Immature Platelet Fraction: A New Prognostic Marker in Acute Coronary Syndrome

Fracción de plaquetas inmaduras, un nuevo marcador pronóstico en el síndrome coronario agudo

To the Editor,

The role of platelets in the pathogenesis of acute coronary syndrome (ACS) is well recognized.[1] Persistent platelet activation despite antithrombotic therapy has an influence on the severity of ischemic cardiomyopathy.

Reticulated platelets are the youngest form of circulating platelets. They are larger than senescent platelets, contain residual RNA that confers a reticulated appearance, and are hemostatically more active because they express more glycoprotein Ib and IIb/IIIa receptors. Currently, a fast, automated method is available to quantify reticulated platelets by the immature platelet fraction (IPF), calculated as the ratio between immature platelets and total platelets.

The mean platelet volume is an indicator of platelet reactivity. An elevated mean platelet volume in the acute phase of myocardial infarction is associated with a poorer short-term prognosis.[2] IPF determination may be more sensitive and specific than the mean platelet volume for evaluating platelet reactivity.[3] It has been observed that, in patients with coronary disease, the IPF is elevated relative to the healthy population,[4] and it is also increased in ACS with respect to stable coronary disease.[5]

In our study, reticulated platelets were analyzed by plasma IPF determination in hospitalized ACS patients with the aim of determining the short-term prognostic value (predictor of in-hospital mortality) of this parameter.

Between January 2007 and April 2008, 251 hospitalized ACS patients were studied. ACS was established based on symptoms of myocardial ischemia in the 24 h prior to admission together with elevated cardiac biomarkers and/or electrocardiographic abnormalities (ST deviation≥0.5 mm and/or T wave changes, consisting of negative T waves≥2 mm in 2 or more contiguous leads). The sample for IPF determination was obtained in the morning of the first day of hospitalization. IPF was determined with a Sysmex XE-2100 automated hematology analyzer (Sysmex; Kobe, Japan), which, in relation to the platelet volume and RNA content, distinguishes the percentage of immature platelets.

A descriptive statistical analysis was performed. We calculated descriptive statistics of frequency of the continuous variables studied (median [interquartile range]) and the categorical variables (percentages). The Mann-Whitney *U* test was used to compare quantitative variables, and the Pearson chi-square test to determine associations between qualitative variables. The predictive factors of in-hospital mortality were established by univariate analysis, and statistically significant variables were included in a binary multivariate logistic regression analysis. All statistical analyses were carried out with the IBM SPSS Statistics 18 program. Statistical significance was set at a *P*-value of<.05.

The characteristics of the study population are shown in Table 1. The comparison of IPF values in ACS patients with and without ST segment elevation showed no significant differences between the 2 groups: 5.20% [3.60%-7.60%] vs 4.75% [3.12%-7.42%] (*P*=.289). Thirty-one patients (12.3%) died during hospitalization. The IPF value was higher in patients who died than in those who survived: 6.60% [4.20%-10.80%] vs 4.80% [3.10%-6.95%] (*P*=.002). In-hospital mortality increased as the IPF tertile increased, such that the probability of death was higher in patients in the third tertile (IPF>6.2%) than in those in the first (IPF<3%) (22% vs 6%; *P*=.003). Mortality observed in the high-risk group determined by the global registry of acute coronary events (GRACE) risk score (≥140) was 10%, 15.7%, and 25% (*P*=.148) for the first, second, and third IPF tertiles, respectively, and in the non-high-risk group (GRACE score<140), mortality was 2.3%, 3.1%, and 15.3% (*P*=.057) for the first, second, and third tertiles, respectively.

Table 1
Characteristics of the Population

Age, y	68±11
Older than 75 years	85 (34)
Males	185 (74)
HT	104 (41)
Diabetes mellitus	82 (33)
Dyslipidemia	110 (44)
Active smokers	63 (25)
Previous myocardial infarction	41 (16)
Killip>1 at admittance	58 (23)
GRACE>140	148 (59)
LVEF<40%	25 (10)
Mean glomerular filtration (MDRD), mL/min/m²	67.7±23.14
Leukocyte count at admission, ×10³/μL	9±4.15
NSTEACS	141 (57)
Ischemia on electrocardiogram	60 (42)
Elevated cardiac markers	87 (62)
Invasive management	115 (82)
Coronary revascularization	102 (72)
STEACS	110 (43)
Primary angioplasty	58 (53)
Fibrinolysis	30 (27)
Without perfusion	22 (20)
Antithrombotic treatment	
ASA	244 (97)
Clopidogrel	188 (75)
Anti-GPIIb/IIIa	116 (46)
Heparin (NFH/LMWH)	66 (26)/174 (69)
Type of revascularization	
Percutaneous	170 (68)
Surgical	26 (10)
Not revascularized	56 (22)

ASA, acetylsalicylic acid; GPIIb/IIIa, glycoprotein IIb/IIIa; LMWH, low molecular weight heparin; HT, hypertension; LVEF, left ventricular ejection fraction; MDRD, modified diet in renal disease; NFH, non-fractionated heparin; NSTEACS, non-ST-segment elevation acute coronary syndrome; STEACS, ST-segment elevation acute coronary syndrome.

After adjusting for other covariables (age, diabetes mellitus, heart failure at hospitalization, ST deviation on electrocardiographic study, and troponin elevation) multivariate analysis showed that the third tertile of IPF remained as an independent predictor of in-hospital mortality: odds ratio=2.42 (95% confidence interval, 1.08-5.43; *P*=.032) (Table 2).

Table 2
Multivariate Analysis of In-hospital Mortality

Variable	OR (95%CI)	*P*
Age	1.023 (0.985-1.061)	.241
Diabetes mellitus	0.509 (0.208-1.242)	.138
Admittance Killip>1	2.795 (1.179-6.627)	.020
ST deviation	1.139 (0.468-2.774)	.775
Elevated troponin I	2.449 (0.786-7.617)	.122
Third tertile of IPF	2.423 (1.080-5.439)	.032

95%CI, 95% confidence interval; IPF, immature platelet fraction; OR, odds ratio.

Our study has 2 main limitations. The first is possible selection bias, since the IPF was determined in the first morning blood test following hospitalization, and this sample is collected in patients at highest risk. Hence, our results would be valid for this population. The second limitation is the small sample size and limited number of adverse events, which impedes precise adjustment for all the variables potentially related to mortality, and limits the robustness of the results.

Therefore, we conclude that in patients hospitalized for ACS, elevated IPF values determined in the first 24 h following admission are associated with a poorer in-hospital prognosis due to an increase in mortality, even among patients who are not considered at high-risk according to the GRACE score. These patients, who can be identified by standard blood testing, may benefit from more intensive medical treatment or use of a prompt revascularization strategy. Future studies should confirm the association between IPF and mortality and investigate the pathophysiology of these findings.

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Early Anticoagulation May Improve Preprocedural Patency of the Infarct-related Artery in Primary Percutaneous Coronary Intervention

La anticoagulación precoz podría mejorar la permeabilidad de la arteria causante del infarto antes de la angioplastia primaria

To the Editor,

Primary percutaneous coronary intervention (pPCI) is the preferred reperfusion strategy in most patients with ST-segment elevation myocardial infarction (STEMI). In these patients, adjuvant antithrombotic therapy (antiplatelet and anticoagulant) is essential to prevent thrombotic events mediated by platelet activation or the coagulation cascade.[1] In pPCI, various parenteral anticoagulants are used, such as unfractionated heparin (UFH), enoxaparin and bivalirudin. However, the optimal time at which to start anticoagulation therapy in patients with STEMI–whether at diagnosis or at the start of pPCI–is unknown and consequently there are no recommendations on this issue in the current clinical practice guidelines.[2,3] The aim of this study was to evaluate the impact of early administration of anticoagulation therapy (at diagnosis) compared with its application in the cardiac catheterization laboratory at the start of the procedure on the initial patency of the infarct-related artery (IRA) in patients undergoing pPCI as a reperfusion strategy.

All consecutive patients (between October 2009 and November 2011) admitted to a tertiary center with a diagnosis of STEMI who underwent pPCI were prospectively registered. Patients diagnosed in the tertiary center and in other centers or by the emergency service in their homes and who were transported to the catheterization laboratory for pPCI were included. Patients who had received early enoxaparin therapy were excluded due to their small number and the heterogeneity of doses and routes of administration used. The patients were thus divided into 2 groups according to the treatment received at diagnosis (group 1: those receiving early UFH; group 2: those not receiving anticoagulation therapy until their arrival at the catheterization laboratory). The glycoprotein IIb/IIIa inhibitors and the anticoagulant employed in the catheterization laboratory (in patients in group 2) were used according to the operator's criteria. Once in the catheterization laboratory, group 1 patients underwent ACT (activated clotting time) determination and could receive an extra dose of UFH to achieve an ACT of 250-350 s (in those receiving glycoprotein IIb/IIIa inhibitors, the ACT target was 200-250 s), while group 2 patients received intravenous UFH doses of 1 mg/kg, except for 8% of the patients, who received bivalirudin. The patency of the IRA was evaluated with the initial Thrombolysis in Myocardial Infarction (TIMI) flow grade dichotomized into 2 arbitrary categories: poor flow (TIMI 0-1) vs good flow (TIMI 2-3). This categorization was used because TIMI grade 2-3 flow allows complete visualization of the distal area of the lesion, facilitating the procedure. The statistical analysis was performed by using a logistic regression model (backward stepwise method), which included initial TIMI flow (dichotomized) as the dependent variable and anticoagulation therapy (groups 1-2) as the independent variable, adjusting by variables considered clinically relevant and baseline characteristics not evenly distributed between the 2 groups ($P<.20$).

A total of 1075 patients were included, of which 95 were excluded because they had received early enoxaparin therapy. Therefore, 980 patients were included in this analysis, divided into the following 2 groups: group 1, n=566 (intravenous UFH 0.75-1 mg/kg), and group 2, n=414. None of the patients received glycoprotein IIb/IIIa inhibitors before reaching the hospital. Among the baseline characteristics (Table), differences were found in the following variables (included in the model): prior acute myocardial infarction, prior PCI, Killip class on admission, clopidogrel loading dose, and the time between activation of the catheterization laboratory to the start of coronary angiography. In the multivariable analysis, the only predictor was the early use of UFH, which was associated with a significantly higher percentage of TIMI 2-3 flow in the IRA (27% vs 16.7%; odds ratio=1.84 [confidence interval,