Atherosclerotic Coronary Artery Disease: Usefulness of C-Reactive Protein for the Identification of the "Vulnerable" Plaque and the "Vulnerable" Patient

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Despite advances in basic and clinical cardiovascular research, coronary artery disease remains one of the main causes of death and disability in the western world. Inflammation of the arterial wall is an etiologic and pathogenic mechanism involved in the onset, development and destabilization of the atherogenic process. Indeed, atherosclerosis is currently considered to be an inflammatory disease. Of the many biological markers of this inflammatory process, such as serum amyloid protein A, fibrinogen, white blood cell count, neopterin, endothelial adhesion molecules and cytokines, C-reactive protein (CRP) is the marker which has received most attention over recent years.

Accumulated evidence suggests that high-sensitivity CRP is a predictor of cardiovascular risk in patients with established heart disease and in apparently healthy persons. Indeed, it has recently been suggested that CRP is a more powerful predictor of risk than levels of low density lipoprotein cholesterol (LDL-C) and that it provides added prognostic information to the conventional Framingham score.[1] Arterial inflammation and blood levels of CRP are lowered by several drugs, such as aspirin, reductase inhibitor 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA), angiotensin converting enzyme (ACE) inhibitors, thienopyridines, and peroxisome proliferator-activated receptor (PPAR) agonists, which reduce morbidity and mortality in patients with cardiovascular disease and in apparently healthy subjects. However, whether inhibition of the inflammation and the consequent reduc-

tion in CRP result in a reduction in clinical events is currently unknown. The benefit in terms of mortality resulting from the use of statins or ACE inhibitors cannot be explained simply by their respective lipid lowering or antihypertensive effects; rather they appear to be at least partly mediated by their anti-inflammatory effects. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a primary prevention study in 5742 subjects at low to moderate risk of developing coronary artery events, showed treatment with lovastatin to be highly effective in reducing such events among subjects with baseline LDL-C values above 149 mg/dL (the median LDL-C distribution in the overall study population). However, treatment with lovastatin has also been shown to be just as effective at reducing coronary artery events in subjects with normal LDL-C values and high levels of CRP.[2] The results of this latter study are particularly interesting, not only because they confirm that raised levels of CRP predict cardiovascular risk and that the measurement of CRP together with a lipid workup improves the overall evaluation of risk, but also because they suggest that HMG-CoA reductase inhibitors are even effective in apparently healthy persons with no hypercholesterolemia but who have a tendency to develop cardiovascular events, as detected by raised CRP levels. Indeed, the recent clinical guidelines published by the American Heart Association/Centers for Disease Control and Prevention (AHA/CDC) consider the measurement of high-sensitivity CRP a class IIa recommendation in the stratification of the primary prevention of cardiovascular disease. This is especially so in persons who are at moderate overall risk for coronary events (10%-20% at 10 years, according to the conventional Framingham score), for whom the physician needs additional information before deciding on diagnostic techniques, recommending a more aggressive modification in life-style, or starting cardioprotective therapy with such drugs as aspirin, statins, or ACE inhibitors.[3]

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C-reactive protein is also a predictor of the short- and long-term recurrence of cardiovascular events and death in patients with acute coronary syndromes (ACS), and its prognostic capacity has even been shown independently of other risk markers, such as troponins or B-type natriuretic peptide.[4] In this issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA Sanchís et al[5] analyze the relationship between high-sensitivity CRP, troponin I, and the angiographic complexity of the culprit lesion in 125 patients with non-ST segment elevation ACS and important single coronary vessel disease.[5] The patients in this study with elevated CRP values had more thrombotic culprit lesions, more lesions with a TIMI flow <3 and elevated troponin I concentrations. Sanchís et al[5] therefore suggest that the inflammatory activity of both the vessel wall and the focus of the myocardial necrotic lesion could be involved in the raised CRP levels in patients with ACS. The authors point out, though, that the partial contribution of the arterial inflammation or the necrotic myocardium to the elevation in inflammatory markers depends on the moment these markers are measured. The concentrations of high-sensitivity CRP, measured a median of 72 h after hospital admission, were very widely distributed, with an interquartile range of 6-65 mg/L in those patients with thrombotic lesions. Bearing in mind that 85% of the thrombotic lesions in this study were identified in patients with elevated troponin I levels, it is difficult to determine whether the high CRP concentration in these patients reflects the magnitude of the non-specific inflammatory reaction in the acute phase of myocardial necrosis, or the inflammatory process leading to coronary arteriosclerotic destabilization, or a combination of both mechanisms.

In earlier studies, Katritsis et al[6] found a significant relation between CRP concentrations and the angiographic complexity of the atherosclerotic plaque, specifically with the presence of intracoronary thrombosis, the eccentric location of the lesion and the irregularity of its outline.[6] Although the morphology of the angiographic lesions may identify a high number of vulnerable plaques, not all the angiographic features which define an atherosclerotic plaque as "complex," or type C in the AHA/ACC classification, are the result of an acute inflammatory process or reflect the persistence or activity of the initial atherogenic process. The angiographic markers of complexity are more likely to reflect unstable inflamed plaque in patients with ACS, such as those included in the study by Sanchís et al,[5] than in patients with chronic stable angina. However, it is currently the clinical context, rather than the angiographic morphology of the lesion, which defines the acute inflammatory instability of the plaque. Studies by our group showed that the correlation between CRP and the angiographic complexity of the plaque in patients with ACS was not seen in pa-

tients with chronic stable angina.[7-9] The ulceration, irregularity and eccentricity, all defining elements of a complex plaque, may represent rupture of a partially scarred plaque, a recanalized thrombotic lesion or the sequelae of a ruptured plaque in patients with stable angina, not necessarily an acute inflammatory event. It is the composition (e.g. cell infiltrate, lipid nucleus and inflammatory molecules) rather than the angiographic morphology which really determines the vulnerability of the atherosclerotic plaque. Nonetheless, despite the inherent limitation of angiography in characterizing the composition of the plaque, angiographic evaluation of the complexity correlates strongly with the vulnerability assessed by intravascular ultrasound (IVUS).[10] Clinical and pathologic studies have confirmed the direct association of CRP and inflammatory mechanisms with plaque vulnerability. Moreover, these studies have shown that patients with ACS have generalized pancoronary inflammation which leads to the development of multiple vulnerable, complex plaques.[11-14] Buffon et al[11] found widespread inflammatory activity throughout the coronary tree, independently of the location of the culprit lesion. Rioufol et al[12] also found evidence of this pancoronary involvement when they used IVUS to identify at least 2 plaque ruptures in 79% of the patients with ACS. The same results were obtained with angioscopy[13] and in pathologic *post mortem* samples. The measurement of inflammatory markers such as CRP may represent an advance in this sense and provide the physician with a feasible marker to identify which lesions and which patients have an inflammatory process capable of triggering an acute coronary event. Studies by our group in patients with ACS have shown a close correlation between different markers of inflammation, including CRP, neopterin, and neutrophil count, and the number of angiographically complex lesions, a reflection of destabilization and increased pancoronary vulnerability.[7,8] Our results indicate that CRP is a marker of the clinical activity in patients with coronary disease and that it may be considered a biological marker of the diffuse inflammatory process leading to the multifocal coronary destabilization which causes acute coronary events and progression of coronary disease. In this respect, the study by Sanchís et al[5] also provides relevant information as, despite studying only patients with single vessel disease, CRP was significantly related to markers of clinical and angiographic instability of the atherosclerotic coronary process. Apart from this prognostic capacity, CRP provides no additional clinical information to that given by the patient's symptoms, electrocardiographic changes and elevation of the markers of myocardial damage (troponin I or T) regarding the indication for diagnostic procedures and medical or invasive therapy. Studies of CRP and other markers of inflammation in patients with ACS do, however, provide important pathophysiological informa-

tion about the involvement of inflammatory mechanisms in the destabilization of the atherogenic process and the development of complex plaque. Rather than a mere biological marker, CRP has recently been suggested to be a cardiovascular risk factor directly involved in the genesis of vulnerable atherosclerotic plaque. CRP exerts a multitude of effects on the endothelial biology, favoring a proinflammatory and proatherogenic phenotype: CRP reduces the transcription of endothelial nitric oxide synthase (eNOS), increases levels of endothelin 1 (ET-1) and promotes the expression of endothelial adhesion molecules (ICAM-1, VCAM-1) and chemotactic proteins (MCP-1). Results of preliminary studies even suggest that CRP activates the signaling pathway of the nuclear transcription factor kappa B (NF-κB) in endothelial cells, reducing the differentiation and survival of endothelial stem cells. The proatherogenic effects of CRP are not restricted just to endothelial involvement, they increase the expression of the angiotensin type 1 receptor (AT_1-R) in smooth muscle cells, promoting their proliferation and migration, as well as the production of free oxygen radicals.[15]

The high risk of recurrence of cardiovascular events in patients with elevated CRP concentrations, the involvement of inflammatory markers in the genesis of vulnerable plaque and the findings of the interesting study by Sanchís et al,[5] particularly the relation between CRP and the presence of a thrombotic culprit lesion or a TIMI<3, or both, give rise to a series of important clinical questions which should be investigated with specially designed studies. Bearing in mind the close relation between CRP and the vulnerability and complexity of the culprit lesion, do high CRP concentrations recommend percutaneous coronary intervention (PCI) with the concomitant use of stents and glycoprotein IIb/IIIa inhibitors?, do they recommend the use of distal protection devices during PCI?, do they recommend prior treatment with statins, even in patients with normal cholesterol figures? Moreover, given the high risk of events after PCI in patients with elevated CRP concentrations,[16] should PCI be delayed until the CRP concentration is normalized? Independently of any action to stabilize the culprit lesion clinically, and considering the usefulness of CRP as a biological marker of pancoronary vulnerability,[7,8,14] the identification by CRP of the "vulnerable" patient and a medical strategy based on lowering CRP concentrations after progressive establishment of drugs with proven arterial anti-inflammatory effects (aspirin and clopidogrel, statins, ACE inhibitors, PPAR agonists such as fibrates and thiazolidinediones, and perhaps beta-blockers) could control, or even revert, the atherosclerotic inflammatory process and reduce the risk of death, myocardial infarction, or stroke, as well as the requirement for revascularization and rehospitalization. Finally, we should also ask

whether CRP is really the most suitable marker of inflammation to identify the risk of recurrence of cardiovascular events in patients with ACS. The "Systemic Inflammation Evaluation in patients with non-ST segment elevation Acute coronary syndromes" (SIESTA) study[17] was designed for this purpose and its results are expected in the coming months. According to results from earlier studies and the findings of Sanchís et al,[5] the use of markers of inflammation may well represent an important advance in the identification of vulnerable patients. These patients could then clearly benefit from the establishment of therapies which prevent progression of coronary disease and development of cardiovascular events.

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