ORIGINAL ARTICLE

Suboptimal Reperfusion in Patients with ST-Segment Elevation Acute Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention: Predictors and Prognostic Value

Reperfusión subóptima en pacientes con infarto agudo de miocardio con elevación del segmento ST tratados con angioplastia primaria: Predictores y valor pronóstico

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ABSTRACT

Background: Although there is evidence that suboptimal reperfusion has short-term prognostic impact in patients with ST-segment elevation acute coronary syndromes, there is little information about its associated factors.
Objectives: The aim of this study was to analyze the factors associated with suboptimal reperfusion in patients with acute ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI).
Methods: Patients from the SCAR (Acute Coronary Syndromes in Argentina) registry diagnosed with acute STEMI undergoing PCI were included in the study. The association of classical clinical and laboratory variables and the leuko-glycemic index with suboptimal reperfusion was analyzed. Suboptimal reperfusion was defined as TIMI III post-PCI angiography with less than 50% ST-segment decrease in the ECG.
Results: Overall, 197 patients (76.4%) out of 258 patients with STEMI met the inclusion criteria. Among them, 8.6% (n: 17) had suboptimal reperfusion, with an incidence of in-hospital death of 17.6% (n: 3) versus 1.7% (n: 3) in patients without suboptimal reperfusion (p=0.007). In the univariate analysis, variables associated with suboptimal reperfusion were diabetes [OR: 3.2 (1.09-9.43) p=0.026], previous revascularization [OR: 5.8 (1.74-19.07) p=0.008], leuko-glycemic index (>2159) [OR 3.7 (1.32-10.22) p=0.009], and pain-to-balloon time (>159 minutes) [OR: 6.9 (0.88- 53) p=0.045]. Age >70 years, male sex, high blood pressure, smoking, previous or anterior-wall infarction, and Killip and Kimball 3-4 and TIMI 0-1 flow on admission were not significantly different between patients with or without suboptimal reperfusion. Prior to the analysis, the cutoff point for the leuko-glycemic index associated with suboptimal reperfusion was established at 2159 points by ROC curve analysis (NPV: 94%), and the pain-to-balloon time at 159 min (NPV: 96%). In logistic regression analysis, only previous revascularization [OR: 5.3 (1.53-18.55)] and leuko-glycemic index [OR: 3.2 (1.11-9.28)] were associated with suboptimal reperfusion.
Conclusions: Suboptimal reperfusion was significantly associated with a higher incidence of in-hospital death, while previous revascularization and LGI (>2159) were independent factors associated with suboptimal reperfusion.

Key Words: Reperfusion Injury - ST Elevation Myocardial Infarction

RESUMEN

Introducción: Existe evidencia de que la reperfusión subóptima tiene impacto pronóstico a corto plazo en los pacientes con síndromes coronarios agudos con elevación del segmento ST, pero hay poca información sobre los factores vinculados a esta.
Objetivos: Analizar los factores asociados a la reperfusión subóptima en pacientes con infarto agudo de miocardio con elevación del segmento ST, tratados con angioplastia primaria.
Material y métodos: Se analizaron los pacientes con diagnóstico de infarto agudo de miocardio con elevación del segmento ST que recibieron tratamiento de revascularización con angioplastia primaria en el registro SCAR (Síndromes Coronarios Agudos en Argentina). Se analizó la asociación entre las variables clínicas clásicas, de laboratorio y el índice leucoglucémico con la reperfusión subóptima. Se definió reperfusión subóptima como TIMI III angiográfico pos-ATC con descenso del segmento ST en el ECG menor del 50%.
Resultados: Se analizaron 258 pacientes con infarto agudo de miocardio con elevación del segmento ST, de los cuales 197 (76,4%) cumplieron los criterios de inclusión. De estos, el 8,6% (n = 17) tuvieron reperfusión subóptima. La incidencia de muerte intrahospitalaria entre los pacientes con reperfusión subóptima fue del 17,6% (n = 3) versus 1,7% (n = 3) en aquellos sin reperfusión subóptima (p = 0,007). En el análisis univariado, las variables asociadas a reperfusión subóptima fueron: diabetes (OR: 3,2 [IC95% 1,09-9,43] p = 0,026), revascularización previa (OR: 5,8 [1,74-19,07] p = 0,008), índice leucoglucémico (> 2159) (OR 3,7 [1,32-10,22] p = 0,009), y el tiempo dolor/balón (>159 min) (OR: 6,9 [0,88-53] p = 0,045). El Killip-Kimball al ingreso fue de 3-4; la edad, mayor de 70 años; el sexo masculino, la hipertensión arterial, el tabaquismo, el infarto previo o anterior y el flujo TIMI 0-1 al ingreso no

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fueron significativos. Antes del análisis se estableció por curva ROC el punto para el índice leucoglucémico asociado a RSO en 2159 puntos (VPN = 94%), y el de tiempo dolor/balón en 159 min (VPN = 96%). En la regresión logística, solo la revascularización previa (OR: 5,3 [1,53-18,55]) y el índice leucoglucémico (OR: 3,2 [1,11-9,28]) estuvieron asociadas a reperfusión subóptima.
Conclusiones: La reperfusión subóptima se asoció significativamente con mayor incidencia de muerte intrahospitalaria; mientras que la revascularización previa y el índice leucoglucémico (>2159) se asociaron con reperfusión subóptima.

Palabras clave: Reperfusión - Infarto del miocardio con elevación del ST

Abbreviations

CI	Confidence interval	**OR**	Odds ratio
EF	Ejection fraction	**PCI**	Percutaneous coronary intervention
LGI	Leuko-glycemic index	**SOR**	Suboptimal reperfusion
MVO	Microvascular obstruction	**STE-ACS**	ST-segment elevation acute coronary syndrome
NPV	Negative predictive value	**STEMI**	ST-segment elevation myocardial infarction
OPR	Optimal reperfusion		

INTRODUCTION

Among patients with acute ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI), partial reduction of ST-segment is associated with short and long-term adverse events, a situation observed even in those cases in which mechanical reperfusion was successful and coronary flow was restored with TIMI III flow. (1) On the other hand, ST-segment reduction among patients with STEMI has been widely studied in the fibrinolytic era and has been established as an indicator of reperfusion treatment quality and a sensitive indicator of tissue perfusion restoration in cardiologic practice. (2-7) The angiographic concept of no-reflow was promptly recognized with the use of primary PCI as the treatment of choice for acute myocardial infarction (AMI), and is defined as the presence of slow flow (TIMI ≤2) in a patent vessel. However, despite improvements in coadjuvant medical treatment, its incidence is still around 20%. (8)

On the other hand, the concept of suboptimal reperfusion (SOR) refers to a clinical and electrocardiographic situation that is defined by the partial reduction of ST-segment (less than 50%) after either mechanical or pharmacological reperfusion treatment. The causes of SOR are persistent stenosis or thrombosis, dissection or coronary spasm, distal macroembolism, acute stent thrombosis, no-reflow phenomenon, reperfusion injury, endothelial cell edema, and myocyte inflammation. (9-19)

These concepts have suggested that the incidence of SOR among patients treated with primary PCI is not negligible, and that it is probably associated with a higher incidence of severe events such as shock, and either in-hospital or short term death. The aim of this study was thus to analyze the variables associated with SOR in a cohort of patients undergoing PCI for STEMI, with TIMI III epicardial flow post-primary PCI and less than 50% ST-segment reduction. In addition, the probable association between SOR and in-hospital death was analyzed. (20-21)

METHODS

The information collected in the SCAR (Acute Coronary Syndromes in Argentina) Multicenter Registry developed by the Research Area and the Cardiovascular Emergency Council of the Argentine Society of Cardiology was analyzed. This was a cross-sectional, multicenter study that consecutively included patients over 18 years of age with acute coronary syndrome in 87 centers throughout the country, during a three-month inclusion period in each center. The study was performed between June and September 2011. Patients with active hematologic or infectious diseases were excluded.

Among the total sample of 1,330 patients with acute coronary syndrome, 476 patients with diagnosis of STEMI were selected, 197 of which met the full inclusion criteria of primary PCI and TIMI III post-PCI. (Tables 1 and 2)

The inclusion criteria for this subanalysis were patients with STEMI who presented TIMI III epicardial flow post-primary PCI.

Clinical and laboratory variables were analyzed, and the leukoglycemic index (LGI) was calculated as the product of glycemia (mg/dl) on admission, by the white blood cell count (mm3) divided by 1000.

Electrocardiographic ST-segment reduction was analyzed by ST-segment summation between the ECG on hospital admission and the first ECG obtained after PCI, on admission to the coronary care unit.

Suboptimal reperfusion was defined as ST-segment reduction <50% of the summation of the compromised leads on admission to the coronary care unit in patients with TIMI III epicardial flow post-primary PCI. Conversely, optimal reperfusion (OPR) was defined when the summation of ST-segment reduction was ≥50%.

The final endpoint analyzed was the incidence of SOR and its relationship with the variables associated with in-hospital death.

Statistical analysis

The normal distribution of the continuous variables was evaluated with the Kolmogorov-Smirnov goodness of fit test. The continuous variables were compared and evaluated with Student's t test or the Mann-Whitney U test according to the type of distribution, and were expressed as mean and standard deviation, or as median and interquartile range.

Table 1. Baseline characteristics of optimal revascularization vs. suboptimal revascularization patients

	OPR	SOR	OR	p
n = 197	180 (91.37%)	17 (8.62%)		
Age	59.8 ± 11.5	60.6 ± 13.8		0.794
Age >70 years	36 (20.45%)	5 (29.41%)	1.62 (0.53-4.89)	0.36
Male sex	137 (76.1%)	12 (70.6%)	1.33 (0.44-3.98)	0.567
Diabetes	26 (14.4%)	6 (35.3%)	3.21 (1.09-9.43)	0.026
Smoking	76 (42.2%)	4 (23.5%)	2.37 (0.75-7.57)	0.196
Hypertension	105 (58.3%)	12 (70.6%)	1.69 (0.57-5.00)	0.441
Prior AMI	14 (7.8%)	4 (23.5%)	3.60 (0.08-0.95)	0.056
KK 3/4 on admission	10 (5.75%)	2 (11.8%)	2.26 (0.45-11.3)	0.28
Prior revascularization	12 (6.7%)	5 (29.4%)	5.76 (1.74-19.07)	0.008

OPR: Optimal revascularization. SOR: Suboptimal revascularization. AMI: Acute Myocardial infarction. KK: Killip and Kimball.

Table 2. Baseline characteristics of optimal revascularization vs. suboptimal revascularization patients

	OPR	SOR	OR	p
n = 197	180 (91.37%)	180 (91.37%)	180 (91.37%)	
Door-to-balloon time >159	126 (70.0 %)	126 (70.0 %)	126 (70.0 %)	0.045
EF (<40%)	43 (26.38%)	43 (26.38%)	43 (26.38%)	0.15
Maximum CK >695 U	30 (21.6%)	30 (21.6%)	30 (21.6%)	0.129
Previous AMI	94 (52.81%)	94 (52.81%)	94 (52.81%)	0.075
LGI >2159	35 (19.44%)	35 (19.44%)	35 (19.44%)	0.009
TIMI on admission 0/1	141 (86.50%)	141 (86.50%)	141 (86.50%)	0.78

EF: Ejection fraction. CK: Creatine kinase. AMI: Acute myocardial infarction. LGI: Leuko-glycemic index.

Discrete variables were expressed as percentages and were compared using the chi square test. The ratio of cross products was expressed as odds ratio (OR) with its corresponding 95% confidence interval (95% CI). Areas under the ROC curves were estimated for the analysis of the variables' discriminatory power of events with respect to the primary endpoint. The LGI was expressed as a dichotomous variable, and the best cutoff point was established by analyzing the ROC curve and the Youden index; the same methodology was used for the pain-to-balloon time and maximum CK values. A stepwise logistic regression analysis was performed including the variables that in the univariate analysis obtained a p value ≤0.10 and other widely recognized historical confounders. A two-tail alpha error of 5% was considered statistically significant. Medcalc 11.6.1 (Mariakerke, Belgium) and SPSS 19.0 for Windows (Chicago, ILL, USA) software packages were used for the statistical analysis.

Ethical considerations

The study protocol was approved by the Bioethics Committee of the Argentine Society of Cardiology, waiving the request for informed consent as no sensitive or clinical follow-up data was required (Law 25,326 of Habeas data on Protection of Personal Data).

RESULTS

Among the 258 patients in the SCAR registry treated with primary PCI, 197 (76.4%) met the inclusion criteria and had complete data for the analysis. Overall mean age was 60±10 years, 25% of patients were older than 70 years and 33% were women; 66% of the patients were hypertensive and 27% were diabetic. Half of the population had history of dyslipidemia and 38% were active smokers; 17% had history of prior AMI and 15% had received some revascularization treatment.

Thirteen percent of the patients treated with primary PCI had TIMI III epicardial flow ≤2 post-primary PCI, and 8.6% (n=17) of the 197 patients treated with primary PCI who achieved TIMI III post-primary PCI had SOR.

The incidence of in-hospital death among patients with SOR was 17.6% (3/17), while in patients without SOR it was 1.7% (3/180) (p = 0.007).

The comparison among the variables associated with optimal/suboptimal reperfusion is shown in Table 3. The best cutoff point for SOR was defined as 2159 points for LGI (negative predictive value [NPV]: 94%) and 159 min for pain-to-balloon time (NPV=96%).

Furthermore, LGI behavior analyzed with a cutoff point of 2159 points showed that 47.1% of patients with SOR had values above this threshold vs. 19.4% of patients with OPR. (p=0.009).

The median pain-to-balloon time in the overall population of patients treated with primary PCI in the SCAR registry was 120 minutes. When analyzing the pain-to-balloon time as a binary variable with a cutoff point of 159 min, 94.1% of the patients with SOR exceeded this value, versus 70% of the patients with OPR (p = 0.045).

Table 3. Univariate analysis of the factors associated with suboptimal revascularization in patients with ST-segment elevation myocardial infarction treated with TIMI III primary percutaneous coronary intervention

	OPR	SOR	OR	p
n = 197	180	17		
Age	59.8 ± 11.5	60.6 ± 13.8		0,794
Age >70 years	36 (20.45%)	5 (29.41%)	1.62 (0.53-4.89)	0.36
Male sex	137 (76.1%)	12 (70.6%)	1.33 (0.44-3.98)	0.567
Diabetes	26 (14.4%)	6 (35.3%)	3.21 (1.09-9.43)	0.026
Smoking	76 (42.2%)	4 (23.5%)	2.37 (0.75-7.57)	0.196
Hypertension	105 (58.3%)	12 (70.6%)	1.69 (0.57-5.00)	0.441
Prior AMI	14 (7.8%)	4 (23.5%)	3.60 (0.08-0.95)	0.056
Door-to-balloon time>159	126 (70.0 %)	16 (94.1%)	6.85 (0.88-53)	0.045
KK 3/4 on admission	10 (5.75%)	2 (11.8%)	2.26 (0.45-11.3)	0.28
EF (<40%)	43 (26.38%)	7 (43.75%)	2.17 (0.76-6.18)	0,15
Maximum CK >695 U	30 (21.6%)	5 (45.5%)	3.03 (0.86-10.6)	0.129
Anterior AMI	94 (52.81%)	13 (76.45%)	2.90 (0.91-9.25)	0.075
LGI >2159	35 (19.44%)	8 (47.06%)	3.68 (1.32-10.22)	0.009
TIMI on admission 0/1	141 (86.50%)	14 (87.50%)	1.09 (0.23-5.13)	0.78
Prior Revascularization	12 (6.7%)	5 (29.4%)	5.76 (1.74-19.07)	0.008

OPR: Optimal revascularization. SOR: Suboptimal revascularization. AMI: Acute Myocardial infarction. KK: Killip and Kimball. EF: Ejection fraction. CK: Creatine kinase. LGI: Leuko-glycemic index.

Post-infarction ventricular function assessed through ejection fraction (EF) was slightly lower in the SOR group (EF<40% in 43.8% vs. 26.8% of patients, p=0.150).

A cutoff point for maximum CK associated with SOR was established at 695 units. In 45.5% of cases, patients with SOR exceeded this value versus 21.6% of patients with OPR (p=0.121).

In 76.5% (n=13) of cases, patients with SOR had anterior myocardial infarctions versus 52.8% (n=95) in patients with OPR (p=0.075).

Finally, variables that in the univariate analysis had p<0.10 entered a logistic regression model, where only previous revascularization (OR: 5.32, 95% CI: 1.53-18.55) and LGI >2159 (OR: 3.22, 95% CI: 1.11-9.28) were significantly associated with SOR as independent variables. (Table 4)

Table 4. . Multivariate analysis

Variable	OR	95% CI	p
LGI >2159	3.22	1.11-9.28	0.030
Previous revascularization	5.32	1.53-18.55	0.009

LGI: Leuko-glycemic index.

DISCUSSION

The main finding of our study is that patients treated with primary PCI presented SOR in 8.6% of cases, and that LGI >2159 and history of previous revascularization were independent predictors of this outcome, with 1.7% vs. 17.6% mortality for OPR versus SOR (p=0.007)

The cutoff point for ST-segment reduction was established in the protocol according to other authors' publications (14-16) in this subgroup of patients with ST-segment reduction <50%, and higher risk for mortality as has been extensively published. (10-13)

Several studies have suggested that a simple ECG analysis can be very useful for identifying patients with SOR within the group of patients with ST-segment elevation-acute coronary syndrome (STE-ACS) treated with PCI. (12-16) However, different criteria and indices have been proposed and applied to define ST-segment reduction (19). The cutoff values (between 50% and 70% ST-segment reduction post-PCI) to achieve an accurate diagnosis of SOR still remain controversial.

A direct correlate of post-PCI suboptimal reperfusion was incomplete resolution of ST-segment elevation as observed by other authors in 42% of cases of a series of 1,005 consecutive patients with STEMI treated with primary PCI, and the independent predictors of incomplete resolution observed by these authors were prior AMI, Killip and Kimball 3-4, diabetes and TIMI flow grade <2 before PCI and <3 post-PCI. (6, 9, 10)

Glycemia was analyzed on admission as well as white blood cell count which is perhaps one of the most novel findings. Other authors have analyzed hyperglycemia as a marker of reperfusion injury (one of the causes of SOR), as well as larger AMI and worse outcome without correlating them with white blood cell count, as was done in our study. These findings are similar to those previously published in STE-ACS and non-ST-segment elevation ACS patients, with similar interpretation in SOR findings, larger lesion and necrosis, greater ventricular dysfunction, and greater expression of adrenergic and inflammation response markers (hyperglycemia-leukocytosis), which are likely to be indicators of high risk rather than risk factors per se as other authors point out. (22, 23)

It has been shown that fluctuations in blood glucose levels during STE-ACS are related to suboptimal reperfusion, turning their control into a therapeutic goal. (22)

History of previous revascularization was the other independent predictor of SOR which has its clinical correlation, as these are patients with more severe multi-vessel coronary artery disease with worse outcome, as observed in our analysis, with higher in-hospital mortality (18% vs. 1.8%).

Other non-significant predictors of the univariate analysis in the SOR group were higher incidence of Killip and Kimball 3-4, and greater delay to PCI (door-to-balloon time) since, as extensively published (24, 25), it is reasonable to assume the time dependence of therapeutic interventions during the acute phase of AMI.

The hypothesis of the pathophysiological concept that would explain the lack of resolution of ST-segment elevation in the presence of TIMI III epicardial flow post-primary PCI as an expression of SOR, could be due to a NON-effective functional reperfusion with incomplete reduction of ischemia, perhaps linked to microvasculature damage, endothelial dysfunction and microvascular obstruction (MVO). (18, 19, 26)

Limitations

This subanalysis, performed using data from the multicenter SCAR registry (Acute Coronary Syndromes in Argentina) and developed by the Research Area and the Cardiovascular Emergency Council of the Argentine Society of Cardiology in an unselected population of ACS, was not designed for the endpoints presented here, which implies a limitation in the number of events analyzed; therefore, the interpretation only generates hypothesis.

The ST-segment summation in the ECG before PCI analyzed in this study corresponds to the one performed on hospital admission and not immediately before PCI.

CONCLUSIONS

Prior revascularization and LGI (>2159) were associated with SOR.

Suboptimal reperfusion was associated with an increased risk of in-hospital morbidity and mortality.

Early identification and appropriate management of patients with SOR have prognostic implications.

Conflicts of interest

None declared. (See authors' conflicts of interest forms on the website/Supplementary material).

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