Inflammation in Cardiovascular Disease

Cart, Horse, or Both?

Russell P. Tracy, PhD

In this issue of Circulation, Ridker and colleagues\(^1\) discuss the incremental value of CRP as a predictor of future CVD events. Their conclusion is that CRP is at least additive to HDL and total cholesterol with respect to risk prediction. In fact, there is some evidence that lipids and CRP are better predictors jointly than would be expected by adding up their individual predictive powers. CRP appeared to predict events in those at low risk on the basis of lipids, and CRP-lipid relationships to events were minimally altered by adjustment for other known CVD risk factors. These findings have important implications for CVD risk assessment and risk management.

CRP is an acute-phase reactant, the levels of which increase dramatically (100-fold or more) in response to severe bacterial infection, physical trauma, and other inflammatory conditions.\(^2\) Several roles have been postulated for CRP, including that of an opsonin, promoting the phagocytic uptake of invading microorganisms, and that of a procoagulant, promoting the expression of tissue factor on the monocyte surface. As a marker of inflammation, CRP is unique among the major plasma proteins in the fold increase that is observed and in that its levels appear to be unaffected by hormones and anti-inflammatory drugs but are regulated primarily by the proinflammatory cytokines, especially IL-6.\(^3\) Traditionally, 10 mg/L has been used as the cut point to signify clinically important levels, with values in the healthy reference range at or below the lower limit of sensitivity of most assays.

Recently, elevated levels of CRP, although still for the most part in the healthy reference range, have been associated with increased risk of future CVD events. Initially, Liuzzo et al\(^4\) and Haverkate et al\(^5\) established the prognostic usefulness of CRP in the setting of angina. This was followed by studies in otherwise healthy individuals. With the use of new, sensitive CRP assays, CRP was identified as an independent, prospective CVD risk factor in the higher-risk middle-aged men of MRFIT,\(^6\) the healthy middle-aged men of the PHS\(^7\) and the MONICA-Augsburg cohort,\(^8\) and the elderly men and women of the CHS and the Rural Health Promotion Project.\(^9\)

CRP is known to be related to smoking\(^10\) and the MRFIT data indicated that although there was no confounding effect, there was an interaction of smoking with CRP: CRP better predicted events in smokers than in nonsmokers, independently of smoking cessation.\(^6\) Consistent with this finding, CRP levels were associated with lifetime exposure to cigarette smoke, independently of cessation, in cross-sectional analyses in the elderly.\(^11\) Interestingly, Howard et al\(^12\) have recently shown an association of carotid wall thickness with lifetime exposure to cigarette smoke. Taken together, these findings raise the speculation that CRP, at least in some people, may mark permanent underlying endothelial damage due in part to smoking. It is important to note that in the PHS, CRP predicted future events just as well in nonsmokers as in smokers. However, smoking levels were relatively low in the PHS, and event follow-up was from 1 to 7 years, whereas in MRFIT it was from 6 to 17 years.

Other important independent correlates of CRP are obesity, markers of fibrinolytic activity, and subclinical atherosclerosis.\(^11\) The association of CRP with markers of fibrinolytic activity such as plasmin-α2-antiplasmin complex provides an important link between coagulant/fibrinolytic activity and inflammation. The nature of the link to obesity remains unclear. A possible mechanism may involve the association of adipose tissue with fibrinolysis inhibition.\(^13\)

Taken together, these data strongly support the position that CRP, as a marker of low-level inflammation, indicates increased risk of myocardial infarction and stroke in otherwise healthy individuals. Other acute-phase reactants have been used to indicate increased risk of CVD events.\(^14\) Fibrinogen has been shown in a wide variety of studies to consistently predict future CVD events in an independent manner.\(^15\) Factor VIII has recently been shown to predict events in middle-aged and older healthy adults.\(^16,17\) Plasminogen activator inhibitor-1 predicts second myocardial infarctions in survivors of a first infarct\(^18\) and, owing to specificity issues of the assays involved, is probably the reason for the important observed association between tissue plasminogen activator antigen and future events in PHS.\(^19\) Markers used to estimate serum iron (ferritin) and serum copper (ceruloplasmin) are also acute-phase reactants and have been identified as risk factors in recent studies.\(^20,21\) During the acute-phase reaction, albumin levels go down, and low levels of albumin predict future events,\(^22\) as do low levels of bilirubin (most of which is bound to albumin).\(^21\) Even plasma lipids are associated with inflammation, with levels of HDL cholesterol dropping and triglycerides rising,\(^23\) both consistent with CVD event prediction. The only “outlier” is total cholesterol, which...
also drops with inflammation. Finally, the cytokine mediators of inflammation themselves, specifically IL-6, are risk factors.5

This raises several questions. First, are all of these measures equivalent with respect to risk prediction? Although there are few head-to-head comparisons, the answer is likely to be no, because although they all respond to inflammation, the factors that regulate many of these proteins are not identical.26 Some respond to both the more “immediate” IL-1/tumor necrosis factor cytokines as well as the more “secondary” IL-6/IL-6–like cytokines, whereas others respond only to the latter. Some are under major hormonal regulation, whereas other are not. Technically, the assays for some are much better than for others, and some factors exhibit much larger within-subject variation than do others. It is unclear which of these is the best assay from the standpoint of prediction, or which group would make the best panel of assays.

The report of Ridker and coworkers1 in part addresses this issue. In the PHS, at least, CRP appears to give added information when lipids are considered and is statistically independent of other CVD risk factors. Similar results have been shown for fibrinogen.5

Second, is the inflammation that these measures reflect an epiphenomenon of atherosclerotic disease or is it in the CVD-event causal pathway? The best current answer to this question is probably both. Many cross-sectional studies have determined that markers such as fibrinogen, CRP, and others have strong associations with underlying atherosclerotic disease and, given their status as acute-phase proteins that respond to tissue damage, probably reflect atherosclerotic damage. However, there are many plausible mechanistic links between all the above-mentioned variables, including increased clot formation, lipid oxidation, and cell activation and proliferation. Taken together, these data support the position that inflammation is not only a response to the underlying disease process but also an integral part of it.

Third, are these markers independent of other estimates of subclinical CVD? Studies in the CHS were characterized by a design that matched cases and controls on the degree of subclinical disease as assessed by carotid wall thickness and several other variables.7 The results suggested that although CRP levels in part reflect underlying atherosclerosis, prediction was not confounded by subclinical CVD. Rather, there appeared to be effect modification, because prediction was stronger in those with subclinical disease than in those without it in the elderly group. This suggests there is added benefit to measuring CRP even if noninvasive measures of atherosclerotic burden are used as well.

Fourth, should anti-inflammatory intervention strategies use CRP levels? Although we have limited data on this issue, the original results from the PHS indicated that although aspirin, with respect to incident myocardial infarction, had a protective effect in all CRP strata, this effect was greatest in those with the highest CRP levels at baseline.7 Although this is suggestive, we do not know if long-term aspirin use affects CRP levels. More work is needed on this issue.

What may we conclude from these studies? Taken together, these data suggest that it may be time to add a marker of inflammation to the list of CVD risk factors commonly used to assess risk in otherwise-healthy middle-aged men. CRP is a good candidate because (1) levels appear reasonably stable over time,27 (2) levels are affected by little other than inflammation,2,3 (3) prediction is independent of other known CVD risk factors including lipids,1 (4) prediction appears additive to other noninvasive measures of subclinical atherosclerotic disease,5 (5) CRP predicts future events in both middle-aged and elderly healthy individuals,5,7,9 and (6) sensitive, inexpensive assays are becoming available,27 with WHO reference material available for assay standardization.

Before it can be put into general use, however, there are several outstanding issues remaining. CRP levels predicted events in middle-aged men, with no indication of an interaction with time to event. However, in the elderly, there was a strong time-to-event dependency, with CRP predicting events <1 year after blood collection better than events >1 year later.9 Therefore, more work is needed to better understand the chronological relationship of CRP to future events in different age groups. In addition, we have little information about CRP and middle-aged women. Other inflammatory factors such as fibrinogen predict events in women as well as men,26 but studies are needed of CRP in middle-aged women, especially because in the elderly, CRP was a better predictor of events in women than in men.9

References


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