

3. ROLE OF INFLAMMATION IN THE PATHOGENESIS OF ACUTE CORONARY SYNDROMES

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Acute coronary syndromes share with other forms of ischemic heart disease a common atherosclerotic and thrombotic background, but are characterized by the sudden development of a life-threatening condition associated with plaque destabilization and thrombus formation. The evidence that plaque rupture may account for only about 60% of causes of myocardial infarction, and that all the well-established risk factors, such as cholesterol, smoking, familiarity and so on, may explain no more than half of the cases of myocardial infarction, suggest that the causes of acute coronary syndromes cannot be confined to atherosclerosis and thrombosis. Nowadays, a growing body of evidences suggests that inflammation plays a pivotal role among the different factors that are involved with the development of acute coronary syndromes, and that assessment of inflammatory markers may be clinically useful in these syndromes.

3.1 Histological features of unstable plaques

In patients with unstable angina, coronary atherosclerotic plaques are characterized by the presence of foam cells, macrophages, lymphocytes and mast cells [1]. These cells were found to be particularly abundant in the shoulder region of the plaques, an area of predilection for disruption and have been found to be activated. As macrophages are capable of degrading extracellular matrix by secreting proteolytic enzymes, these cells are likely to play an important role in plaque disruption and activation. The results of post-mortem studies of patients who died of acute ischemic syndromes have been confirmed by in vivo studies of atherectomy specimens from culprit lesions responsible for unstable rest angina or non-Q-wave MI.

3.2 Systemic markers of inflammation

3.2.1 Inflammatory Cells Activation

Neutrophils and monocytes have been shown to be activated in acute coronary syndromes by several authors, confirming previous epidemiological data linking leukocyte number and risk of a future myocardial infarction. Inflammatory cells may be involved in develop-

ment of a procoagulant state, as reported by Neri Serneri et al. [2], who also proposed that unstable angina is associated with an acute transient burst of inflammation, with lymphocyte activation triggered by unknown factors.

3.3 Serological markers

Evidence of increased levels of fibrinogen and of other acute-phase proteins were already available in literature from the eighties but, only in last 5 years, accumulating data on the role of the prototypic acute phase reactant C-Reactive Protein (CRP) have established a role for serological markers of inflammation in acute coronary syndromes. In 1994 we [3] observed that CRP and serum amyloid A protein (SAA) were elevated on admission in the majority of unstable patients who had complicated in-hospital courses. The absence of an associated elevation of troponin T, ruled out the possibility that the acute-phase response was caused by myocardial necrosis; subsequently we also ruled out the possibility that the acute phase response was caused by thrombus formation or ischemia. As CRP and SAA are produced in the liver under stimulation by γ -interleukin-6 (IL-6) and interleukin 1 (IL-1), we also assessed the levels of these two cytokines and found that not only are they elevated in patients suffering of acute coronary syndromes, but also that they are associated with prognosis (4). Recently in patients with acute myocardial infarction the response of acute-phase proteins to necrosis was found to be independent of the area of necrosis, but dependent on the baseline CRP levels; these observations may open the way to novel patho-physiological approach to acute coronary syndromes, including the possibility that an hyper-responsive state may exist in patients with acute coronary syndromes. CRP has been consistently shown to be a reliable marker of subsequent event in unstable angina and non-Q wave infarction, as we have found that elevated levels of CRP predict a poor one-year event-free survival in unstable angina (5). Surprisingly CRP levels have been found to predict the long-term risk of myocardial infarction and stroke up to 8 years after sampling in normal subjects, either at low or at high risk (6)

3.4 Possible causes of inflammation

A variety of stimuli, such as mechanical, anoxic, chemical (oxidized LDL, homocysteine and endotoxin), immunologic or infectious ones, are responsible for activation of the endothelium. Recently Chlamydia pneumoniae has been found to have prothrombotic properties, a characteristic that may represent a link between acute coronary syndromes and this infective agent. Although much claim has been raised on the hypothesis that the plaque plays a central role in acute coronary syndromes and in the inflammatory process, an intriguing observation is that the inflammatory process is likely to be rather diffuse, and not confined to a single plaque. We have found that patients with unstable angina and increased levels of CRP have an

exaggerated production of both IL-6 and CRP after PTCA and after coronary angiography. This suggests that plaque rupture is not a crucial mechanism in the inflammatory process in acute coronary syndromes, and confirms that the inflammatory system may hyper-react to different stimuli.

3.5 Conclusions

Inflammation is a major finding in unstable angina and infarction, and may represent a leading cause of destabilization. No information is yet available on the causes of inflammation, or on its systemic or coronary localization, however accumulating evidences indicates that serological markers of inflammation, and in particular the prototypic acute phase protein CRP may be clinically useful in the prognostic stratification, and, in the near future in the tailoring of appropriate therapy to patients with acute coronary syndromes.

Recommended literature:

- 1 Hansson GK, Holm J, Jonasson L. Detection of activated T lymphocytes in the human atherosclerotic plaque. *Am J Pathol* 1989; 135:169-75.
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- 4 Biasucci LM, Vitelli A, Liuzzo G, Altamura S, Caligiuri G, Monaco C, Rebuzzi AG, Ciliberto G, Maseri A. Elevated levels of interleukin-6 in unstable angina. *Circulation* 1996; 94:874-7.
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- 6 Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336:973-9.