C-Reactive Protein
Linking Inflammation to Cardiovascular Complications

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In the present issue, Chew and colleagues\(^1\) show that elevated baseline C-reactive protein (CRP) levels before percutaneous coronary intervention (PCI) are associated with a progressive increase in the risk of death or myocardial infarction at 30 days. The independent association of risk attributable to the marker CRP remained, even after adjusting for a number of baseline variables that are known to influence early events after PCI. This finding is not a surprise to those who have followed the trail of CRP in the last few years. However, to those who have not followed the CRP story, some explanation is in order.

Our understanding of atherosclerosis has evolved immensely over the years. When William Osler wrote his textbook of medicine more than a century ago, atherosclerosis was viewed as being caused by the hardening of blood vessels as a consequence of the aging process. More recently, the perils of hypercholesterolemia and its causative association with atherosclerosis at all ages were uncovered through many large epidemiological studies.\(^2\) However, cholesterol deposits in the arterial wall do not fully explain all the features of the proliferation of smooth muscle cells that attempt to form scars to wall off these lipid deposits. With the discovery of growth factors and their role in tissue repair, the “response to injury” hypothesis has become a dominant paradigm. In the last decade, however, a new perspective on atherosclerosis has been developed based on accumulating evidence that the entry of inflammatory cells such as monocytes into the arterial wall plays a pivotal role in this disease.\(^3,4\) This new paradigm might be collectively called the inflammation hypothesis. Any inflammatory stimulus, such as oxidized LDL or infection, alters the endothelial lining of the artery to make it “sticky” through the expression of adhesion molecules (such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1) and the secretion of chemokines (such as monocyte chemoattractant protein-1) on the luminal surface. The sticky endothelium attracts or captures circulating monocytes or other inflammatory cells onto the arterial surface. Once monocytes are arrested on the surface of the endothelium, they travel across the junction between 2 endothelial cells and become tissue macrophages, which can ingest lipid deposits to form foam cells. With the continuous entry of monocytes into the arterial wall, the lesion develops from the initial fatty streak to the more advanced fibrous plaque. If one can prevent the entry of monocytes into the arterial wall, then one can ameliorate the development of atherosclerosis. This prediction has been tested and proved in many animal models.\(^5\)

As inflammation began to be recognized as a major contributor to the pathogenesis of atherosclerosis, cardiologists started to ask whether markers of inflammation could be used to predict the clinical outcome of cardiac patients. In 1982, de Beer et al\(^6\) showed that individuals with myocardial infarction developed elevated CRP levels and that there was a significant correlation between the peak CRP and creatine kinase (CK) MB values. In uncomplicated cases, CRP levels tended to return to normal; however, in complicated cases, CRP levels remained elevated. This early study confirmed the role of CRP as an acute phase reactant, but it added little to the clinical management of myocardial infarction. In 1992, Berk et al\(^7\) showed that average CRP values were significantly different for patients with unstable angina compared with those with stable angina. Two years later, Luizzo et al\(^8\) demonstrated that the elevation of CRP and serum amyloid A protein at the time of hospital admission predicted a poor outcome in patients with unstable angina. In 1997, Ridker et al\(^9\) reported that baseline CRP levels predicted the future risk for the development of myocardial infarction or stroke in apparently healthy men participating in the Physicians’ Health Study. This finding was extended to apparently healthy women participating in the Women’s Health Study.\(^10\) Also in the Women’s Health Study (which was published last year), additional markers of inflammation, such as serum amyloid A, interleukin-6, and soluble intracellular adhesion molecule-1, were also measured. However, serum CRP level remains the strongest univariate predictor of the risk of cardiovascular events.

CRP was originally isolated as protein that binds to the C-polysaccharide of the cell wall of pneumococci;\(^11\) it is made up of 5 identical 23-kDa subunits arranged in a ring resembling a donut. For many years, CRP was known as an acute phase reactant that could raise its level 100-fold within 24 to 48 hours during an inflammatory process. CRP is synthesized and secreted mainly by hepatocytes in response to cytokines such as interleukin-6 and has a plasma half-life of 19 hours. CRP levels are elevated in many inflammatory disorders and have been used to predict clinical outcomes. Thus, CRP level may reflect the degree of underlying
inflammatory response and provide a useful measure of immune injury to tissues. Another intriguing possibility is that CRP could directly participate in amplifying the immune response, thus leading to further tissue damage. CRP has been shown to bind to damaged tissues, to nuclear antigens, to lipoproteins, and to apoptotic cells. It also participates in complement activation and tissue damage. Interestingly, CRP is present in atherosclerotic plaques but not in the normal vessel wall, and CRP deposits in early atherosclerotic lesions may precede the appearance of monocytes. Recently, we found that CRP can induce the expression of adhesion molecules and chemokines in human endothelial cells. We also have evidence that CRP acts synergistically with lipopolysaccharide in the activation of endothelial cells. Interestingly, CRP may also act synergistically with lipopolysaccharide to induce tissue factor production by monocytes. Thus, CRP is not only a marker of inflammation, but also an amplifier of it. The pro-inflammatory activities of CRP most likely are the mechanism by which elevations in baseline values before PCI predict complications after PCI.

The clinical questions arising from this work and others like it include the following: if a patient is scheduled for PCI and the baseline CRP level is elevated, indicating increased risk, should the PCI be performed? Or, should the PCI be postponed until a later time when the CRP has decreased and would the risk then be lessened? Are there medications that may help decrease the CRP value and will that reduce risk? If the PCI is performed in a patient with elevated CRP, should additional medications be used, and if so, which ones? At the present time, statins and aspirin seem to be the only therapeutic agents shown to reduce CRP levels. The general anti-inflammatory agent aspirin is already used routinely in patients with coronary disease undergoing PCI, and statin use is common but not universal. Should statins be used in all patients with elevated CRP undergoing PCI, regardless of cholesterol level? How long should treatment or pretreatment last? Additional data will be needed to answer these questions. Is PCI potentially harmful or helpful here? A similar situation existed in the recent past, only the clinical setting was unstable angina and non-Q–wave infarction. Instead of CRP, the marker was CK MB (indicating non–Q-wave myocardial infarction). There was a body of opinion, well supported by data, that PCI in patients with elevated CK MB or troponin I or T levels was associated with increased risk. Interestingly, CRP is present in atherosclerotic plaques but not in the normal vessel wall,12,13,14 and CRP deposits in early atherosclerotic lesions may precede the appearance of monocytes.15 Recently, we found that CRP can induce the expression of adhesion molecules and chemokines in human endothelial cells. We also have evidence that CRP acts synergistically with lipopolysaccharide in the activation of endothelial cells. Interestingly, CRP may also act synergistically with lipopolysaccharide to induce tissue factor production by monocytes. Thus, CRP is not only a marker of inflammation, but also an amplifier of it. The pro-inflammatory activities of CRP most likely are the mechanism by which elevations in baseline values before PCI predict complications after PCI.

The current study by Chew et al1 reminds clinicians and interventionists that atherosclerosis is an inflammatory disorder, and this needs to be considered along with lesion characteristics and the clinical status of the patient before intervention. It also speaks to the need to design future trials to determine appropriate strategies for managing patients with high serum CRP levels. Finally, the higher event rates noted in the cohorts with elevated serum CRP values suggest an excellent opportunity to screen and identify patients likely to benefit from novel anti-inflammatory strategies as adjunctive therapies to PCI.

References


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