Predictors of Myocardial Tissue Reperfusion after Angioplasty in Acute Myocardial Infarction

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SUMMARY

Background
The efficacy of primary angioplasty is limited due to the fact that a considerable number of patients do not achieve adequate levels of myocardial tissue perfusion. The degree of reperfusion depends on multiple clinical, angiographic and therapeutic factors.

Objectives
To identify the independent factors associated with the absence of myocardial tissue reperfusion after primary angioplasty.

Material and Methods
A total of 140 patients included in the Protection of Distal Embolization in High-Risk Patients with Acute ST-Segment Elevation Myocardial Infarction Trial (PREMIAR) were analyzed. This study evaluated the use of filter distal protection device during angioplasty in patients with acute ST-segment elevation myocardial infarction at high risk of thrombosis (only including baseline TIMI grade 0-2 flow). The primary end point of the study was the rate of complete ST-segment resolution at 60 minutes, defined as ≥ 70% recovery compared with baseline during continuous ST-segment monitoring. A model of logistic regression was developed to identify independent predictors.

Results
Complete resolution of ST-segment deviation 60 minutes after angioplasty was observed in 82 patients (63%), while 53 patients (37%) presented partial ST-segment resolution which was associated with rates of mortality, reinfarction and/or heart failure at 30 days of 8.5% and 18.9%, respectively (p=0.07). The variables associated with absence of adequate myocardial tissue reperfusion were anterior infarction (79% versus 33%; p=0.001), higher heart rate (81±20 versus 70±15; p=0.001) and history of current smoking (25% versus 51%; p=0.002), compared to optimal tissue reperfusion. In addition, there was a trend towards greater prevalence of diabetes (26% versus 16%; p=0.13), longer time interval from the onset of symptoms to angioplasty (minutes) (217±167 versus 182±134; p=0.19) and Killip class >1 (30% versus 17%; p=0.07), respectively. Multivariate analysis demonstrated that anterior myocardial infarction was associated with absence of complete reperfusion (OR 8.22, 95% CI 3.67-18.4; p<0.001), while the use of glycoprotein IIb/IIIa inhibitors (OR 4.21, 95% CI 1.34-13.22; p=0.014) and current smoking (OR 3.84, 95% CI 1.58-9.50; p=0.003) correlated with complete reperfusion.

Conclusions
A considerable proportion of patients undergoing primary angioplasty do not achieve adequate myocardial tissue reperfusion. This phenomenon is associated with adverse outcomes. Anterior myocardial infarction correlates with less degree of tissue reperfusion. Conversely, current smoking and the use of glycoprotein IIb/IIIa inhibitors are associated with better tissue reperfusion after primary angioplasty.

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Key words > Myocardial Infarction - Angioplasty - Myocardial Reperfusion

Abbreviations >

ECG Electrocardiogram	**AMI** Acute myocardial infarction

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BACKGROUND

An adequate myocardial reperfusion at the tissue level after thrombolytic therapy or primary angioplasty in patients with ST-segment elevation acute myocardial infarction (AMI) minimizes myocardial damage as it preserves ventricular function, increasing survival with low incidence of complications. (1) Primary angioplasty is the most efficient therapeutic strategy in AMI as it allows recanalization of the culprit vessel in most cases. (2) Yet, inadequate tissue reperfusion is a frequent finding in a great proportion of patients despite recanalization of the infarct-related artery. (3-7) Assessment of ST-segment resolution on 12-lead electrocardiogram (ECG) after myocardial reperfusion is useful to evaluate restoration of myocardial tissue perfusion and for risk stratification purposes. (8-10)The degree of reperfusion after angioplasty depends on multiple clinical and therapeutic factors.

The aim of this study is to identify the independent factors associated with myocardial tissue reperfusion after primary angioplasty in ST-segment elevation acute myocardial infarction.

MATERIAL AND METHODS

A total of 140 patients included in the Protection of Distal Embolization in High-Risk Patients with Acute ST-Segment Elevation Myocardial Infarction Trial (PREMIAR) were analyzed. This study evaluated the use of a filter distal protection device during angioplasty in patients with acute ST-segment elevation myocardial infarction at high risk of thrombosis (only including patients with baseline TIMI grade 0-2 flow). The PREMIAR study was a prospective, randomized, controlled clinical trial performed at 20 institutions in three different countries. The details of the study design and its outcomes have been previously published. (11) Briefly, 140 patients who presented with AMI within 12 hours from symptoms onset referred to primary or rescue angioplasty were included in the study. Patients with cardiogenic shock or baseline TIMI grade 3 flow were excluded. After signing a written consent, subjects were further randomized to angioplasty with adjunctive distal protection device or angioplasty alone. For 24 hours, all patients underwent continuous ST-segment monitoring to assess the extension, speed, and stability of tissue reperfusion. All patients received 325 mg of aspirin and a loading oral dose of 300 to 600 mg of clopidogrel before the procedure. After catheter introduction, all subjects received intravenous boluses of 70-100 U/kg of heparin. Use of glycoprotein IIb/IIIa inhibitors was at the discretion of the investigator. Clopidogrel was recommended to be continued for 12 months. Angioplasty was performed following the usual standards and a SpideRXâ (ev3, Plymouth, Minnesota, USA) distal embolic protection system was used according to randomization. Mortality, reinfarction and heart failure rate were assessed 30 days after the procedure in all patients. The use of a filter protection device during angioplasty was not associated with an improvement of ST-segment elevation resolution or clinical outcomes. (11)

ST-segment Monitoring

Continuously ST-segment analysis was performed for all patients at the Electrocardiogram Core Laboratory (Duke University, Durham, North Caroline, USA) irrespective of the treatment assigned and of clinical outcomes. ST-segment analysis was initiated before the angioplasty and continued for 24 hours. Patients with conditions precluding evaluation of ST-segment changes on the admission electrocardiogram, such as left bundle branch block, pacemaker rhythm, ventricular tachycardia, Wolff- Parkinson-White syndrome, or a technically inadequate electrocardiogram were excluded from the analysis. ST-segment deviation was measured in 11 leads (except in aVR) 20 ms after the end of QRS complex (J-point) with the PR segment considered as baseline. ST-segment deviation was calculated as the sum of ST-segment elevation in leads I, aVL, and V1 to V6 for anterior myocardial infarction and leads II, III, aVF, V5, and V6 for nonanterior myocardial infarction plus the sum of ST-segment depression from leads with 0.1 mV depression or greater in leads II, III, and aVF for anterior infarction and in leads V1 to V4 for nonanterior infarction. All ECGs were categorized according to ST-segment resolution comparing basal ECG with ECG obtained 60 minutes after angioplasty. Percent resolution of ST-segment elevation was categorized in an arbitrary cut-off point 60 minutes after angioplasty, based on the clinical predictive power and on the parameters of ventricular function from previous studies, including the PREMIAR trial. (6, 12)

Adequate ST-segment analysis was achieved in 135 patients (96.4%).

The study population was divided in two groups according to the percentage of ST-segment resolution at 60 minutes compared to baseline: complete resolution (≥ 70%) and incomplete resolution (< 70%).

Statistical analysis

Categorical variables were expressed as percentage and continuous variables as mean and standard deviation or median and interquartile range for parametric or non parametric distributions, respectively. The association between variables and events was expressed using odds ratio (OR) with its corresponding 95% confidence interval (CI). Student's *t* tests or Wilcoxon test were used to compare continuous variables and chi-square test for categorical variables.

We performed a multivariate logistic regression analysis with the variables with a $p < 0.20$ obtained with the simple logistic regression in order to identify predictors for incomplete resolution of the ST-segment after angioplasty as a dichotomous variable (ST-segment resolution < 70% 60 minutes after angioplasty). A p value < 0.05 was considered statistically significant.

RESULTS

Primary angioplasty was successful in 95.7% of patients and TIMI grade 2-3 flow was achieved in 95% of cases (TIMI 2 in 12% and TIMI 3 in 83%). Figure 1 shows the percentage of patients with completes ST-segment resolution in different time intervals after the final contrast injection (0, 30, 60, 90, 120, 180, 240 minutes). In total, 63% of patients (n = 82) had complete ST-segment resolution at 60 minutes compared to 37% (n = 53) with incomplete resolution.

The relations between demographic data and the degree of tissue reperfusion after angioplasty are shown in Table 1. The group of patients with incomplete ST-segment resolution had greater proportion

of anterior infarctions, more incidence of hemodynamic involvement and lower proportion of current smokers. They presented greater prevalence of diabetes and longer time interval from the onset of symptoms to angioplasty (p = ns).

The population was divided into quartiles depending on the time interval from symptoms onset to angioplasty, and in two groups according to myocardial infarction localization - anterior and nonanterior localization - with the aim of performing a more profound analysis of the relation between ischemia duration and infarction localization with the degree of reperfusion (Figure 2). A significant interaction between the time interval from symptoms onset and the degree of ST-segment resolution could not be established; however, reperfusion was greater in patients with anterior infarction treated early compared to those treated later (see Figure 2).

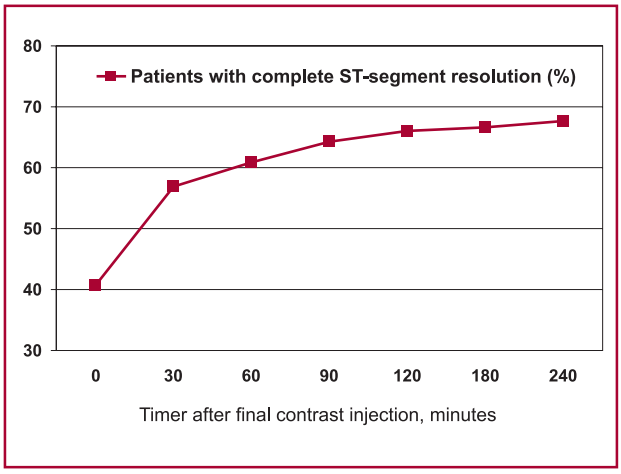

Fig. 1. Percentage of patients with complete ST-segment resolution (≥ 70%) in different time intervals after angioplasty.

Patients with anterior infarctions were significantly younger, hemodinamically unstable and had less development of collateral circulation in basal angiography compared to those with nonanterior localization (Table 2).

Patients' baseline and angiographic characteristics according to the degree of ST-segment resolution are shown in Table 3. The use of a protection filter device and stents had no significant effect in the degree of ST-segment resolution; yet, the use of glycoprotein IIb/IIIa inhibitors was associated with better tissue reperfusion (Table 3). Despite the degree of TIMI grade 3 flow was similar in both groups, patients with incomplete ST-segment resolution had greater incidence of angiographic distal embolization and worse angiographic blush grade.

Mortality and heart failure rates were lower in patients with complete resolution (Figure 3) and reinfarction was similar in both groups (5.3% versus 4.2%, respectively; p = 0.68).

Multivariate analysis demonstrated that anterior myocardial infarction was associated with incomplete ST-segment resolution (OR 8.22, 95% CI 3.67-18.4; p < 0.001), while the use of glycoprotein IIb/IIIa inhibitors (OR 4.21, 95% CI 1.34-13.22; p = 0.014) and current smoking (OR 3.84, 95% CI 1.58-9.50; p = 0.003) correlated with complete ST-segment resolution.

DISCUSSION

Our study demonstrates that although angioplasty is effective to reestablish coronary epicardial flow in most patients, approximately 40% fail to achieve ad-

Table 1. Baseline characteristics according to degree of ST resolution

	Complete resolution (n = 82)	Incomplete resolution (n = 53)	p value
Age, years (mean ± SD)	60.9 ± 10	59.8 ± 10.2	0.53
Female gender	22	15	0.32
Diabetes mellitus, %	16	26	0.13
Dyslipemia, %	42	52	0.16
Current smoking, %	51	25	0.002
Previous infarction, %	17	16	0.21
Anterior localization, %	33	79	< 0.001
Basaline hear rate, bpm (mean ± SD)	70 ± 15	81 ± 20	< 0.001
Killip class ≥ 2, %	17	30	0.07
Symptom onset to admission, minutes (mean ± DE)	182 ± 134	217 ± 167	0.19
Anterior localization, %	38	81	0.001
Baseline ST-segment elevation*, μV (mean ± SD)	3.1 ± 2.8	4.1 ± 2.0	0.02**

* Measured in most abnormal lead. **Kruskal-Wallis test.

equate tissue reperfusion according to the degree of ST-segment reperfusion. Our findings are consistent with previous studies in the sense that patients with suboptimal tissue reperfusion have poor outcomes with greater incidence of heart failure and mortality and a similar risk of reinfarction. (13-16) Thus, the degree of tissue reperfusion is closely related to the preservation of left ventricular function. (17) Multiple clinical and therapeutic factors may interact in the vulnerability of myocardial tissue to the ischemic insult.

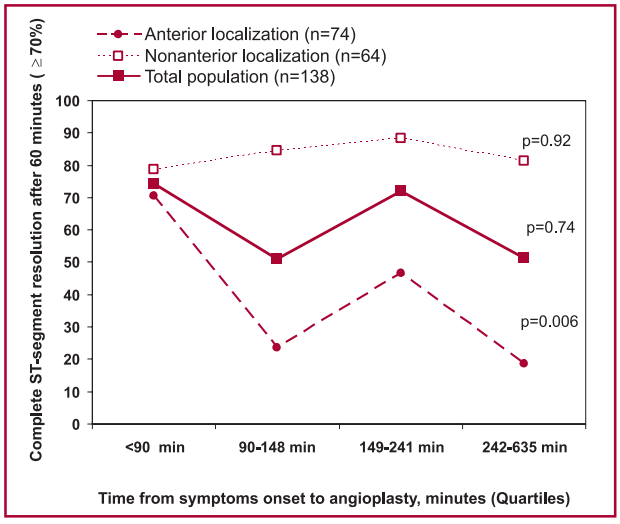

Fig. 2. Mortality, reinfarction, heart failure and combined events at 30 days according to the degree of ST-segment resolution 60 minutes after angioplasty.

Patients with anterior myocardial infarction present less degree of tissue reperfusion compared with those who have nonanterior localization. (9, 15, 18) The greatest amount of myocardial territory compromised together with less development of collateral circulation is probably more frequent in patients with anterior infarction. In addition, patients with anterior infarction were hemodinamically unstable with higher heart rate and worse Killip class. This may account for the greater prevalence of anterior localization as an indicator of hemodynamic involvement at multivariate analysis. We did not observe any relation between the duration of ischemia with the degree of tissue reperfusion in the general population; yet patients with anterior localization seem to be more vulnerable to time to angioplasty with rapid reduction in the degree of myocardial reperfusion. Conversely, in patients with nonaterior localization, the degree of tissue reperfusion is independent of time from symptoms onset. If this hypothesis is confirmed by other studies, community programs focused on reducing time to reperfusion therapy should pay special attention to the group of patients with anterior infarction.

The use of glycoprotein IIb/IIIa inhibitors is associated with better tissue reperfusion after angioplasty. Recent studies have also demonstrated that these potent agents improve microvascular perfusion. (19, 20)

Interestingly, current smoking was independently associated with a better degree of myocardial reperfusion. This paradoxical effect might be explained by clinical or physiopathological variables which still remain unknown. (21, 22) Current smok-

Table 2. Baseline clinical and angiographic characteristics according to infarct localization

	Nonanterior localization (n = 64)	Anterior localization (n = 74)	p value
Age, years (mean ± SD)	62.3 ± 9.6	58.7 ± 10.3	0.003
Female gender	22	16	0.36
Diabetes mellitus, %	19	20	0.26
Basaline hear rate, bpm (mean ± SD)	68 ± 13	80 ± 15	0.001
Killip class ≥ 2, %	16	28	0.09
Use of glycoprotein IIb/IIIa inhibitor, %	22	25	0.66
Baseline angiographic data			
Collateral circulation, %	43	22	0.017
Diameter stenosis (%), (mean ± SD)	96 ± 9	95 ± 15	0.99
Baseline TIMI grade 0 flow, %	78	78	0.99
Results after angioplasty			
Diameter stenosis (%), (mean ± SD)	4 ± 15	6 ± 18	0.25
Final TIMI grade 3 flow, %	84	81	0.49
Final angiographic perfusion grade 3, %	79	60	0.026
Distal embolization, %	10	8	0.60
ST-segment resolution at 60 minutes, % (mean ± SD)	87 ± 15	62 ± 17	< 0.001

	Complete resolution (n = 82)	Incomplete resolution (n = 53)	p value
Baseline TIMI grade 0-1 flow, %	86	75	0.34
Baseline diameter stenosis (%), (mean ± SD)	95 ± 14	96 ± 9	0.86
Collateral circulation, %	36	26	0.25
Angiographic thrombosis, %	86	90	0.39
Multivessel disease, %	52	56	0.60
Distal filter device, %	49	50	0.91
Stents used, %	98	94	0.76
Use of glycoprotein IIb/IIIa inhibitor, %	27	17	0.18
Stent length, mm (mean ± SD)	26 ± 11	25 ± 17	0.44
Maximum inflation pressure, ATM (mean ± SD)	14 ± 2	14 ± 2	0.95
Multiple stents (≥ 2), %	26	28	0.74
Successful angioplasty, %	97	94	0.48
Distal embolization, %	5	11	0.15
Final TIMI grade 3 flow, %	84	81	0.74
Final angiographic perfusion grade 3, %	78	55	0.002

Table 3. Baseline angiographic and therapeutic characteristics according to the degreeof ST-segment resolution

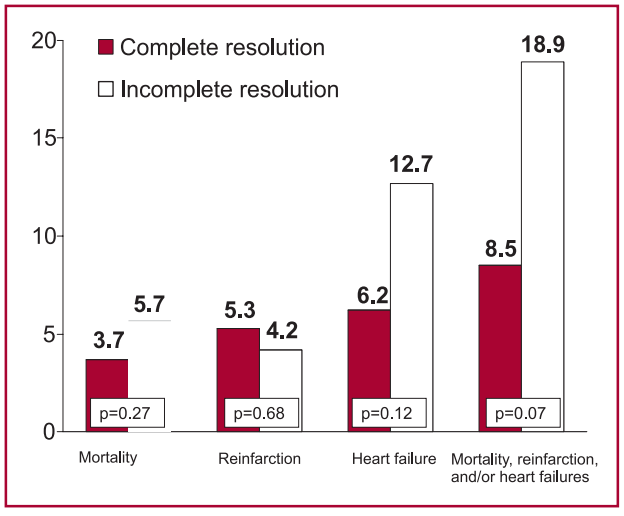

Fig. 3. Mortalidad, reinfarto, insuficiencia cardíaca y eventos combinados a los 30 días según el grado de resolución del segmento ST a los 60 minutos posangioplastia.

ers who present with AMI are younger than non-smokers (55.9 ± 7.6 years versus 62.2 ± 10.6 years; p < 0.001). However, we did not find any significant differences in the prevalence of diabetes (14 versus 23; p = ns), female gender (14 versus 21; p = ns), Killip class ³ 2 (22 versus 23; p = ns) and anterior presentation (50 versus 57; p = ns) compared to non-smokers. In this way, this paradoxical effect might be due to the fact that myocardial infarction occurs at earlier stages of atherosclerotic disease, when coronary plaques present greater thrombotic burden; in consequence, these lesions have better response to pharmacological or interventional reperfusion therapies. (21, 23-25)

Some limitations to our study deserve to be discussed. This was a selected population of patients with AMI; patients presenting 12 hours from symptoms onset, those in cardiogenic shock or with conditions precluding evaluation of ST-segment changes on the admission electrocardiogram were excluded. The fact that patients with TIMI grade 3 flow at baseline coronary angiography were also excluded may explain the high rate of events such as mortality and heart failure. We based our analysis in measuring ST-segment resolution as equivalent of the degree of tissue reperfusion. Patients with failed angioplasty or poor angiographic outcomes were not excluded from the analysis. It is important to consider that our analysis was focused on identifying predictors of tissue reperfusion that may be different from predictors of mortality in acute myocardial infarction.

CONCLUSIONS

Although primary angioplasty is considered the ideal strategy in acute myocardial infarction, a considerable proportion of patients undergoing primary angioplasty do not achieve adequate myocardial tissue reperfusion. These patients have poor outcomes with greater incidence of heart failure and mortality. Patients with anterior myocardial infarction present less degree of tissue reperfusion, while current smokers achieve better reperfusion. The use of glycoprotein IIb/IIIa inhibitors during primary angioplasty is associated with better tissue reperfusion. Time from symptoms onset to primary angioplasty may play a key role in patients with anterior localization.

RESUMEN

Predictores de reperfusión miocárdica tisular luego de la angioplastia en el infarto agudo de miocardio

Introducción

La angioplastia primaria tiene una eficacia limitada ya que deja a un grupo considerable de pacientes sin lograr una reperfusión miocárdica tisular adecuada. Los factores clínicos, angiográficos y terapéuticos que influyen en el grado de reperfusión no han sido claramente establecidos.

Objetivos

Identificar los factores independientes asociados con la ausencia de reperfusión tisular luego de la angioplastia primaria.

Material y métodos

Se analizaron 140 pacientes incluidos prospectivamente en el estudio aleatorizado Protection of Distal Embolization in High-Risk Patients with Acute ST-Segment Elevation Myocardial Infarction Trial (PREMIAR). Este estudio evaluó la utilización de un filtro de protección distal durante la angioplastia en el infarto agudo de miocardio con supradesnivel del segmento ST en pacientes de alto riesgo trombótico (solamente incluyendo flujo coronario basal TIMI 0-2). El punto final primario fue la resolución completa del segmento ST a los 60 minutos, definida como disminución del ST ≥ 70% con el empleo de monitorización continua del segmento ST. Se desarrolló un modelo de regresión logística para identificar los predictores independientes.

Resultados

Se observó resolución completa del segmento ST a los 60 minutos luego de la angioplastia en 82 pacientes (63%), mientras que 53 pacientes (37%) presentaron resolución incompleta que se asoció con una tasa de mortalidad, reinfarto y/o insuficiencia cardíaca a los 30 días del 8,5% y 18,9%, respectivamente (p = 0,07). Los pacientes que no lograron una reperfusión tisular adecuada tuvieron con más frecuencia compromiso de localización anterior (79% *versus* 33%; p = 0,001), mayor frecuencia cardíaca (81 ± 20 *versus* 70 ± 15; p < 0,001) y menor proporción de fumadores actuales (25% *versus* 51%; p = 0,002) respecto de aquellos con reperfusión tisular óptima. Se observó además una tendencia a mayor presencia de diabetes (26% *versus* 16%; p = 0,13), mayor tiempo desde el inicio de los síntomas a la angioplastia (minutos) (217 ± 167 *versus* 182 ± 134; p = 0,19) y clase Killip > 1 (30% *versus* 17%; p = 0,07), respectivamente. El análisis multivariado demostró que el infarto de localización anterior (OR 8,22, IC 95% 3,67-18,4; p < 0,001) se asoció con ausencia de reperfusión completa, mientras que el uso de inhibidores de la glicoproteína IIb/IIIa (OR 4,21, IC 95% 1,34-13,22; p = 0,014) y el tabaquismo actual (OR 3,84, IC 95% 1,58-9,50; p = 0,003) se correlacionaron con una reperfusión completa.

Conclusiones

Una proporción considerable de pacientes sometidos a angioplastia primaria no logran una reperfusión tisular adecuada. Este fenómeno se asocia con peor pronóstico. La presencia de infarto de localización anterior se correlaciona con una extensión menor del grado de reperfusión tisular. Contrariamente, el tabaquismo actual y el uso de inhibidores de la glicoproteína IIb/IIIa se asocian con una reperfusión tisular más profunda luego de la angioplastia primaria.

Palabras clave > Infarto del miocardio - Angioplastia - Reperfusión miocárdica

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Clinical Sites and Investigators:

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