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Original article

Clinical variables associated with no-reflow after percutaneous coronary intervention in ST-segment elevation myocardial infarction: Secondary analysis of PERSTEMI I and II registries

Cynthia Paredes-Paucar[1,a], **Piero Custodio-Sánchez**[2,a], **Manuel Chacón Diaz**[3,4,a]

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Authors' Affiliation
[1] Instituto del Corazón, Clínica San Pablo. Lima, Peru
[2] Hospital Almanzor Aguinaga Asenjo. Chiclayo, Peru
[3] Instituto Nacional Cardiovascular. Lima, Peru
[4] Universidad Científica del Sur. Lima, Peru
[a] Cardiologist

Correspondence
Cynthia Paredes-Paucar

Email
cpaola.paredes@gmail.com

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ABSTRACT

Objective. To determine the clinical factors associated to no-reflow after percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) in Peru. **Methods.** Case - control retrospective study, derived from the PERSTEMI (Peruvian Registry of ST-elevation myocardial infarction) I and II. Cases (group 1) were those patients who presented no-reflow after PCI, defined by a TIMI flow < 3, and controls (group 2) were those with a TIMI 3 flow after the intervention. Clinical and angiographic variables were compared between both groups, and a multivariate analysis was performed looking for associated factors to no-reflow. **Results.** We included 75 cases and 304 controls. The incidence of no-reflow was 19.8%. There was a higher frequency of no-reflow in patients with primary PCI compared to the pharmacoinvasive strategy, in patients with one-vessel disease and in those with TIMI 0 before PCI. In-hospital mortality and heart failure were higher in patients with no-reflow (21.3% vs. 2.9% and 45.3% vs. 16.5, respectively; p<0.001). After multivariate analysis, the ischemic time > 12 hours, Killip Kimball (KK) > I, TIMI 0 before PCI, and one-vessel disease were the factors significantly associated with no-reflow after PCI. **Conclusions.** The ischemic time greater than 12 hours, the highest KK score, the presence of an occluded culprit artery (TIMI 0) before PCI and an one-vessel disease, were factors independently associated with no-reflow in patients with STEMI in Peru.

Keywords: No-Reflow Phenomenon; ST Elevated Myocardial Infarction; Percutaneous Coronary Intervention; Peru (source: MeSH NLM).

introduction

ST-segment elevation myocardial infarction (STEMI) is one of the leading causes of death in Peru and in the world. In our country, it is associated with heart failure incidence in 25 to 28.5%, with in-hospital mortality (8.5 to 10.1%) and with one-year mortality of 15% [1-3].

Percutaneous coronary intervention (PCI) of the culprit artery (CA), either primary PCI or as a pharmacoinvasive strategy (rescue or early systematic) is the final reperfusion treatment recommended in all patients [4,5]. However, after adequate recanalization of the CA by PCI, effective reperfusion of the ischemic myocardium is sometimes not achieved. This phenomenon is known as "no-reflow" or microvascular obstruction due to its implications at the microvasculature level [6,7].

The no-reflow phenomenon can be assessed in different ways: a) by angiography using techniques such as Thrombolysis in Myocardial Infarction (TIMI) score (flow < 3 without significant residual obstruction, dissection, spasm or *in situ* thrombosis), myocardial blush grade (MBG) or TIMI frame count (TFC) and invasive measurements such as the index of microvascular resistance (IMR) and coronary flow reserve (CFR); b) by noninvasive imaging techniques, such as myocardial contrast echocardiography, gadolinium enhanced magnetic resonance imaging (MRI), or nuclear imaging; or c) by the use of electrocardiography after PCI, measuring ST-segment resolution [8,9].

The incidence of NRF in the context of STEMI occurs (depending on the population and the diagnostic method used) in 5 to 50% of PCI cases; its pathophysiology involves ischemia-related damage, reperfusion-related damage, endothelial dysfunction, distal thromboembolism, and microvascular spasm [9,10]. The consequences of NRF are adverse ventricular remodeling, expansion of the infarct area, increased incidence of ventricular arrhythmias and heart failure, being an independent predictor of poor prognosis in acute myocardial infarction, with worse short- and long-term clinical outcomes such as increased heart failure, cardiogenic shock, and death [8-10].

Risk factors for NRF include clinical ones such as female sex, older age, hypertension, diabetes mellitus, smoking, dyslipidemia, renal failure, chronic inflammatory processes, history of atrial fibrillation, ischemia time, Killip Kimball ≥ II; anatomical or procedure-related factors, such as vessel size, complete occlusion (TIMI 0 flow before PCI), high thrombus burden, culprit lesion length, PCI in venous bridges, PCI in the anterior descending artery, high-pressure insufflations, and the use of intracoronary atherectomy devices; in addition, associated inflammatory and genetic markers have been described [11-13].

In our country, there is no previous information on the characteristics of the population with NRF and the clinical variables associated with this event. Therefore, the objective of our study was to determine -in an exploratory manner - which variables are associated with the possibility of NRF after PCI in patients treated for STEMI in different hospitals in Peru.

Methods

Design and study population

The PERSTEMI I and II registries were two prospective and multicenter cohorts of patients with STEMI who were treated at different hospitals across the country between February 2016 and February 2017, and 2020 respectively. The full design and analysis of the results of these registries have been previously published [1,3].

The present study is a sub analysis of the aforementioned studies with a case-control design that analyzes the presence of NRF retrospectively. We considered as cases (group 1) those patients from the PERSTEMI I and II study who presented the phenomenon of NRF after PCI, defined in this study by TIMI < 3 flow after PCI, and controls (group 2) those with TIMI 3 flow after PCI.

Patients over 18 years of age, of both sexes, with a diagnosis of STEMI who underwent percutaneous coronary intervention (whether primary, rescue or as part of a pharmacoinvasive strategy) within the first 24 hours of symptoms onset were included.

Patients who did not receive reperfusion or only received fibrinolytics, patients with PCI after 24 hours of symptom onset or with left main coronary artery (LMCA) obstruction, and those who did not have complete information for the analysis were excluded.

Variables

Clinical and epidemiological variables were included such as age, sex, clinical history (hypertension, diabetes mellitus 2, smoking, chronic kidney disease (GFR < 60 mL/min/1.73 m^2), time of infarct evolution (in hours), infarct location and culprit artery, admission hemodynamic state as assessed by Killip and Kimball (KK), reperfusion strategy used (primary or pharmacoinvasive PCI).

Following are the definition of some of the variables used: a) Culprit artery (CA): artery where the rupture or erosion event of the atherosclerotic plaque occurs, leading to the thrombus formation that can completely or partially occlude the blood flow and cause ischemia in the underlying myocardium; b) KK I: Patient with no clinical signs of left heart failure; c) KK II: Patient with rales, third heart sound and increased jugular venous pressure; d) KK III: Patient with acute pulmonary edema; e) KK IV: Patient with cardiogenic shock (hypotension and hypoperfusion due to cardiac cause); f) Primary PCI: Emergent PCI (within 12 hours of STEMI onset) with balloon, stent or other device, performed in the CA without prior fibrinolytic therapy; y g) Pharmacoinvasive strategy: Fibrinolysis combined with rescue PCI (in case of failed fibrinolysis) or systematic strategy of early PCI (in case of effective fibrinolysis).

TIMI flow constituted the dependent variable where the patient was assigned dichotomously based on having TIMI <3 flow (NRF definition for our study) vs. having TIMI 3 flow. The classification described for this variable is: a) TIMI 0: no antegrade flow beyond the coronary occlusion; b) TIMI 1: although the entire coronary vessel is not filled, flow beyond occlusion is achieved; c) TIMI 2: although antegrade flow is slow, it manages to fill the entire vessel; and d) TIMI 3: the entire vessel is filled with an antegrade flow comparable to the non-infarct arteries.

Statistical analysis

Data were obtained from the records of patients included in the PERSTEMI I and II registries. All analyses were performed using Stata 17 (Stata Corporation, College Station, Texas, USA).

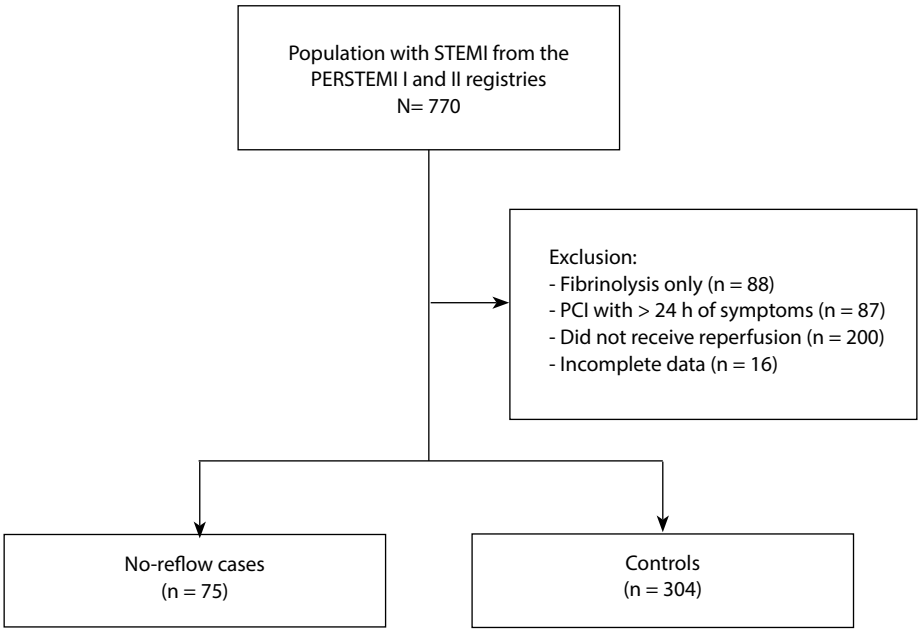
Categorical variables were expressed as absolute and relative frequencies and numerical variables as means or medians and their respective dispersion measures according to the normality of the variable. The chi-square test was used for the comparative analysis of the categorical variables between both groups, as well as Student's t-test and Wilcoxon rank sum for the numerical variables. Bivariate and multivariate analysis was performed by logistic regression to identify variables related to the presence of NRF and to rule out the presence of potential confounding factors; matching was not used due to the exploratory design of the study. The criteria applied for the selection of variables for the multivariate model were statistical and epidemiological. A value of $p < 0.05$ was considered statistically significant.

Ethical considerations

This study was conducted on the basis of secondary data from the PERSTEMI I and II studies, which had ethical approval for their development [1,3].

Results

Of 770 patients with STEMI included in the PERSTEMI I and II registries, after application of the inclusion and exclusion criteria **(Figure 1),** we found 75 patients with NRF (case group)



STEMI: ST-segment elevation myocardial infarction. PERSTEMI: Peruvian registry of ST-segment elevation myocardial infarction I and II, PCI: percutaneous coronary intervention.

Figure 1. Flow chart of the study population.

and 304 without NRF (control group) after PCI. Therefore, in our study the incidence of NRF after PCI was 19.8%.

The clinical and angiographic characteristics and medical history of the patients in both groups are detailed in **Tables 1** and 2. A higher frequency of hypertension, chronic kidney disease, KK II-IV on admission, and cardiac arrest was observed in patients who presented NRF. Likewise, there was a higher frequency of NRF in patients who underwent primary PCI compared to pharmacoinvasive PCI, in one-vessel disease, and in patients with TIMI 0 initial flow in the CA.

In-hospital mortality and the occurrence of post-infarction heart failure were higher in patients with NRF (21.3% vs. 2.9% and 45.3% vs. 16.5%, respectively, p value < 0.001 in both cases).

After logistic regression analysis to determine the factors associated with the presence of NRF, we found that ischemic time > 12 hours, altered hemodynamic status on admission (KK > I), the presence of TIMI 0 flow from the CA at the first coronary injection, and the finding of one-vessel disease were the clinical variables independently associated with the presence of NRF after PCI **(Table 3).**

Discussion

NRF or microvascular obstruction, is an entity that refers to the impossibility of reperfusing the coronary microcirculation in a previously ischemic region, despite the opening of the epicardial vessel, which leads to adverse in-hospital and long-term effect [7-10,14-16]. In the present study, we found that total ischemia time greater than 12 hours, KK > 1, one-vessel lesion, and initial TIMI 0 flow before PCI were the independent markers of NRF. Among these, having KK IV, cardiogenic shock, was the variable most associated with the possibility of NRF.

NRF can be determined in different ways [8-9,17-19], therefore, its incidence varies according to the diagnostic method used and the clinical context. In our study, the assessment of NRF was by TIMI flow score, because it was based on a retrospective analysis, which despite being considered a semiquantitative, subjective and less sensitive assessment, has been reported to be useful in pointing out the importance of this phenomenon as an independent predictor of adverse events in previous studies such as the study by Morishima *et al.* [19].

Table 1. Epidemiological background of participants included after percutaneous coronary intervention in ST-segment elevation myocardial infarction.

Variable	No-reflow, n (%) (n = 75)	Control, n (%) (n = 304)	P-value
Age (in years), mean ± SD	65.8 ± 12.8	64.2 ± 11.8	0.288*
Male	61 (81.3)	253 (83.2)	0.697
Ischemia to reperfusion time (min.), median (IQR)	420 (285-720)	330 (200-480)	< 0.001**
Hypertension	46 (61.3)	148 (48.7)	0.050
Diabetes mellitus 2	17 (22.6)	81 (26.6)	0.481
Dyslipidemia	39 (52.0)	123 (40.4)	0.070
Smoking	14 (18.7)	98 (32.2)	0.021
Chronic coronary syndrome	1 (1.3)	13 (4.3)	0.319
Previous coronary revascularization	2 (2.7)	15 (4.9)	0.542
Chronic kidney disease	9 (12.0)	10 (3.3)	0.002

SD: standard deviation; min: minutes; RIQ: interquartile range.

* p-value obtained from Student's t-test ** p-value obtained from Wilcoxon rank sum test. Rest of categorical variables evaluated by the chi-square test.

Table 2. Clinical and angiographic characteristics of patients with no-reflow after coronary intervention in acute ST-segment elevation myocardial infarction.

Variable	No-reflow, n (%) (n = 75)	Control, n (%) (n = 304)	P-value *
Cardiac arrest on admission	7 (9.3)	6 (1.9)	0.006
Killip Kimball Class			
KK I	39 (52.0)	222 (73.0)	< 0.001
KK II	24 (32.0)	74 (24.3)	
KK III	2 (2.7)	3 (0.9)	
KK IV	10 (13.3)	5 (1.6)	
Type of coronary intervention			
Primary	54 (72.0)	161 (52.9)	0.003
Pharmacoinvasive	21 (28.0)	143 (47.1)	
Culprit artery			
Anterior descending	42 (56.0)	183 (60.2)	0.575
Right coronary artery	31 (41.3)	107 (35.2)	
Circumflex	2 (2.7)	14 (4.6)	
Initial TIMI coronary flow			
TIMI 0	51 (68.0)	89 (29.3)	< 0.001
TIMI 1	12 (16.0)	53 (17.4)	
TIMI 2	10 (13.3)	65 (21.4)	
TIMI 3	2 (2.7)	97 (31.9)	
One-vessel lesion	43 (57.3)	133 (43.8)	0.035

KK: Killip y Kimball.
* p-value obtained from chi-square test.

Muller *et al.* described an incidence of NRF of 2% in elective PCI, 20% in PCI on saphenous vein grafts, and 26% in the context of acute myocardial infarction [20], Morishima *et al*. described an incidence of 25% in STEMI [19], similar to approximately 20% found in our study. In contrast, other studies have described higher numbers of NRF: Cura *et al*. analyzed NRF by ST fall (< 70% at 1 hour after primary angioplasty) finding an incidence of 37% [21], and Sorajja *et al.* found an incidence of 39.9% evaluating NRF by the sum of ST fall < 70% and a MBG 0/1 [22]. Therefore, as reported by Niccoli *et al*. [17], depending on how the NRF is measured, the clinical context, the population and the sum of clinical predictors, its frequency will vary.

Moreover, similar to our study, in the sub analysis of the TOTAL study, it was found that thrombotic burden (TIMI thrombus score 3-5) and KK clinical presentation (II-IV), were the variables most associated with the likelihood of NRF [23]. On the other hand, Jin Wen Wang *et al*. [24] in a prospective analysis of STEMI patients found that the presence of a high neutrophil count (≥ 8.81, 10 9/L) had the highest correlation to independently predict NRF (*odds ratio* [OR] 6.36), followed by thrombotic burden (TIMI thrombus score ≥ 2) pre-ICP (OR 3.23).

In our study, having a one-vessel disease increased the risk of developing NRF, possibly explained by the lower ischemic preconditioning in these patients, in relation to those patients with multiple vessel lesions or with preexisting collateral circulation, which had been previously described by Jin Wen Wang *et al*., where a low degree of collateral circulation increased the probability of NRF by 1.5 times [24].

Among clinical factors, time is a key and common variable, and often the explanation for the outcomes in STEMI and NRF studies [24-28]. Thus, we observed that NRF rates were significantly

Table 3. Clinical variables associated with no-reflow after coronary intervention in ST-segment elevation acute myocardial infarction.

Variable	Bivariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Ischemia time > 12 hours	4.50 (1.96-10.40)	< 0.001	5.30 (1.86-15.38)	0.002
Chronic kidney disease	4.00 (1.56-10.20)	0.004	2.34 (0.78-6.94)	0.125
Cardiac arrest	5.10 (1.70-15.70)	0.004	2.63 (0.53-13.10)	0.236
Killip Kimball Class				
KK I	Reference		Reference	
KK II	1.80 (1.04-3.27)	0.036	2.04 (1.04-3.98)	0.036
KK III	3.70 (0.61-23.40)	0.151	3.90 (0.48-32.5)	0.199
KK IV	11.30 (3.70-35.10)	< 0.001	10.70 (2.39-48.70)	0.002
Primary PCI	2.28 (1.30-3.90)	0.003	1.08 (0.52-2.23)	0.821
One-vessel lesion	1.72 (1.03-2.87)	0.036	2.16 (1.15-4.04)	0.016
Initial TIMI 0 flow	5.10 (2.90-8.80)	< 0.001	6.90 (3.43-13.8)	< 0.001
Hypertension	1.60 (0.90 -2.80)	0.051	1.18 (0.57-2.46)	0.645
Diabetes mellitus	0.80 (0.40-1.40)	0.482	Not included	
Dyslipidemia	1.60 (0.90-2.60)	0.072	1.04 (0.50-2.13)	0.911
Smoking	0.48 (0.25-0.90)	0.023	0.78 (0.38-1.59)	0.500

Multivariate analysis performed with variable with statistical significance (< 0.05) in addition to clinical-epidemiological significance.

OR: odds ratio; KK: Killip y Kimball; PCI: percutaneous coronary intervention; CI: confidence interval.

higher in patients who received primary angioplasty versus those who received a pharmacoinvasive strategy, possibly explained by the difference in ischemic time between the two strategies (6.8 vs. 4 hours, respectively) [1,3]. Likewise, those who exceeded an ischemiac time greater than 12 hours were five times more at risk of developing NRF in an independent and significant manner. In the same line, the subanalysis of HORIZONS-AMI study already indicated that an ischemic time > 4 hours duplicated the possibility of having NRF, independent of the clinical risk of the patient with STEMI, and this relationship was also significant with the patient's delay, when this exceeded 2 hours (compared to ≤ 1 hour) [27]. Therefore, whatever the cause of the delay, health systems should try to shorten it. Likewise, more recent studies such as STREAM and our own registries emphasize that ischemia time matters, and regardless of the strategy used, it should be adapted to the clinical reality of the population in order to have a comparable impact on clinical outcomes [28-30]. As Eugene Braunwald had already mentioned 50 years ago, in STEMI there is no better message than say: "time is muscle" and this should be the starting point for our actions and their conclusions [31].

In general, NRF is considered a complex pathophysiological process involving multiple risk factors, which could make it difficult to predict. Identifying in our setting the associated variables in order to subsequently create a predictive clinical score, would help us to prevent the possibility of NRF and reduce its incidence. Predictive scores have been published, as in the study by Bayramoglu *et al.* which showed an area under the curve (AUC) of 0.8 with the use of seven independent variables [25]. More recent studies using artificial intelligence techniques achieved an AUC of 0.78 to anticipate its occurrence [26].

On the other hand, in our study, patients with NRF had a significantly higher frequency of in-hospital death and heart failure. Although this analysis was in the short-term, its long-term implication has been previously reported by Ndrepepa *et al*. where they found that NRF was an important predictor of regional and global recovery, adverse remodeling, and mortality with a follow-up of up to 5 years [15,32].

In its treatment, several proposals have been made to reduce NRF, none of them with consistent success, possibly due to the complexity of its multicausal pathophysiology that makes it difficult to think of a single effective agent for all patients. Annibali *et al*. proposed an interesting algorithm according to the patient's clinical condition [33].

In the future, research aims to evaluate endogenous

protection mechanisms against ischemia, such as pre- and post-conditioning, or therapies that act on the contraction of pericytes (contractile cells located at the capillary level) in order to prevent the progression of microvasculature damage [14,17,34]. Other proposals have focused on technical aspects related to the interventional procedure, such as the use of micromesh stents to trap thrombi, slow reperfusion, prolonged insufflation and early detection in the procedure room with the measurement of the index of microcirculatory resistance (IMR) to intensify and optimize patient treatment [35,36]. Once again emphasizing that all this is still experimental and that it is always worthwhile to act from prevention, as Niccoli *et al*. said: "Again prevention is better than treatment" [17].

The present study, derived from the national multicenter PERSTEMI I and II registries, is the first to identify the clinical and angiographic variables associated to NRF, thus taking a step forward to its prevention. Nevertheless, our analysis has some limitations that should be discussed. First, this study is a sub analysis of the PERSTEMI I-II registries; the results derived from our analysis are hypothesis-generating and should be confirmed in prospective research. Second, the study population was small, and the confidence intervals of the multivariate analysis are wide, so these data should be interpreted with caution. Third, we used the angiographic scores TIMI-flow for the definition of NRF, whereas other more objective and accurate parameters exist, the latter may underestimate the actual number of cases, predictors, and clinical outcomes in our national population due to the lack of other information derived from the main study.

In conclusion, from the secondary analysis of the PERSTEMI I and II registries, it was observed that ischemic time greater than 12 hours, highest KK score, the presence of TIMI 0 flow in the culprit artery before PCI and one-vessel disease, are factors independently related to the presence of NRF after PCI.

Acknowledgments

To PERSTEMI I and PERSTEMI II researchers.

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