

# Review Article

## Inflammation in Acute Coronary Syndrome

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### Abstract

This article reviews the role of inflammation in coronary artery disease, particularly its conversion from a chronic to an acute illness. An overview is provided about various inflammatory markers and their role in inflammation which lead to the development and progression of atherosclerotic vascular disease and its clinical consequences, especially acute coronary syndromes. The very episodic nature and the common short duration of acute coronary syndromes suggest the role of inflammatory stimuli. Causes of inflammation may be multiple and not necessarily the same in all patients, and their effect is probably modulated by the individual immunological and inflammatory response.

**Key Words:** Atherosclerosis, Coronary inflammation, Thrombosis, Vasoconstriction.

### Introduction

Inflammation is becoming an intriguing focus of research as a possible pathogenetic component and therapeutic target in ischemic heart disease. However, the potential links between inflammation and ischemic heart disease are present at three levels at least. First, the inflammatory response has been known for many years to play a major role in schamaemia/reperfusion injury, and its reduction can limit myocardial damage<sup>1</sup>. Second, inflammation is a very common feature of the chronic atherosclerotic process, as first described by Virchow in 1856<sup>2</sup> and recently comprehensively reviewed by Ross<sup>3</sup>. Finally, inflammation may be an acute pathogenetic component of instability in approximately half of patients with acute coronary syndromes (ACS), independently of the atherosclerotic and ischaemic burdens<sup>4</sup>.

There may be several actual triggers of inflammation. The inflammatory response may influence prognosis through modulating the consequences of ischemia and necrosis in some individuals, through sudden development of instability, or through atherogenesis in others. The present review focuses on the independent role of inflammation in ACS.

The final common pathway through which instability precipitates ACS is represented by a variable combination of coronary thrombosis and vasoconstriction in epicardial arteries and in resistive coronary vessels, superimposed on a variable atherosclerotic background<sup>5</sup>. Thrombosis is the most obvious acute component, spasm and vasoconstriction are transient, however, and can only be detected by chance, when critical stenoses are relieved by nitrates<sup>6</sup>, or by design, when provocative tests are used<sup>7,8</sup>; coronary microvascular constriction can only be inferred by special studies<sup>9</sup>.

A substantial percentage of patients do not respond sufficiently to thrombolytic, anticoagulant and antiplatelet agents. Moreover, at 4–6 months after hospital discharge, patients with ACS in the aggressive arms of interventional<sup>10</sup> and medical trials<sup>11</sup> still have a 9–12% incidence of major cardiac events. Thus, only a clearer understanding of the actual triggers of instability could lead to major improvements in therapeutic efficacy.

### Elevated inflammatory markers associated with adverse prognosis

Elevated values of circulating inflammatory markers, such as CRP, serum amyloid A protein, interleukin-6 (IL-6) and interleukin-1 (IL-1) receptor antagonist, are commonly found in ACS. Such elevation is associated with in-hospital and short-term adverse prognosis<sup>12–19</sup>, and may reflect a primary inflammatory trigger of coronary instability.

The contribution of each of these secondary and primary mechanisms of inflammation to prognosis may vary in different groups of patients according to the criteria used for their selection. In turn, the short-term prognostic role of elevated CRP levels in ACS may be at least partly correlated with the long-term prognostic role of CRP levels within the normal range in normal individuals<sup>20,21</sup> and with that of elevated levels in chronic coronary disease<sup>22</sup>.

### C-Reactive Protein (CRP)

CRP is the inflammatory marker receiving the most attention to date. It is an acute phase reactant normally present in plasma at low levels, and increases > 100-fold in response to inflammatory stimuli. It is produced by hepatocytes in response to stimulation by IL-6. It is also produced by human coronary artery smooth muscle

cells.<sup>23</sup> Although initially considered only a "marker" of inflammation, CRP itself has been shown to possess proinflammatory and proatherogenic properties. It stimulates endothelial cells to express adhesion molecules and secrete cytokines<sup>24,25</sup> and it decreases the expression of endothelial NO (Nitric Oxide) synthase.<sup>26</sup> CRP accumulates in macrophage-rich regions of nascent atherosclerotic lesions and activates the macrophages to express cytokines and tissue factor, while enhancing macrophage uptake of LDL (Low Density Lipoproteins).<sup>27</sup> It also amplifies proinflammatory effects of several other mediators including endotoxin.<sup>28,29</sup> In a post mortem study of 302 autopsies of men and women with atherosclerosis, median CRP levels were higher with acute plaque rupture than in stable plaques or controls.<sup>30</sup> The levels correlated with the staining intensity for CRP in macrophages and the lipid core of plaques, and it increased with the number of thin cap atheromas found in coronary arteries.

Plasma CRP levels at the upper end of the reference range in apparently healthy men and women, in the absence of other sources of inflammation, correlated with increased risk of future cardiovascular events, including myocardial infarction (MI), peripheral vascular disease with claudication and stroke.<sup>31</sup> These data support the view that systemic CRP accurately reflects the number of vulnerable atherosclerotic plaques.

Unfortunately, many other factors affect CRP. For example, CRP levels are related to abdominal obesity.<sup>32</sup> They are elevated in patients with metabolic syndrome and type 2 diabetes, and CRP levels correlate with the severity of the glycemic state and insulin resistance.<sup>33-35</sup> In a German health and nutrition survey, there was an almost linear relation between the number of components of the metabolic syndrome and median CRP concentrations.<sup>36</sup> Cigarette smoking is the strongest environmental stimulus for CRP production. Current smokers usually have 2-fold higher concentration of both fibrinogen and CRP compared with those who never smoked. Hormone replacement therapy (HRT) raises CRP, and levels were 2 times higher in 493 healthy post-menopausal women in the Women's Health Study who were taking HRT than among women not taking HRT. The difference was present in all subgroups, including those with no history of hypertension, hyperlipidemia, obesity, diabetes, cigarette consumption or a family history of premature coronary artery disease.<sup>37</sup> Renal insufficiency (serum creatinine > 1.3 mg/dl in women and > 1.5 mg/dl in men) was independently associated with elevations in CRP, which may explain in part the increased cardiovascular risk in patients with kidney disease<sup>38</sup>.

## Myocardial necrosis and ischaemia

The first demonstration that elevated CRP is correlated with adverse short-term prognosis, independently of necrosis and ischaemia, was provided by Liuzzo et al<sup>13</sup>. Those investigators studied selected patients with unstable angina, in Braunwald class IIIB, who had no evidence of myocardial necrosis and an ischaemic burden similar to that of necrosis and an ischaemic

burden similar to that of patients without CRP elevation. Those findings were subsequently corroborated by the observed absence of CRP elevation in patients with variant angina and large ischaemic burden<sup>39</sup> and by the persistence of elevated CRP values in 50% of unstable patients after discharge, which were associated with recurrent episodes of instability and infarction<sup>16</sup>. The in-hospital and short-term prognostic value of elevated CRP level, independently of necrosis, ischaemia and atherosclerosis, suggests that inflammation may play a primary pathogenetic role in the development of instability in at least some patients with ACS.

## Cytokines

IL-6 (an interleukin) is the major cytokine of the acute phase response and is intimately involved in the pathogenesis of ACS<sup>40</sup>. It stimulates production of fibrinogen and CRP, triggers the expression of adhesion molecules and TNF (Tumour Necrosis Factor), stimulates macrophages to produce tissue factor and MMPs, and stimulates vascular smooth muscle cell proliferation and platelet aggregation.

Data from the FRISC-II study group found that circulating levels of IL-6 are a strong independent marker of increased mortality among patients with unstable angina and may be useful in directing subsequent care<sup>41</sup>. As seen with other markers of increased risk, an early invasive strategy led to a 65% relative reduction in 1-year mortality among patients with elevated IL-6 levels. By contrast, among those with low IL-6 levels (i.e., lower risk), an early invasive strategy did not confer any significant benefit over a noninvasive strategy.

Furthermore, among patients randomized to the non-invasive arm, the risk associated with elevated IL-6 levels was markedly attenuated if they were assigned to therapy with dalteparin rather than placebo.<sup>42</sup>

**TNF- $\alpha$**  is a cytokine produced by a variety of cells, including macrophages, endothelial cells and smooth muscle cells. It has an essential role in the amplification of the inflammatory cascade. High levels of TNF-identify stable patients with CAD at risk for recurrent cardiovascular events<sup>43</sup>, but its short plasma half-life has limited its clinical utility as a screening tool.

## CD40 Ligand

CD40L is a transmembrane protein that is structurally related to TNF-. Soluble CD40L (sCD40L) is released from both stimulated lymphocytes and activated platelets.

## Lipoprotein-Associated Phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>)

The West of Scotland study group reported that baseline levels of Lp-PLA<sub>2</sub> were a strong independent predictor for incident coronary heart disease in a cohort of high-risk hyperlipidemic men.<sup>44</sup> The results showed that those with the highest levels of Lp-PLA<sub>2</sub> had twice the risk of an event compared to those with

the lowest levels, even after adjustment for traditional risk factors and other inflammatory mediators, including CRP.

Elevated PLA<sub>2</sub> has also been associated with increased risk of cardiovascular events in women.<sup>45</sup> The Atherosclerosis Risk in Communities (ARIC) study showed that elevated levels of Lp-PLA<sub>2</sub> are higher in incident coronary disease cases. In individuals without elevated LDL levels (i.e., < 130 mg/dl), Lp-PLA<sub>2</sub> levels were independently associated with coronary disease, even after adjustment for traditional risk factors and CRP.<sup>46</sup>

## Matrix Metalloproteinases (MMPs)

MMPs are a family of enzymes involved in the focal destruction of extracellular matrix. Recent findings have revealed enhanced expression of MMP in the shoulder regions of plaque at sites where fissuring is commonly observed. This renders plaque more susceptible to mechanical stresses and therefore more vulnerable to rupture.

Inflammatory mediators, such as TNF- $\alpha$ , CD40L and IL-1, upregulate MMP activity in macrophages and this interaction may represent a link between inflammation and plaque degeneration. Circulating MMP-1, -2 and -9 were elevated on admission in patients with acute MI and unstable angina, and high levels of MMP-9 were identified in atherectomy specimens from patients with recent plaque rupture.<sup>47-51</sup>

## Cellular Adhesion Molecules

In the ARIC study, subjects in the highest quartile for ICAM-1 had more than 5 times the risk for incident coronary heart disease or carotid atherosclerosis compared with subjects in the lowest quartile, even after adjustment for other risk factors. The findings from ARIC were confirmed in the Physicians' Health Study,<sup>52</sup> in which relative risk for MI was 1.6 in men with circulating or soluble ICAM-1 in the highest quartile compared with the lowest. This association persisted after adjusting for other risk factors, and in multivariate analyses, the risk for MI was 80% higher in men with sICAM-1 in the highest quartile.

## Prevalence of inflammation

In patients with ACS the prevalence of a primary inflammatory pathogenetic component of coronary instability, as detected by elevated CRP level, varies considerably. Elevated CRP (above 3 mg . l<sup>-1</sup>) is found in fewer than 10% of normal individuals and in fewer than 20% of patients with chronic stable or variant angina. However, elevated CRP is found in more than 65% of patients with unstable angina and Braunwald class IIIB, and in more 90% of patients with acute infarction preceded by unstable angina, but in fewer than 50% of those in whom the infarction was totally unheralded (in samples taken before elevation of markers of necrosis)<sup>13,19,53</sup>.

The absence of elevated CRP in over 30% of patients with severe unstable angina and in over 50% of those with acute myocardial infarction not preceded by unstable angina suggests that inflammation may not be the trigger of coronary instability in all patients.

## Chronic inflammatory component of atherosclerosis

Angiographic studies show that the severity and extension of coronary atherosclerosis is significantly less in patients who first present with infarction or unstable angina than in those who first present with chronic stable angina<sup>54,55</sup>. Moreover, the results of the International Pooling Project show that, in approximately half of the individuals older than 50 years who died from non-cardiac causes, about 50% of the coronary intima is covered by raised fibrous plaque.

## Inflammatory stimuli

None of the putative inflammatory stimuli, either infectious (e.g. Chlamydia pneumoniae, Helicobacter pylori and cytomegalovirus) or non-infectious (e.g. oxidized lowdensity lipoprotein, homocystein and toxins), appear to be a sufficiently prevalent cause of instability<sup>16,56-61</sup>. The incidence of seropositivity for infectious agents in patients with ACS is higher than that in control individuals, but is not significantly different from that found in patients with chronic stable coronary disease, and some patients with ACS are seronegative.

Finally, seropositivity for infectious agents does not correlate with elevated levels of CRP<sup>16</sup>. A more likely inflammatory cause of instability appears to be related to immunologically mediated mechanisms<sup>62-66</sup>, which may develop in response to a variety of infectious and non-infectious stimuli.

Unusual lymphocytes that undergo clonal expansion and produce large quantities of interferon- $\gamma$  and pro-inflammatory cytokines in response to very restricted antigenic stimulation, which are commonly found in unstable angina, may represent mechanisms of disease similar to those postulated for rheumatoid arthritis.

The poor correlation between potential inflammatory agents and CRP levels may be at least partly explained by a variable individual response to inflammatory stimuli.

## Inflammation as a trigger of instability

An inflammatory trigger of instability fits with some clinical and coronary histopathological features that are prevalent in ACS. It also provides plausible pathogenetic mechanisms of acute thrombosis and vasoconstriction, both of which are also individually modulated.

Waxing, waning and persisting inflammatory stimuli would fit nicely with the clinical pattern of waxing,

waning and recurrent instability lasting some weeks that is common in ACS. Recurring thrombotic stimuli also fit with the common autopsy finding of thrombi formed by separate layers of different age and composed of platelets<sup>67</sup>, which suggests that such thrombi develop as a result of repeated, separate, weak thrombogenic stimuli persisting long enough to allow the progressive accumulation of platelets, but not strong enough to produce an occlusive red thrombus.

## Coronary thrombosis & vasoconstriction

Activation of the vascular wall by pro-inflammatory cytokines causes the endothelium to change its properties from vasodilator and antithrombotic to constrictor and prothrombotic, to express adhesive receptors for circulating leucocytes and for platelets, and to express tissue factor. Such changes, which may be amplified by elevated CRP<sup>68</sup>, appear by themselves sufficient to cause the formation of a local platelet-rich thrombus.

Metalloproteases, produced by activated macrophages, can cause endothelial erosion and rupture of fibrous plaques that, when highly thrombogenic, may provide a stronger stimulus capable of causing rapidly an occlusive red thrombus. For patients without signs of inflammation, typically those with infarction not preceded by unstable angina, the sudden coronary occlusion may be caused by a mechanical rather than inflammatory plaque rupture, by an irreversible coronary spasm, or by a local inflammatory process that is not detectable systemically.

However, thrombus growth is determined by individual haemostatic and vasoconstrictor responses.

## Conclusion

We need to ascertain whether the inflammatory process detected systemically by elevated CRP originates in the coronary arteries or somewhere else in the body; what causes the primary or secondary inflammatory involvement of the coronary arteries; and whether the coronary vulnerable plaques are few or many.

Any single, common, putative trigger cannot explain such rarity. Thus, ACS are either the result of a very exceptional local event or of a very unusual coincidence of multiple, adverse, local and possibly systemic events that may not have the same prevalence in different ethnic, geographical, age and sex groups.

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#### IMMEDIATE "GIK" MAY PREVENT DEATH

In a study presented at the American College of Cardiology's 61st Annual Scientific Session, Dr. Harry P. Selker and his co-investigators, claim that immediate administration of glucose mixed with insulin and potassium ("GIK") in acute coronary syndrome reduces the mortality by 50%. This is based on the assumption that the glucose provides the much needed energy to the ischaemic heart, the insulin helps to transport the glucose into the cells and the potassium corrects the hypokalaemia induced by insulin administration. Besides, the therapy is quite cheap and can be administered by trained paramedics. Whether GIK will be useful or not in a particular case is decided by using predictions of ECG based ACI-TIPI (Acute Cardiac Ischaemia - Time Insentive Predictive Instruments). The beneficial effect of this treatment is not only immediate but persists much longer to reduce the future occurrences of cardiac arrest and heart failure.

- Dr. K. Ramesh Rao

