Inflammation is becoming an intriguing focus of research as a possible pathogenetic component and therapeutic target in ischaemic heart disease. However, the potential links between inflammation and ischaemic 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 ischaemia/reperfusion injury, and its reduction can limit myocardial damage\(^1\). Second, inflammation is a very common feature of the chronic atherosclerotic process, as first described by Virchow in 1856\(^2\) and recently comprehensively reviewed by Ross\(^3\). 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\(^4\).

There may be several actual triggers of inflammation, the individual inflammatory response may vary, and the mechanisms through which inflammation correlates with the development of cardiovascular events in epidemiological studies may be multiple and not necessarily the same in all patients. The inflammatory response may influence prognosis through modulating the consequences of ischaemia 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 and on the short-term and mid-term prognostic value of inflammatory markers.

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 (Fig. 1)\(^5\). Thrombosis is the most obvious acute component, because its frequent persistence makes it detectable at autopsy, angioscopy and angiography. Spasm and vasoconstriction are transient, however, and can only be detected by chance, when critical stenoses are relieved by nitrates\(^6\), or by design, when provocative tests are used\(^7,8\); coronary microvascular constriction can only be inferred and revealed by special studies\(^9\). Thrombosis is also a much more effective therapeutic target as compared with vasoconstriction, because vasodilator drugs, when given systemically, usually do not counter the constrictor effect of substances released by thrombi locally\(^6\).
A substantial percentage of patients do not respond sufficiently to thrombolytic, anticoagulant and antiplatelet agents, but more aggressive treatments tend to increase bleeding complications. Moreover, at 4–6 months after hospital discharge, patients with ACS in the aggressive arms of interventional[10] and medical trials[11] 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.

Growing evidence indicates that in ACS elevated circulating inflammatory markers, in particular C-reactive protein (CRP), are significantly associated with an unfavourable in-hospital and short-term prognosis, and this association is independent of the atherosclerotic and ischaemic burden. A comprehensive assessment of the potential pathogenetic role of inflammation in ACS, which is a key step in the development of novel therapeutic approaches, requires a careful analysis of the prevalence and causes of inflammation, as well as of the mechanisms through which it may trigger instability.

Elevated values of circulating inflammatory markers, such as CRP, serum amyloid A protein, interleukin-6 and interleukin-1 receptor antagonist, are commonly found in ACS. Such elevation is associated with in-hospital and short-term adverse prognosis[12-19], and may reflect not only a high prevalence of myocardial necrosis, ischaemia/reperfusion damage and severe coronary atherosclerosis but also 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[20,21] and with that of elevated levels in chronic coronary disease[22].

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.[13]. 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 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[23] 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[16].

Coronary atherosclerosis

Elevation in CRP levels in unstable patients does not appear to be simply related to the extent and severity of atherosclerosis, because only approximately 20% of patients with chronic stable angina and a high prevalence of multivessel disease have elevated CRP values, as compared with 70% of patients with unstable angina[13]. Those findings were recently confirmed[24]. Moreover, CRP levels in patients with peripheral vascular disease severe enough to require revascularization procedures are not significantly different from those observed in patients with unstable angina and single-vessel disease[25].

Independent inflammatory components

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. Such an independent prognostic role of short-term elevated CRP in ACS is more likely to be detectable in groups of patients without other major determinants of prognosis, such as positive troponins\[15\].

**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 .1\(^{-1}\)) 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).\[13,19,26\]

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 and that its prevalence may vary in different ACS. Whether the long-term predictive value of CRP in normal and in stable patients identifies all patients who develop ACS or only those with elevated CRP is unknown.

**Causes of inflammation**

The very episodic nature and the common short duration of ACS suggest that the inflammatory stimuli that cause the systematically detectable inflammatory process could be unrelated to the chronic inflammatory component of the atherosclerotic background. Its causes may be multiple and not necessarily the same in all patients, and their effect is probably modulated by the individual immunological and inflammatory response.

**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\[27,28\]. Moreover, the results of the International Pooling Project\[29\] 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. Because inflammatory cell infiltrates are also very common in chronic stable coronary disease and present on average only quantitative differences\[30–32\], they cannot by themselves easily explain rare, short-lasting episodes of instability and the very occasional development of infarction. Thus, it would appear reasonable to speculate that the acute inflammatory stimuli that suddenly trigger instability may not be necessarily the same as those most commonly involved in atherogenesis.

**Inflammatory stimuli**

None of the putative inflammatory stimuli, either infectious (e.g. *Chlamydia pneumoniae*, *Helicobacter pylori* and cytomegalovirus) or non-infectious (e.g. oxidized low-density lipoprotein, homocystein and toxins), appear to be a sufficiently prevalent cause of instability\[16,33–38\]. 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\[16\].

A more likely inflammatory cause of instability appears to be related to immunologically mediated mechanisms\[39–43\], 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-β and pro-inflammatory cytokines in response to very restricted antigenic stimulation\[41–43\], which are commonly found in unstable angina, may represent mechanisms of disease similar to those postulated for rheumatoid arthritis.

**Individual response**

The poor correlation between potential inflammatory agents and CRP levels may be at least partly explained by a variable individual response to inflammatory stimuli. The increase in CRP and interleukin-6 observed in response to the vascular trauma caused by coronary angioplasty or by uncomplicated cardiac catheterization\[44\] and that observed after acute infarction\[26\] was found to be linearly correlated to baseline CRP and interleukin-6 levels. This non-specific enhanced response observed in vivo may be related to monocyte responsiveness. Indeed, in vitro, interleukin-6 production by isolated monocytes from unstable patients with elevated CRP and interleukin-6 is significantly greater than that produced by monocytes from patients with normal values\[45\]. Thus baseline CRP values, even those within the normal range, may be indicators of inflammatory responsiveness\[46\].

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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. Major issues remain elusive and require well co-ordinated clinical and basic research strategies for their definition.

Clinical and histopathological features

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 thrombogenic stimuli also fit with the common autopsy finding of thrombi formed by separate layers of different age and composed of platelets[47], 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 and vasoconstriction

Activation of the vascular wall by pro-inflammatory cytokines causes the endothelium to change its properties from vasodilator and antithrombotic to constrictor and pro-thrombotic, to express adhesive receptors for circulating leucocytes and for platelets, and to express tissue factor. Such changes, which may be amplified by elevated CRP[48], 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 not only by the persistence and intensity of inflammatory stimuli and by their recurrence, but also by the individual haemostatic and vasoconstrictor responses (Fig. 2).

Plaque vulnerability

The vulnerable plaque concept is suggested by the localization of thrombosis and vasoconstriction at the sites of coronary plaques, which appear fissured in 60–80% of cases and often contain a central lipid core and inflammatory cell infiltrates. However, in some cases only endothelial erosions in the absence of a lipid core are found, and conversely plaque fissures are found in 10–25% of individuals who die from non-cardiac causes[49,50]. Thus, plaque fissure does not appear in itself to be a necessary or a sufficient trigger of instability. A widespread coronary inflammatory process appears to be a more likely substrate for coronary instability, with thrombosis and vasoconstriction developing at the sites where such a process is most intense.

This hypothesis is suggested by an angiographic report of multiple coronary unstable plaques in acute infarction[51]. It is consistent with autopsy reports of multiple fissured

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**Figure 2** Vicious circles that lead to the formation of an occlusive thrombus. An occlusive red thrombus can form rapidly within minutes at the site of highly thrombogenic injury (e.g. the rupture of a strongly thrombogenic plaque). An occlusive platelet thrombus can form gradually at the site of a weak, but very persistent thrombogenic stimuli (e.g. a persisting inflammatory process). A mural thrombus resulting from a plaque fissure or from a local inflammatory process may evolve in an occlusive thrombosis in the presence of pro-thrombotic states or of blood flow stasis induced by local or distal coronary constriction. The components of these vicious circles and their presence may have variable importance and prevalence in different groups of patients. Pro-thrombotic states may result from any acquired or genetic alteration that leads to enhanced platelet reactivity and/or thrombin formation, or to reduced fibrinolysis. (Modified from Maseri[5].)
plaque(s) and of multiple thrombi in patients who died from ACS, and with the significant activation of neutrophils as they traverse non-culprit coronary arteries recently observed in patients with unstable angina (Buffon et al., unpublished data).

**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, and remain potentially vulnerable for weeks or months.

In the complex pathogenetic scenario outlined above, there are no grounds for generalization. ACS are rare, occasional events, even in patients with extensive coronary atherosclerosis and with pro-thrombotic states. 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.

**References**


