

New Data on the Prognostic Value of Inflammatory Markers in Patients with Acute Coronary Syndrome

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The PACS study (Prognosis in Acute Coronary Syndromes) was conducted in 1500 patients with non-ST-segment elevation acute coronary syndrome (NSTEMACS) in 11 coronary care units of Argentina from January 2000 to May 2002. (1, 2) The purpose of this prospective, multicentric study was to establish the prognostic value of different biomarkers in these patients' risk stratification. (1, 2) The study of Hirschson Prado et al. (3) published in this issue of the Argentine Journal of Cardiology specifically addressed whether white blood cell (WBC) count on admission is related to the complexity of coronary lesions and prognosis of patients with NSTEMACS. Out of the total number of patients with NSTEMACS included in the angiographic PACS substudy, the authors selected for their analysis 580 patients undergoing early coronary angiography (median time of 48 hours) and WBC count within 24 hours of admission. The study population was divided into percentiles according to WBC count (< 7700, between 7700 and 11500 and > 11500/mm³). Results showed that patients with higher WBC level frequently presented more complicated plaques and visible thrombus in the coronary angiography as well as more extensive coronary disease. In addition, at 6-month follow-up, the incidence of the composite adverse event of death or myocardial infarction was double in these patients. (3) Study results show that in patients with NSTEMACS, elevation of WBC on admission is associated not only with more complex coronary lesions but also with worse mid-term prognosis.

These findings are very relevant, firstly, for the simplicity of the proposal in studying WBC count on admission in patients with NSTEMACS, and secondly, due to its relevant implications. (3) Moreover, the study generates many interesting considerations. (3) As in any observational study, it would be important to know whether the population selected for this analysis differs from the general population of the PACS study to justify the external validity of results. It is probable that only the most severely ill patients were selected for early coronary angiography and that they under-

went more complete analytical studies. The analysis described here allows a better stratification of risk in more severely-ill patients, but we do not know its usefulness in the general population with NSTEMACS. A study limitation is that the low number of events prevents an isolated analysis of mortality, which is the outcome most closely associated with WBC elevation in patients with acute myocardial infarction. On the other hand, we do not know whether WBC or other late inflammatory markers were elevated during a certain period of time, which could also condition a more adverse prognosis. In addition, WBC elevation on admission was associated with more complex angiographic lesions and more extensive coronary disease. These two factors already predispose patients to a worse prognosis. Although the adverse prognosis could simply be due to these more unfavorable anatomical characteristics, the multivariate analysis performed by the authors lead us to assume that the poor prognosis could be the expression of a greater inflammatory condition. Effectively, the key about the possible diagnostic and prognostic value of early WBC elevation in patients with NSTEMACS lies in establishing whether this analytical marker is an independent prognostic predictor or it depends on its association with other risk markers. In the present study, the initial WBC count provided an additional prognostic value to conventional clinical variables but could not be identified as an independent predictor of adverse events when the statistical model included other analytical variables. (3) This is important as study patients with elevated WBC levels on admission also presented high C-reactive protein (CRP) and troponin values. (3). However, it is specially interesting that in the pre-specified subgroup of patients with elevated CRP (> 3 mg/dL), WBC count allowed better prognostic stratification. (3) Finally, it would also be very interesting to know whether in this context coronary revascularization or the administration of specific adjuvant pharmacological treatment (especially antiplatelet agents and statins) could improve the outcome of patients at higher risk.

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DIFFERENT PERSPECTIVES ON VASCULAR INFLAMMATION

Inflammation plays a crucial role in the development of coronary atherosclerosis, both in its initial phases as in complications occurring in more advanced phases. (4-7) We can therefore study vascular inflammation from the beginning of endothelial injury, but also in the thrombotic complication of a mature plaque. Similarly, we may study the inflammatory state at the systemic level. Finally, in patients where an acute coronary syndrome (SCA) has produced cardiac necrosis, we may study inflammation at the myocardial level. (4-7)

At the vascular wall level, any initial injury on the vascular endothelium increases leukocyte adhesion and their in-situ activation. (4-7) The process is self-regulated by the local release of adhesion molecules, chemotactic factors and proinflammatory cytokines which eventually end by favoring the initial development of the atheromatous plaque. (4-7) Moreover, there are consistent data on the fundamental role of inflammation as trigger of thrombotic complications in patients with mature vulnerable plaques. Currently, new intracoronary imaging techniques enable the direct identification of different anatomopathological substrates in patients with ACS. (8) Hence, presence of plaque rupture with associated thrombus is more frequent in patients with ST-segment elevation ACS (STEACS) than in patients with NSTEMACS. (8) In addition, erosion of the fibrous plaque instead of the classic thin cap fibroatheroma rupture occurs in some patients with ACS. Interestingly, recent data suggest that this different culprit anatomical substrate is also associated with specific inflammatory and thrombotic patterns. (9, 10) Thus, patients, with fibrous plaque erosion also have higher serum myeloperoxidase levels and hence, a different inflammatory pattern than those with plaque rupture. (9) Similarly, in patients with plaque erosion the associated thrombus is mainly formed by platelet aggregation and is less rich in fibrin. (10) Actually, some techniques as optical coherence tomography allow direct vision of macrophage aggregates in the plaques of patients with ACS. (11) In turn, the importance of inflammation at the systemic level has been well defined by the elevation of numerous inflammatory biomarkers and the demonstration of simultaneous plaque rupture in different vascular beds. (4-7) Finally, also myocardial necrosis itself produces an intense inflammatory reaction. (4-7) In patients with acute myocardial infarction neutrophils arrive early to the injured myocardium, but it is macrophages - derived from intravascular monocytes - the ones that nest in that area, locally releasing toxic substances and favoring collagen production. Although monocytes arrive later, their effect is more enduring, releasing proinflammatory substances, such as interleukin-6 which stimulates hepatic CRP production. (4-7) As we know, CRP is the most studied inflammatory marker in cardiovascular pathology. (1-7)

Despite the overwhelming evidence demonstrating the physiopathological role of inflammation in the gen-

eration of ACS, it should be born in mind that most therapeutic strategies specifically directed against the inflammatory cascade (steroids, anti-complement or anti-lymphocyte antibodies, etc) have not produced the expected results in these patients. (4-7) As a result, it has been suggested that leukocytosis is more a biomarker than an agent responsible for this process. (5) More recent studies, however, emphasize the importance of identifying new therapeutic targets focused on the physiopathological link associating vascular inflammation with platelet activation pathways and thrombosis. (12)

PREVIOUS STUDIES

The relevance of leukocytosis as inflammatory parameter has been studied both in patients with STEACS and NSTEMACS. (4-7) In STEACS patients, leukocyte response has been classically interpreted as an acute phase reactant triggered by the ischemic insult, but also very associated with microvascular perfusion alteration and necrosis extension. (13-16). Microvascular injury seems to be determined, at least in part, by local neutrophil accumulation in the necrotic myocardium. (15-16) However, leukocytes also seem to play an essential role in the subsequent reparation process. Numerous studies have shown that WBC count on admission is associated both with short and long-term mortality in patients with STEACS. (13-16) In patients with myocardial infarction, initial leukocytosis has also been associated with congestive heart failure, while peripheral monocytosis has been mainly related to ventricular dysfunction and development of aneurysms. (15) Even though total WBC level is a fundamental prognostic factor in these patients, some studies suggest that neutrophilia and lymphopenia have different prognostic implications. (13-16) Actually, some investigators have suggested that the neutrophil / lymphocyte ratio provides greater benefit in prognostic studies. (16)

A study of the Mayo Clinic (14) in patients with STEACS treated with primary angioplasty suggested that leukocytosis predicted the presence of complete occlusion in the culprit artery, a larger infarct size and worse clinical outcome. In this study, leukocytosis was not associated with the degree of epicardial or myocardial reperfusion following the intervention. However, Mariani et al (15) also showed, in patients treated with primary angioplasty, that peak neutrophils and monocytes was associated with improved myocardial blush and earlier resolution of ST-segment elevation. In this study, neutrophils, but not monocytes were associated with peak CPK. Moreover, both monocyte levels as the degree of myocardial perfusion were associated with ventricular function recovery at 6-month follow-up. (15) Finally, Nuñez et al., (16) in a series of 515 consecutive patients with STEACS, found that elevated WBC count on admission ($> 100000/\text{mm}^3$) was an independent predictor of mortality, a value which doubled the 3-year follow-up mortality.

Initial leukocytosis values in patients with NSTEMI have also been studied. (17-21) In these patients, as there is less or no myocardial necrosis, leukocytosis may allow a more precise estimation of the primary inflammatory component at the vascular level. (17-21) Classical studies demonstrated an association between leukocytosis on admission and prognosis of these patients. (17, 18) However, in these initial studies leukocytosis values were not adjusted by the presence of other classical risk factors or other potentially confounding variables. (17-18) For example, leukocytosis has been more frequent in smokers, and this finding is also confirmed in the study by Hirschson Pardo et al. we comment here. (3) More recent studies have focused in analyzing whether leukocytosis is an independent prognostic predictor. In a series of 634 patients with NSTEMI, Sanchís et al. (19) showed that leukocytosis is an independent predictor of mortality, even after adjustment for maximum troponin values. Leukocyte prognostic value was limited to the subgroup of patients with myocardial infarction defined by increased troponin, suggesting that myocardial necrosis could be the main stimulus for WBC elevation, although vascular inflammation must also be greater in patients with infarction. Nonetheless, a high degree of vessel and/or myocardial necrotic region inflammation, as in acute myocardial infarction and less in unstable angina, seems to be required to influence systemic WBC count. (19) In this sense, the present study by Hirschson et al. lacks a separate analysis of the subgroups of patients with elevated and normal troponin. On the other hand, Sánchez et al (20) suggested that the inflammatory component was specially marked in diabetic patients with NSTEMI. In these patients, leukocyte count and also CRP and fibrinogen were independent predictors of cardiovascular mortality. In this study there was also no correlation between these serum inflammatory markers (including leukocytosis) and troponin elevation, indicating that inflammation could not simply be explained by myocardial necrosis. (20) Finally, in a large study including 4329 patients with ACS treated with angioplasty (75% with NSTEMI) one-year mortality was directly related to admission leukocyte count. (21) Curiously, leukocyte count, but not CRP, was identified as an independent predictor of mortality in the multivariate analysis. Moreover, the prognostic value of leukocytosis was confirmed both in patients with NSTEMI and STEMI. Furthermore, leukocytosis was associated with late mortality even in patients receiving statin therapy.

FINAL CONSIDERATIONS

White blood cell count on admission is a simple, inexpensive and globally available variable. We still do not know whether leukocytes should be considered as cause, effect or simply as marker of the underlying physiopathological process. It remains to be established whether the ability to predict the prognosis of

patients with NSTEMI can improve with the incorporation of this simple analytical parameter to conventional risk scales and diagnostic and therapeutic algorithms used in daily practice. As a very illustrative example of this concept, it should be borne in mind that the prognostic implications of CRP are not only well established, but are also independent from other classical prognostic markers. However, incorporation of CRP to conventional risk scales has not yet significantly improved our ability to predict adverse events during follow-up. This is the reason why its routine use in clinical practice is still not consolidated and is only relegated to research purposes. (22) New studies are therefore needed to improve our understanding of the possible prognostic value of early WBC assessment in selected patients with NSTEMI. After the great expectation generated in the literature by the implications of inflammation –both locally as systemically - in the development of ACS, we cannot disregard this new opportunity to definitively establish the importance of this simple and humble, but at the same time potentially relevant parameter, as shown in the study of Hirschson et al., (3) in the prognosis of patients with NSTEMI.

Conflicts of interest

None declared

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