary ultrasound, (16-18, 23-25) have demonstrated to be useful to predict this phenomenon. However, these methods are difficult to be applied because of their high costs, the associated delay to reperfusion and the scarce availability of many of them in most centers.

There is no question about the usefulness of angiographic variables to demonstrate absence of initial flow or extensive thrombosis. (4, 5) However, this information is available relatively late, limiting the early application of therapies intended to prevent this phenomenon.

Therefore, the availability of clinical variables which can be easily obtained at patient evaluation before undergoing primary coronary intervention might allow a better planning of the procedure, using adequate strategies to prevent the no-reflow phenomenon.

Our results indicate that advanced age, anterior infarction and delay to reperfusion are independent predictors of this phenomenon and might be used for initial risk stratification to guide treatments focused on preventing this phenomenon.

Iwakura et al. found no-reflow phenomenon in 79 of 199 patients (39.6%) using myocardial contrast echocardiography 15 minutes after percutaneous coronary intervention. Absence of pre-infarction angina, number of abnormal Q-waves, wall motion score and TIMI grade 0 flow on the initial coronary angiogram were identified as independent predictors of the no-reflow phenomenon. The risk area size and the severity of myocardial damage are closely related with the no-reflow phenomenon. (7) Larger infarct size (anterior infarction) has also been associated with lower tissue

reperfusion. (26)

Consistent with our results, a recent study conducted on 382 consecutive patients treated with primary percutaneous coronary intervention within 12 hours since onset of symptoms showed that advanced age (> 60 years) and delayed reperfusion (≥ 4 hours) were independent predictors of the no-reflow phenomenon. TIMI grade 0 flow before reperfusion, target lesion length and high thrombus burden were also independent predictors of the no-reflow phenomenon. (19)

Other studies indicate that history of diabetes and hypercholesterolemia might predispose to no-reflow. (27, 28) In our study, we found a trend towards greater prevalence of dyslipidemia in our no-reflow patients; however, dyslipidemia and diabetes were not independent predictors.

Previous AMI and absence of pre-infarction angina have also been associated with the no-reflow phenomenon; (4, 7, 9) these findings, however, were not confirmed by our study, while delayed reperfusion was a common factor in all the studies.

Among the multiple strategies postulated to prevent and treat this phenomenon, only manual thrombus aspiration and direct stenting without predilation have demonstrated a net clinical benefit. (29, 30) The use of vasodilators as adenosine, sodium nitroprusside and verapamil has improved myocardial perfusion and ventricular function but not the clinical parameters evaluated (progression to heart failure or mortality) and, in the case of verapamil, with the addition of a mild increase in atrioventricular block and hypotension. (31-33)

Although the pathophysiological mechanism of glycoprotein IIb-IIIa inhibitors is attractive to prevent microvascular obstruction and thrombus extension, they have provided unclear results depending on the characteristics of the population. (34-37)

Probably, a better selection of patients before the procedure and an earlier implementation of the present or other promising strategies, as the combination of thrombus aspiration and intracoronary infusion of IIb-IIIa, (37) might represent a greater benefit.

Limitations

The present study has several limitations. Firstly, it was a retrospective study performed at a single center which could have led to bias and modified the outcomes.

The diagnosis of no-reflow was made considering only the epicardial flow. Other diagnostic methods are more sensitive, as ST-segment resolution 3 hours after reperfusion, (38, 39) the evaluation of myocardial blush grade (39-41) or coronary artery flow assessment with myocardial contrast echocardiography. (42)

Despite these considerations, we think that these results are convincing and highly significant, and should be confirmed by prospective studies.

CONCLUSIONS

Advanced age, anterior infarction and delay to reperfusion are independent predictors of no-reflow. The confirmation of these findings in prospective studies might allow the implementation of strategies to prevent this phenomenon and eventually improve the long term clinical outcomes.

RESUMEN

Predictores clínicos de no-reflujo en la angioplastia coronaria por infarto agudo de miocardio

Introducción

El fenómeno de no-reflujo en el contexto de la angioplastia por infarto agudo de miocardio (IAM) es un hecho relativamente frecuente y asociado con peor pronóstico. La detección de variables clínicas vinculadas a este fenómeno antes del inicio del procedimiento podría ayudar a la adopción de medidas preventivas y por consiguiente a mejorar los resultados.

Objetivo

Determinar predictores clínicos de no-reflujo en el contexto de la angioplastia por IAM con elevación del segmento ST antes del inicio del procedimiento.

Material y métodos

Se analizaron 742 pacientes con IAM de < 12 horas de evolución tratados con angioplastia primaria. Se excluyeron los pacientes con flujo epicárdico TIMI 0 posintervención y se consideró no-reflujo a la presencia de flujo TIMI 1-2 posangioplastia inmediato en ausencia de lesión residual. Se analizaron variables demográficas, factores de riesgo coronario, antecedentes y demora al tratamiento. Se realizó un análisis multivariado por regresión logística múltiple para determinar el valor pronóstico independiente de las variables relacionadas con el no-reflujo.

Resultados

Se incluyeron 675 pacientes. Presentaron fenómeno de no-reflujo 119 pacientes (17,6%). Los pacientes con no-reflujo tenían mayor edad ($60,8 \pm 12$ vs. $57,0 \pm 11$ años; $p = 0,0001$) y menor frecuencia de tabaquismo activo (58,8% vs. 67,8%; $p = 0,03$) y de antecedentes familiares (22,7% vs. 37,8%; $p = 0,0007$), sin diferencias significativas en el resto de los factores de riesgo coronario y antecedentes cardiovasculares. Se observó también con mayor frecuencia localización anterior del IAM (58,8% vs. 43,7%; $p = 0,002$), signos clínicos de insuficiencia cardíaca al ingreso (17,6% vs. 10,1%; $p = 0,01$), así como mayor demora al tratamiento [240 (151-360) vs. 195 (120-302) minutos; $p = 0,02$]. El análisis multivariado determinó que los predictores independientes de no-reflujo fueron: edad > 60 años, localización anterior y demora al tratamiento > 3 horas.

Conclusión

La edad avanzada, la localización anterior y la demora al tratamiento resultaron predictores clínicos independientes de no-reflujo. La confirmación de estos hallazgos en estudios prospectivos permitiría implementar estrategias para prevenir su aparición y, eventualmente, mejorar los resultados clínicos a largo plazo.

Palabras clave > Infarto del miocardio - No reflujo - Angioplastia coronaria percutánea - Reperusión

Conflicts of interest

None declared.

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