

Inflammatory markers of ischemic coronary syndromes

Alessandro Manzoli, Giuseppe Patti*, Germano Di Sciascio*

*Department of Cardiocirculatory System, Hospital S. Giovanni-Addolorata, *Department of Cardiovascular Sciences, University Campus Bio-Medico, Rome, Italy*

(Ital Heart J 2001; 2 (Suppl 3): 29S-30S)

© 2001 CEPI Srl

Address:

Dr. Alessandro Manzoli

*Dipartimento Apparato
Cardiocircolatorio
Ospedale S. Giovanni-
Addolorata
Via dell'Amba Aradam, 9
00149 Roma
E-mail: alemanzoli@
yahoo.it*

Inflammation detectable by systemic markers has recently emerged as an accompanying and prognostic feature of atherosclerosis and ischemic coronary syndromes^{1,2}. Ross³ 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 syndromes⁴. 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 events⁵⁻⁹. 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 angina¹⁰, suggests that activation of the inflammatory system may represent a marker of susceptibility for ischemic heart disease potentially based on a genetic ground¹³.

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)-1 α and IL-1 β , have been implicated in the pathogenesis of several inflammatory diseases¹⁴. IL-1 is mainly produced by macrophages, endothelial cells, keratinocytes, and vascular smooth muscle cells. It acts on a common receptor for IL-1 α and IL-1 β ¹⁵, and has overlapping biological activities with tumor necrosis factor (TNF) and IL-6¹⁶. Its natural inhibitor, the IL-1Ra, is a protein structurally related to IL-1 α and IL-1 β , 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-1 β and the angiographic extent of coronary artery disease has been found²⁴. 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 protein²⁵. 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.

References

1. Berliner J, Navab M, Fogelman A, et al. Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics. *Circulation* 1995; 340: 115-26.
2. De Caterina R. Polymorphisms related to inflammation in the interleukin-1 system genes: a step forward in the search for predisposing conditions to ischemic heart disease. *Cardiologia* 1999; 44: 831-4.
3. Ross R. Atherosclerosis - an inflammatory disease. *N Engl J Med* 1999; 340: 115-26.
4. Buja L, Willerson J. Role of inflammation in coronary plaque disruption. *Circulation* 1994; 89: 503-5.
5. Meade TW, Mellows S, Brozovic M, et al. Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. *Lancet* 1986; 2: 533-7.
6. Wilhelmsen L, Svardsudd K, Korsan-Bengtson K, et al. Fibrinogen as a risk factor for stroke and myocardial infarction. *N Engl J Med* 1984; 311: 501-5.
7. Yarnell J, Sweetnam P, Elwood P, et al. Haemostatic factors and ischaemic heart disease: the Caerphilly study. *Br Heart J* 1985; 53: 483-7.
8. Kannel W, Wolf P, Castelli W, et al. Fibrinogen and risk of cardiovascular disease: the Framingham study. *JAMA* 1987; 258: 1183-6.
9. Thompson S, Kienast J, Pyke S, et al. Haemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. *N Engl J Med* 1995; 332: 635-41.
10. Liuzzo G, Biasucci LM, Gallimore JR, et al. The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. *N Engl J Med* 1994; 331: 417-24.
11. Haverkate F, Thompson S, Pyke S, et al. Production of C-reactive protein and risk of coronary events in stable and unstable angina. *Lancet* 1997; 349: 462-6.
12. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336: 973-9.
13. Maseri A. Inflammation, atherosclerosis and ischemic events: beginning to explore the hidden side of the moon. *N Engl J Med* 1997; 336: 1014-6.
14. Duff GW. Peptide regulatory factors in non-malignant disease. *Lancet* 1989; 1: 1432-5.
15. Dinarello CA. Interleukin-1 and interleukin-1 receptor antagonist. *Blood* 1991; 77: 1627-52.
16. Dinarello CA, Thompson RC. Blocking IL-1: interleukin-1 receptor antagonist in vivo and in vitro. *Immunol Today* 1991; 12: 404-10.
17. Eisenberg SP, Evans RJ, Arend WP, et al. Primary structure and functional expression from complementary DNA of a human interleukin receptor antagonist. *Nature* 1990; 343: 341-6.
18. Manzoli A, Andreotti F, Varlotta C, et al. Allelic polymorphism of the interleukin-1 receptor antagonist gene in patients with acute or stable presentation of ischemic heart disease. *Cardiologia* 1999; 44: 825-30.
19. McIntyre KW, Stepan GJ, Kolinsky KD, et al. Inhibition of interleukin-1 (IL-1) binding and bioactivity in vitro and modulation of acute inflammation in vivo by IL-1 receptor antagonist and anti-IL-1 monoclonal antibody. *J Exp Med* 1991; 173: 931-9.
20. Latini R, Bianchi M, Correale E, et al. Cytokines in acute myocardial infarction: selective increase in circulating tumor necrosis factor, its soluble receptor, and interleukin-1 receptor antagonist. *J Cardiovasc Pharmacol* 1994; 23: 1-6.
21. Biasucci LM, Liuzzo G, Fantuzzi G, et al. Increasing levels of interleukin (IL)-1 Ra and IL-6 during the first two days of hospitalization in unstable angina are associated with increased risk of in-hospital coronary events. *Circulation* 1999; 99: 2079-84.
22. Neumann FJ, Marx N, Gawaz M, et al. Cardiac release of cytokines and inflammatory responses in acute myocardial infarction. *Circulation* 1995; 92: 748-55.
23. Shibata M, Endo S, Inada K, et al. Elevated plasma levels of interleukin-1 receptor antagonist and interleukin-10 in patients with acute myocardial infarction. *J Interferon Cytokine Res* 1997; 17: 145-50.
24. Ikonomidis I, Andreotti F, Economou E, et al. Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin. *Circulation* 1999; 100: 793-8.
25. Patti G, Abbate A, D'Ambrosio A, et al. Long-term variations of interleukin-1 receptor antagonist and C-reactive protein serum levels after successful coronary angioplasty. (abstr) *Eur Heart J* 2000; 21 (Suppl): 164.