Inflammatory markers of ischemic coronary syndromes

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Inflammation detectable by systemic markers has recently emerged as an accompanying and prognostic feature of atherosclerosis and ischemic coronary syndromes[1,2]. Ross[3] has recently highlighted that biochemical and cell biological data support the fact that inflammation is involved in all stages of atherosclerosis, including oxidative damage, cell proliferation and plaque development. Recent experimental evidence also implicates inflammation in plaque instabilization and in the following precipitation of acute coronary syndromes[4]. In response to endothelial injury a focal inflammatory response arises which can lead to plaque instability and rupture and then to acute coronary syndrome.

The involvement of inflammation in the clinical manifestation of ischemic heart disease was first postulated by explaining the association between the acute phase reactant fibrinogen and the ischemic cardiovascular events[5-9]. Subsequent studies[10,11] have focused the attention on C-reactive protein, another acute phase reactant produced by the liver, demonstrating its predictive value in coronary syndromes. In particular, Ridker et al.[12] have observed in normal subjects that the plasma levels of C-reactive protein (even within the normal range) are long-term predictors of myocardial infarction or stroke, independently of traditional risk factors. This, in addition to the short-term prognostic value of elevated serum levels of C-reactive protein in patients with unstable angina[10], suggests that activation of the inflammatory system may represent a marker of susceptibility for ischemic heart disease potentially based on a genetic ground[13].

Fibrinogen and C-reactive protein are not the only markers of inflammation and inflammation-sensitive cardiovascular risk factors. Several investigators have evaluated the role and the clinical significance of cytokines in the setting of acute coronary syndromes, given their regulatory activity in the autoimmune and inflammatory responses. Proinflammatory cytokines, such as interleukin (IL)-1α and IL-1β, have been implicated in the pathogenesis of several inflammatory diseases[14]. IL-1 is mainly produced by macrophages, endothelial cells, keratinocytes, and vascular smooth muscle cells. It acts on a common receptor for IL-1α and IL-1β[15], and has overlapping biological activities with tumor necrosis factor (TNF) and IL-6[16]. Its natural inhibitor, the IL-1Ra, is a protein structurally related to IL-1α and IL-1β, and competes with these molecules for occupancy of the IL-1 cell-surface receptor. IL-1Ra acts as a competitive inhibitor[17,18], and has been shown to be a powerful endogenous anti-inflammatory agent[16,19]. The balance between cytokine production, receptor expression and inhibitor levels seems to be one of the major factors in determining the outcome of the inflammatory response.

Latini et al.[20] have found elevated levels of IL-1Ra, TNF-α and TNF-α soluble receptor in patients with acute myocardial infarction complicated by severe congestive heart failure, but not in those with an uncomplicated course or in control subjects. Biasucci et al.[21] observed that elevated serum levels of IL-6 and IL-1Ra are common in patients with unstable angina, correlate with C-reactive protein levels, and are associated with a poor prognosis. Moreover, Neumann et al.[22] have documented, in patients with acute myocardial infarction undergoing primary angioplasty, a cardiac inflammatory response during

reperfusion (not found in a control group), characterized by an increased cardiac release of IL-6 and IL-8 and by neutrophil activation. Recently Shibata et al.[23] have found that increased plasma levels of IL-1Ra and IL-10 correlated with the clinical severity and hemodynamic instability of patients with acute myocardial infarction. These data suggest a role for IL-1Ra and members of the IL-1 family as prognostic markers in acute ischemic heart disease. In the setting of chronic stable angina, a relation between systemic levels of IL-1β and the angiographic extent of coronary artery disease has been found[24]. Recently our data have shown that IL-1Ra identifies patients with coronary artery disease and clinical instability on admission with greater sensitivity than C-reactive protein[25]. Moreover we observed a significant reduction in IL-1Ra and C-reactive protein serum levels 6 months after successful coronary angioplasty in patients with pre-procedural unstable angina and without evidence of myocardial ischemia during follow-up. Thus, a decrease in IL-1Ra may represent a favorable prognostic factor in revascularized cardiac patients; conversely a lack of reduction may indicate persistent myocardial ischemia or restenosis.

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