

Inflammatory and Anti-Inflammatory Markers in Acute Coronary Syndromes. Ready for Use in the Clinical Setting?

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Our knowledge and understanding of the pathophysiology of coronary atherosclerosis has increased enormously over the last 20 years. During the 1980s the importance of thrombosis in the development of acute coronary syndromes (ACS) and the growth of atherosclerotic plaques was described. Later, in the 1990s, it became clear that inflammation was involved in the initial pathophysiology, development and rupture of the latter. The links between thrombotic and inflammatory phenomena were also recognized.

Inflammation in atherosclerosis is a vascular response to a great variety of damage-causing stimuli. The process is characterized by the movement of cells from the vascular lumen towards the arterial wall at the site of the stimulus, under the influence of locally produced chemotactic factors.¹ When the inflammatory stimulus is persistent or continually repeated, a chronic inflammatory lesion is produced. The immune cell infiltrate typical of chronic inflammation involves macrophages, lymphocytes and plasma cells. The chronic release of inflammation mediators produces a tissue lesion, scarring, and possibly a loss of tissue function.

We currently know of dozens of molecules involved in the process leading to atherosclerosis. Some of these have opposite effects, depending upon the cells on which they act or even environmental conditions. It has been proposed that some of these might be used as markers of the risk of suffering acute coronary events.

Ideally, a marker should be detectable in blood, tissue or urine samples and be either causally related to the disease in question or be a consequence of it, and

thus indirectly related to it. A risk marker should offer diagnostic, prognostic and therapeutic information. It should be able to precisely predict the onset of an event (i.e., it should show excellent sensitivity and specificity), be independent of other markers, and results should be reproducible. It should also be easily and rapidly measured, cost-effective, and should be related significantly to the clinical course of disease. For a marker to be clinically useful, other background conditions need to be met, e.g., the association between the marker and the disease should be observable in independent studies, the results of studies providing biological evidence of the relationship between the marker and the disease should be available, and finally, it should be demonstrated that the modification of marker levels improves patient prognosis. An excellent example of clinically useful markers in ACS is provided by the troponins.

The family of inflammation markers known as the acute-phase reactants (the members of which include C-reactive protein, fibrinogen, sialic acid and serum protein amyloid A levels, the leukocyte count, and the erythrocyte sedimentation rate) has received more attention than most. Over the last 50 years, the association between leukocytosis and the prognosis associated with cardiovascular disease has become apparent.^{2,3} Recently, Danesh et al⁴ reported a meta-analysis that assessed the role of different acute phase reactants in the prognosis of ischemic heart disease. The results corroborated the association between the leukocyte count and this disease. Patients with leukocyte numbers in the highest tertile had a relative risk of coronary artery disease of 1.5 (95% CI, 1.4-1.6) compared to patients in the lowest tertile. Later studies with over 350 000 patients have nearly all confirmed this relationship: patients with high leukocyte counts show significantly higher acute and chronic mortality rates than those with low leukocyte counts.

However, despite the robustness of this relationship, the leukocyte count may be no more than a non-specific marker of other processes that increase the risk of ischemic heart disease. We now know that many of the classic risk factors (smoking, diabetes mellitus, obe-

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sity, hypercholesterolemia, etc) are associated with chronic inflammation.⁵ Therefore, leukocytosis may be just another non-specific marker of the state of chronic inflammation, the direct cause of vascular disease involving other inflammatory processes. However, a number of pathophysiological mechanisms are known via which leukocytes could be involved in the outcome of this disease, e.g., an enhancement of prothrombotic conditions (increase in the level of tissue factor, greater association with activated platelets, changes in fibrinogen levels, greater quantities of circulating aggregates) or vascular effects (changes in hemorheology, an increase in the concentration of superoxide radicals, cytokines or myeloperoxidase, the acceleration of atherosclerosis via an increase in the oxidation of low and high density lipoproteins, and a greater infiltration of monocytes, etc).⁶

This issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA contains a study by Núñez et al⁷ on the relationship between the leukocyte count of patients admitted to the emergency department with ACS and their mid-long term prognosis. This is a large study with 1118 consecutive patients with acute myocardial infarction with or without a raised ST segment, and which excluded patients with infectious, inflammatory, and blood disease. The results obtained are in line with those of previous studies in which the patient inclusion criteria were stricter, and whose conclusions are therefore less applicable to the general population. The work of Núñez et al⁷ is pragmatic in nature since it attempts to look for a marker that is easily, rapidly and cheaply measured, and whose values are easy to interpret. The results they obtained, which are analyzed with great rigor, show that the leukocyte count obtained in the initial, emergency room blood analysis can provide an early prognostic estimate. However, the coherence between the stated objective and the conclusions prevent us from knowing the true value of the variable studied, as the authors themselves point out in the "Limitations" section. This is so because the multivariate analysis did not include a series of clinical variables of known prognostic importance, such as the ejection fraction, the pharmacological treatment provided, or the revascularization treatment followed (percutaneous or surgical), etc. It is to be hoped that the authors will soon publish their results on the predictive value of the leukocyte count after adjusting for these variables.

Until this point, mention has only been made of inflammatory mechanisms, but all inflammatory responses are attenuated by a corresponding anti-inflammatory response. The mechanisms that stimulate the inflammatory response also stimulate the anti-inflammatory mechanisms that limit the problem. If the inflammatory stimulus is persistent or continually repeated, chronic inflammation occurs. This can lead to tissue destruction and the loss of function of the affected organ. The synthesis of interleukin 10 (IL-10)

is one of the anti-inflammatory mechanisms observed in atherosclerosis. In fact, IL-10 is one of the main anti-inflammatory interleukins.⁸ This cytokine is produced by CD4+ (Th2) T lymphocytes, CD8+ T lymphocytes, some B lymphocytes, monocytes activated by LPS, and mastocytes. Its synthesis is reduced in monocytes by IL-4 and IL-10 itself. It acts on different cell types: it is known to regulate the growth of mastocytes, to inhibit the production of cytokines by activated T cells (i.e., those activated by IL-2, tumor necrosis factor alpha [TNF- α], interferon alpha [INF- α], and granulocyte-macrophage colony stimulating factor [GM-CSF]), to increase the viability of B cells, to inhibit the production of IL-1 α , IL-1 β , IL-6, IL-8, TNF- α , INF- α , GM-CSF, and G-CSF by monocytes, and to inhibit the synthesis of IL-1, IL-6, and TNF- α .⁹ The result is the inhibition of T lymphocyte proliferation, the prevention of macrophage activation, and protection against the lethal effects of bacterial endotoxins in septic shock models. Finally, IL-10 reduces the production of proinflammatory cytokines by Th1 lymphocytes and promotes the Th2-type immune response, which is essential in the fight against inflammation.

This issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA also contains a paper by Domínguez Rodríguez et al¹⁰ that analyzes the anti-inflammatory response inherent to all types of ACS in the context of primary percutaneous revascularization in patients with acute myocardial infarction and with an elevated ST segment. The authors measured IL-10 levels and found that, all other factors being equal, those patients with higher blood concentrations of this cytokine had a better prognosis than those with lower levels. This work allows us to better understand the anti-inflammatory process in acute myocardial infarction and its prognostic importance with respect to the development of heart failure.

Both articles reflect the pathophysiological importance of the inflammatory response in acute ischemic heart disease. However, from a clinical point of view, the current need is not so much to determine whether inflammation is of pathophysiological

importance in ACS, but to find some marker of inflammation that can be rapidly, reliably and cheaply determined and that offers clinical information beyond all statistico-methodological doubt. Most studies on markers of inflammation in ACS published to date have had a nested design. By definition, this methodology precludes a precise knowledge of the sensitivity, specificity, and positive and negative predictive value of a marker. Recently, calculations based on earlier-reported results have been published, although the methodology used has been questioned since the authors did not take into account all the data.¹¹ The provocative results show graphically that what appears to be true for large populations (i.e.,

that which is statistically significant) cannot be easily extrapolated to the individual patient (i.e., that which is clinically important).¹² Reasons exist, however, that cast doubt on the applicability of such results in clinical routine. For example, many of the classic risk factors for atherosclerosis (sex, age, metabolic syndrome, diabetes mellitus, smoking, high blood pressure, etc) and pharmacological treatments (aspirin, statins, fibrates) are known to modify inflammation marker levels. Finally, the variability in the levels of these markers must also be taken into account; some differences in frequency reported as statistically significant are actually smaller than the variability in marker levels.¹³

Another question raised by these studies is whether it is justifiable to attempt to specifically reduce the levels of inflammation markers (e.g., the leukocyte count or reactive protein C levels) or to increase the levels of anti-inflammatory molecules (e.g., IL-10) in the treatment of ACS. A review has recently been published which raises this question.⁶ However, in the case of the leukocyte count, the authors recognize that, at the present time, the treatments that might achieve this are leukemogenic. Any benefits gained might therefore be cancelled out by hematological complications. With respect to IL-10,⁹ a number of complications are foreseeable if this molecule is administered chronically; there may also be unknown effects.

In conclusion, the papers by Núñez et al⁷ and Domínguez Rodríguez et al¹⁰ show the need to continue research into the inflammatory mechanisms of atherosclerosis, and to determine the clinical use of new markers of inflammation that might allow patients with ACS to be adequately stratified. For the time being, and in agreement with the clinical guidelines published by the American Heart Association,¹⁴ there is still insufficient information for these markers to be routinely used in clinical practice.

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