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EDITORIAL COMMENT

Another Look at the Age-Old Question

Which Came First, the Elevated C-Reactive Protein or the Atherothrombosis?*

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Multiple histologic studies of atheroma specimens have illustrated the critical role of inflammation in the pathogenesis of atherosclerosis and plaque rupture (1). Proinflammatory cytokines from T cells and macrophages recruit smooth muscle cells and stimulate the production of interstitial collagens and proteoglycans, major components of the extracellular matrix that builds up in atheroma. Competing with plaque formation, however, is plaque degradation, a process that also is driven by inflammation. Specifically, when macrophages accumulate at the shoulders of atherosclerotic lesions and become activated, they release matrix metalloproteinases that can weaken and eventually disrupt the fibrous cap. This results in plaque rupture, intracoronary thrombosis, and an acute coronary syndrome (ACS).

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There are several circulating biomarkers of inflammation, including cytokines such as interleukin (IL)-6, acute phase reactants such as C-reactive protein (CRP), and leukocyte-derived enzymes such as myeloperoxidase. Multiple clinical studies have demonstrated the association between elevated levels of these inflammatory markers and the risk of myocardial infarction (2–4). Yet it has been debated whether the inflammatory state detected by these markers is a primary process that predisposes to atherothrombosis or a consequence of existing subclinical atherosclerosis.

In this issue of the *Journal*, Monaco et al. (5) present the results of an important study in which they compared the atherosclerotic burden and levels of thrombotic and inflammatory markers in patients with unstable angina (UA) to those in patients with peripheral arterial disease who were admitted for elective revascularization. They found that patients with UA had fewer significant arterial stenoses and lower levels of thrombotic markers but much higher levels of circulating inflammatory markers than patients with peripheral arterial disease. On the basis of this discordance, they conclude that inflammation in ACS is unlikely to simply reflect underlying atherosclerosis but, rather, represents a primary systemic process.

Given that the iliac and femoral arterial beds are more extensive than the coronary bed, it is not surprising that peripheral angiography revealed more lesions than coronary angiography. To that end, it would have been helpful to have angiographic confirmation of the true atherosclerotic burden in both vascular beds in both groups of patients. In addition, Liuzzo et al. (6) and Biasucci et al. (7) have previously shown that CRP and IL-6 levels are higher during the index admission in patients with UA than in patients with stable angina (6,7). Moreover, serial studies in patients with UA have demonstrated that CRP and IL-6 levels fall by approximately 50% in the following weeks (8). Thus, the observation in this study that inflammatory markers were nearly twice as high in patients with UA than in patients with stable atherosclerosis, is not unexpected, but does underscore the marked difference between stable and unstable atherothrombotic disease, irrespective of the involved arterial bed.

In support of these observations, several large angiographic studies have shown that no significant correlation exists between the extent of coronary atherosclerosis and the concentration of circulating CRP (9,10). However, follow-up in these cohorts has demonstrated that an elevated CRP predicts death or myocardial infarction independent of the extent of baseline coronary artery disease. These observations emphasize that it tends to be the non–flow-limiting, so-called "vulnerable" lipid-rich lesions with thin fibrous caps and dense inflammatory cell infiltrates that are the culprits in ACS (11).

Once patients present with ACS, there also is a direct contribution to the systemic inflammatory state from the heart. CRP is generated in atherosclerotic plaques and has been shown to be released into the coronary circulation in patients with UA (12). In a series of experiments, Buffon et al. (13) have shown previously that there is neutrophil activation and myeloperoxidase release across the coronary circulation in patients with UA but not in those with chronic stable angina. Intriguingly, this activation was observed across coronary arteries regardless of whether they contained the culprit lesion. Whether this inflammation originates in the coronary vasculature or the myocardium remains unclear (14).

What also is unclear is whether the widespread heightened cardiac inflammation is the culmination of an inflammatory process leading to plaque rupture, a consequence of plaque rupture, or both. Thus, akin to the ancient riddle of which came first, the chicken or the egg, the answer to the question posed in the title of the editorial may be that CRP comes both before *and* after atherothrombosis. Genetic

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predisposition and environmental stimuli may lead to a more vigorous inflammatory state in certain individuals, a state detectable using CRP and other markers. Inflammation places patients with coronary plaques, even nonobstructive ones, at higher risk for rupture and the consequent development of ACS. The latter may then serve as an additional inflammatory stimulus, resulting in a further transient increase in CRP and other inflammatory markers. By underscoring the disproportionate degree of inflammation in the setting of an ACS compared with extensive but stable arterial disease, the authors of this study help to remind us of why anti-inflammatory therapy, currently by statins but hopefully soon by more potent agents, is critical in preventing future cardiac ischemic events in patients without known coronary disease (15), with stable coronary disease (16), and with ACS (17).

Strong support for this position comes from a comparison between two recently published statin trials in patients with ACS. The Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis In Myocardial Infarction (PROVE-IT TIMI)-22 trial compared standard lipid lowering with 40 mg of pravastatin to intensive lipid lowering with 80 mg of atorvastatin (18). The clinical benefit at 30 days observed with the latter regimen was accompanied by a significantly lower CRP (19). In contrast, in the A to Z trial, neither differences in clinical outcome nor in CRP levels at 30 days were observed in patients assigned to 40 mg of simvastatin versus placebo. Yet, later in the trial, when the dose of simvastatin was raised to 80 mg/day, CRP was reduced and a clinical benefit emerged (20). Thus, in the early management of patients with ACS, it may not be sufficient simply to lower the level of low-density lipoprotein cholesterol, as all three statins did in these trials; the goal also must be to reduce inflammation, as reflected by lowering CRP.

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