Impaired myocardial perfusion score and inflammatory markers in patients undergoing primary angioplasty for acute myocardial infarction

J Emilio Exaire,* Robert B Fathi,** Sorin J Brener,** Juhana Karha,** Stephen G Ellis,** Deepak L Bhatt**

Summary

Background: Microcirculatory dysfunction during acute myocardial infarction is mediated by various mechanisms including inflammation, thrombus, or plaque embolization. We hypothesize that patients with acute myocardial infarction and admission Thrombolysis in Myocardial Infarction (TIMI) myocardial perfusion grade (TMP) < 2 had increased inflammatory status as measured by high sensitivity C-reactive protein (hs-CRP). Methods: From January 2002 to December 2003, 166 patients (178 lesions) were referred for primary percutaneous coronary intervention. Patients were stratified based on pre-PCI TMP < 2 or TMP ≥ 2. Univariate and multivariate predictors of in-hospital and 30-day death were determined with logistic regression. Results: Pre-PCI TMP < 2 was found in 66% vs 34% with TMP ≥ 2 (P < .001). Hs-CRP levels were high in both groups but not significantly different (37.9 ± 6 vs 33.7 ± 6 mg/L, P = .63). Patients with TMP < 2 had higher WBC (12.83 ± 4.55 · 10^3 vs 10.83 ± 3.00 · 10^3, P = .04), lower ejection fraction (40 ± 11% vs 46 ± 12%, P < .001), and higher admission CK-MB levels (116 ± 13 ng/mL vs 55 ± 13 ng/mL, P = .006). Death occurred in 12% in the poor TMP group vs 1.8% in the good TMP group (P = .03). Advanced age, use of an intra-aortic balloon pump, and elevated admission WBC were independently associated with in-hospital and 30-day death. Conclusions: High hs-CRP levels were not associated with impaired myocardial perfusion score. Microcirculatory impairment may be related to an increased inflammatory process, independent from high hs-CRP levels.

Resumen

Objetivos: La disfunción de la microcirculación coronaria durante el infarto agudo al miocardio es mediada por varios mecanismos incluyendo inflamación y embolización de placa y/o trombo. La hipótesis del presente estudio es que los pacientes con infarto agudo al miocardio que presentan con niveles bajos de perfusión microcirculatoria (definidos como grado de perfusión Thrombolysis in Myocardial Infarction (TIMI) (TMP) < 2) tienen un aumento en los marcadores inflamatorios, tales como proteína C-reactiva de alta sensibilidad (hs-CRP) y glóbulos blancos, y la correlación de estos niveles con la mortalidad de esta cohorte. Métodos: De enero de 2002 a diciembre de 2003, 166 pacientes (178 lesiones) fueron referidos para intervención percutánea. Los pacientes fueron estratificados para este análisis en TMP < 2 o TMP ≥ 2. Los factores asociados a mortalidad intrahospitalaria fueron determinados con análisis de regresión logística. Resultados: Un TMP < 2 preintervención fue encontrado en 66% vs 34% de los pacientes (P < .001). Los niveles de hs-CRP se encontraron elevados en ambos grupos pero no significativamente diferentes (37.9 ± 6 vs 33.7 ± 6 mg/L, P = .63). Los pacientes con TMP < 2 tuvieron cuentas de glóbulos blancos mayores (12.83 ± 4.55 · 10^3 vs 10.83 ± 3.00 · 10^3, P = .04), menor fracción de expulsión (40 ± 11% vs 46 ± 12%, P < .001), y mayores nive-

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Inflammation plays a central role in cardiovascular disease. Elevated levels of C-reactive protein and white blood cell count (WBC) have been unequivocally associated with adverse outcome in patients with stable and unstable coronary syndromes as well as stroke. However, the impact of an increased inflammatory milieu, such as acute myocardial infarction (AMI), on a microcirculation surrogate such as Thrombolysis in Myocardial Infarction (TIMI) perfusion (TMP) grade has not been entirely elucidated. Thus, we sought to analyze the potential role of inflammation markers on the microcirculation, as measured by admission TMP, as well as its impact on post-percutaneous coronary intervention (PCI) short-term mortality.

Methods
From January 2002 to December 2003, 166 patients (178 lesions) were referred to the Cleveland Clinic Foundation for primary PCI. Demographic and clinical information, procedural technique, and major adverse cardiac events (MACE) (including death or re-infarction during hospitalization and 30-day follow-up), pre- and post-procedural creatine kinase (CK), and CK-MB, high sensitivity CRP levels (hs-CRP), and WBC were recorded prospectively. All patients had clinical and electrocardiographic criteria of acute ST-segment elevation MI. All patients received aspirin, loading doses of Clopidogrel (300 mg) and 75 mg thereafter, and GP IIb/IIIa inhibitors (abeciximab 88%; other 12%). Univariate and multivariate predictors of in-house and 30-day death were determined with logistic regression.

Two independent experienced blinded operators assessed the pre- and post-PCI TMP score according to the established TIMI grading system obtaining an interobserver correlation of 98%. TMP 0 was defined as failure of dye to enter the microvasculature (no ground-glass appearance). TMP 1 was defined as dye slowly entering the microvasculature and failing to exit. TMP 2 was defined as delayed entry and/or exit from the microvasculature (persisting after 3 cardiac cycles). TMP 3 was defined as normal entry and exit of dye from the microvasculature. Patients were stratified based on pre-PCI TMP < 2 or pre-PCI TMP ≥ 2.

Continuous variables were compared using Student’s t test if normally distributed and Wilcoxon rank-sum if not. Binary variables were compared using χ² with normal approximation or Fisher’s exact test when appropriate. A 2-tailed P value of 0.05 was considered significant. In order to analyze the variables associated with post-PCI death a stepwise logistic regression model was performed.

Results
Both groups were similar regarding most admission characteristics (Table I). However, patients with pre-PCI TMP < 2 had higher WBC (12.83 ± 4.55 · 10³ vs 10.83 ± 3.00 · 10³, P = .04), lower ejection fraction as measured by echocardiography (40 ± 11% vs 46 ± 12%, P = .001), and higher CK-MB levels (116 ± 13 ng/mL vs 55 ± 13 ng/mL, P = .006). La muerte ocurrió en 12% del grupo TMP <2 vs 1.8% en el grupo con TMP > 2 (P = .03). La edad avanzada, el uso de balón de contrapulsación y los niveles elevados de glóbulos blancos al momento de la admisión se relacionaron independientemente con la muerte intrahospitalaria y a 30 días. Conclusiones: Los niveles elevados de hs-CRP no se asociaron con disfunción de la microcirculación. La disfunción microcirculatoria puede estar relacionada a un proceso inflamatorio, independiente de los niveles elevados de hs-CRP.
Hs-CRP levels were high in both groups but not statistically different (37.9 ± 6 vs 33.7 ± 6 mg/L, P = .63). Death occurred in 12% (N = 13) in the pre-PCI TMP < 2 group vs 1.8% (N = 1) in the pre-PCI TMP ≥ 2 group (P = 0.03) (Fig. 1).

Univariate predictors of death included advanced age (P = .005), admission Troponin T (P = .04), final visual TIMI flow (P < .001), Admission TMP grade (P < .001), post-PCI TMP grade (P < .001), glucose levels (P = .002), WBC (P < .001), left ventricular ejection fraction (P < .001), peripheral vascular disease (P < .001), systolic blood pressure (P = .01), left anterior descending artery territory AMI (P = .01), and use of intraaortic balloon pump (P < .001), and admission white blood cell counts (P = .01) were independently associated with in-hospital and 30-day death (Beta 0.333) (Table II).

**Discussion**

Impaired myocardial blood flow after AMI is a result of multiple insults including platelet/thrombus microaggregate embolization combined with humoral factors derived from fibrinolysis (increased thrombin) and platelets (adenosine, serotonin, thromboxane A₂). Inflammation and reperfusion injury may also exacerbate the problem by increasing neutrophil capillary plugging, liberating free radicals, and increasing capillary permeability, resulting in tissue edema and further deterioration of myocardial perfusion. Ischemic injury secondary to microvascular obstruction may be amplified in patients with an enhanced inflammatory milieu. In patients undergoing fibrinolysis as primary treatment for AMI, increased levels of CRP were associated with either death or post-infarction complications. Our results suggest that patients with AMI have very high levels of hs-CRP on admission, reflecting an increased inflammatory status. However, this did not translate into lower admission TMP levels. Elevated WBC levels constitute another unspecific marker of inflammation. WBCs make a ma-
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Table II. Univariate and multivariate predictors of death.

<table>
<thead>
<tr>
<th></th>
<th>Univariate R Square</th>
<th>P</th>
<th>Multivariate Beta</th>
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<td>Age</td>
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<td>0.005</td>
<td>0.265</td>
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<td>Diabetes</td>
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<td>COPD</td>
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<td>Renal insufficiency</td>
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<td>PVD</td>
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<td>LVEF</td>
<td>0.097</td>
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<td>Systolic blood pressure</td>
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<td>Admission CK</td>
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<td>Admission CK-MB</td>
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<td>Peak CK-MB</td>
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<td>Admission TMP grade</td>
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<tr>
<td>Final TMP grade</td>
<td>0.340</td>
<td>&lt; 0.001</td>
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CK = Creatine kinase; LAD = Left anterior descending artery; TMP = TIMI perfusion grade; LVEF = Left ventricular ejection fraction; COPD = Chronic obstructive pulmonary disease; PVD = Peripheral vascular disease.

Major contribution to the rheologic properties of blood by altering its adhesive properties under stress (including the stress of ischemia) and participate in endothelial injury, both acutely and chronically, by adhering to endothelium and damaging it with toxic oxygen compounds and proteolytic enzymes. Our results confirm the previously observed link of elevated WBC and death. The mechanism of this association remains uncertain. It suggests that other inflammatory stimuli, beyond CRP, are present. Various mechanisms may be perpetuating the inflammatory response including interleukin (IL)-1, IL-6, TNF-α, adhesion molecules, and platelets. These factors have a pro-inflammatory capacity that may up regulate and amplify a multitude of interactions that result in an increase in substances such as fibrinogen and PAI-1, promoting adhesion of neutrophils and ultimately regulate gene expression of key proteins that potentiate the inflammatory cascade.

Age has been related to poor outcome in AMI patients undergoing PCI. Our results confirm this observation. Patients that needed an intraaortic balloon pump had worse outcome suggesting that this cohort possibly was hemodynamically unstable, and therefore, at higher risk. As previously described, admission glucose was also associated with death as univariate variable. This has been associated to low myocardial perfusion, impairing left ventricular function thus worsening the outcome. Interestingly, the presence of peripheral vascular disease was also associated to death, reflecting the extent of cardiac and extracardiac atherosclerotic disease.

Limitations
The present study should be interpreted in the light of the following limitations. This is not a randomized trial, with all the inherent potential confounding effects of an observational study. TMP grade is a subjective assessment of microcirculation, and the inter-observer variation may bias the results, although the rate of concordance between observers in this study was 98%. The monitoring of other inflammatory markers, such as IL-6, could have added more robust evidence of other inflammatory pathways associated with poor outcome. The time of onset and size of the myocardial infarction may also increase the CRP levels; these factors were not available in our database, therefore we were not able to include them in our analysis.

Conclusions
Hs-CRP levels were not significantly different between patients with or without a patent micro-
circulation before undergoing PCI. An increased inflammatory milieu, not reflected by CRP elevation alone, possibly mediates microcirculation impairment.

References

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