Clinical perspective on C-reactive protein in prognostication of major adverse cardiac events in the elderly with established coronary heart disease

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The systemic response to tissue injury, regardless of cause is characterized by a cytokine-mediated alteration in the hepatic synthesis of a number of different plasma proteins, known collectively as 'acute phase reactants'. These proteins include C-reactive protein, serum amyloid A protein, alpha1-glycoprotein, ceruloplasmin, alpha macroglobulins, complement components (C1-C4, factor B, C9, C11), alpha1-antitrypsin, alpha1-antichymotrypsin, fibrinogen, prothrombin, factor VIII, plasminogen, haptoglobin, ferritin, immunoglobulins and lipoproteins. The initiation of the acute phase response is linked to the production of hormone-like polypeptide mediators now called cytokines, namely interleukin 1 (IL-1), tumor necrosis factor, interferon gamma, interleukin 6 (IL-6), leukemia inhibitory factor, ciliary neurotropic factor, oncostatin M, and interleukin 11 (IL-11).

C-reactive protein (CRP), named for its binding of pneumococcal C-polysaccharide, is the most extensively studied and clinically useful acute phase reactant. Known to rise rapidly after an inflammatory stimulus and possessing a half life of 19 hours, CRP levels can be detected and measured by a simple blood test. CRP is not significantly metabolized and its clearance is not influenced by any known processes. Serum levels are dependent only on its rate of production and excretion. It can be predictably duplicated.

The acute phase reaction is a generalized host reaction irrespective of the localized or systemic nature of the inciting disease. The various components of the response are remarkably consistent despite the considerable variety of pathologic processes that induce it.

However, not all inflammatory disease states are associated with elevated CRP. A refractory state can develop in certain diseases such as scleroderma, ulcerative colitis and lupus erythematosus. This is related to the presence of circulating inhibitors of cytokines, e.g. IL-1 receptor antagonists.

In this issue of the Journal of Geriatric Cardiology, the goal of a clinical investigation by Huang et al. was to elucidate the predictive value of CRP (hsCRP) for major adverse cardiac events as well as a correlation of its serum level with the extent and morphology of coronary lesions.1 The study was conducted on 177 consecutive Chinese elderly patients with established CHD who were referred to the Institute of Geriatric Cardiology for further diagnosis or interventional treatment. The criteria were about as exclusive as possible in order to allay ‘false positives’, thereby improving sensitivity of the test. All patients received standard medical treatment. Median follow up was 8 months and survival analysis was conducted with the Kaplan-Meier and COX proportional-hazards model.

The results showed that there was a concordance between elevated serum CRP and severity of coronary stenosis, multivessel disease, diffuse, eccentric and unsmooth lesions and remodeling of the stenotic segments. At follow up 2 patients (13%) with normal CRP had MACE compared to 13 patients (87%) with elevated CRP. There was a direct correlation between age and morphology of lesions, and, they were independent of whether or not CRP was elevated in these subjects.

There is a preponderance of research data that illustrated strong correlation between CRP and cardiovascular disease, especially when viewed concurrently with other known risk factors – smoking, obesity, high LDL, low HDL, elevated BP, diabetes mellitus and decreased physical activity. Despite the reservations prompted by Kushner and Sehgal (2002), 2 and the US Preventive Services Task Force (USPTF), 3 some physicians and researchers have affirmed the important role of CRP in heart disease contending that half of all CV events have occurred in people with normal cholesterol levels. Dyslipidemia has been widely accepted as a clear indicator of high risk for future CV events. In the group not 'classically' viewed as high risk, other deleterious pathways have been hypothesized; inflammation has shown the greatest promise as the missing link. Whether USPTF criteria used by Kushner and Sehgal are pertinent remain to be seen.

Atherosclerosis is an inflammatory disorder resulting from a combination of processes, and acute exacerbation of this inflammation is the hallmark of acute coronary syndrome (ACS). This associated link is attributable to the fact that the major inducers of CRP are antigenic in nature. As part of this’ innate
defense' CRP binds to monocytes, macrophages, and neutrophils and activates the complement system cascade (protein mediated immune response) that leads to the opsonization of 'foreign' molecules. When this occurs in the endothelial tissues of arteries, fatty deposits will remain with the macrophages in the intima (fatty streaks) of these vessels and thus begins the process of atherosclerosis.

The evolution of advanced atherosclerotic lesions is dependent on concomitant hemodynamic forces such as hypertension and plasma levels of atherogenic lipoproteins (high LDL or low HDL). Progression to the next stage is marked by the formation of fibrous plaques, and if left untreated, will progress to the final and most harmful stage of atherosclerosis. Calcified plaques that may be necrotic and contain thrombi are the hallmark of complicated lesions, which is the final stage of atherosclerosis. Calcified plaques participate in CHD by narrowing the lumen of the vessel directly or by way of rupture and creating massive local inflammation and clotting.

Many people who have heart attacks do not necessarily have severely stenotic lesions, 'vulnerable' plaques may be buried inside the arterial wall and may not always impede luminal blood flow. Inflammation can predispose the lining over these plaques to crack, and, bleed spilling the contents of the intima into the blood stream. Cytokines on the arterial wall capture blood cells, most of which are platelets that rush to the site of rupture. The blood cells and platelets aggregate to form a clot which may continue to grow with time and become large enough to compromise luminal blood flow through the segment. Despite this kind of inflammatory activity, a patient may be asymptomatic.

Researchers from Framingham Heart Study (FHS) inferred that CRP levels in conjunction with coronary calcium measurement indicate increased risk for future cardiovascular events based on sampling of 321 patients and subsequent electron-beam computerized tomography (EBCT) to detect subclinical atherosclerosis, as measured by a coronary artery calcium (CAC) score. Adjusting for other risk factors they found a direct correlation between elevated CRP and higher CAC scores.

The Harbor-UCLA studies confirmed the predictive role of CRP and CAC levels albeit independent of one another. This conclusion was based on a Cox regression analysis in 967 asymptomatic, non diabetic patients with known intermediate risk factors to determine whether the risk factor adjusted relative risks of CAC and CRP influenced the incidence of nonfatal MI or CHD related mortality including strokes and coronary revascularization. The investigators concluded that risk stratification based on hsCRP and CAC may be of benefit as both factors are independently associated with an increase in CV events.

Using data collected from 27,939 female cohorts followed for an average of 8 years as part of the Women Health Study and comparing varying levels of plasma CRP and LDL cholesterol, they found a linear relationship between a higher level of each variable measured and higher degree of risk for MACE, however, the risk was much higher for all levels of elevated CRP compared with varying levels of LDL cholesterol. This is proof of need to rethink the conventional wisdom surrounding LDL cholesterol as a major risk factor for CV events. Of particular interest was the fact that those with high levels of CRP and low LDL cholesterol were at significantly higher risk than those with high levels of LDL and low CRP! The latter group should be targeted for the most aggressive intervention. A large scale trial involving the use of statins in cohorts with low LDL and high CRP is warranted. Statins work through multiple independent mechanisms, and, regardless of their effects in lowering LDL, the drugs protect against first and recurrent heart attacks by lowering hsCRP.

However long use of hormone replacement therapy (HRT) has been associated with elevated CRP. Using data from Women's Health Initiative (WHI) involving 75,343 women with no history of heart disease, researchers sought to determine the correlation between plasma CRP, HRT use and IL-6 and their influence on CV events. The analysis (JAMA) compared 304 postmenopausal women who experienced MACE to a well matched group of 304 women who remained event free. Women who had experienced MACE had higher baseline levels of IL-6 and CRP compared with controls; the variables were independently associated with a 2-fold increase in MACE regardless of whether women received HRT or not.

A majority of studies showed evidence that strongly suggests that high levels of hs CRP are predictors of CV risk. In conjunction with other screening methods, this is an invaluable tool for primary prevention of CHD; it also presents as a strong prognosticator in secondary prevention. The current study showed that in elderly patients with established CHD, elevated plasma CRP has a positive predictive value for MACE and direct correlation with morphology of lesions and their severity. There is proven strong correlation between elevated CRP, increased BMI and waist circumference, high CAC scores and physical inactivity.

Inflammation represents an attractive target for patients at high risk for CV diseases. Monitoring of CRP is an invaluable complement to traditional risk factors and aggressive treatment of underlying conditions with emphasis on lifestyle modification. Moderate elevations in CRP typically present in apparently healthy individuals are postulated to be a strong predictor of future CV events. Elevated CRP in established CHD has been deployed in this study to prove beyond any reasonable doubt a direct correlation with MACE. The relationship between increased CV risk and CRP is based on the premise that inflammation correlates with presence of atherosclerosis. Research has shown convincingly that lowering markers of inflammation reduces CV events; however, the exact relationship between inflammation, atherosclerosis and CHD needs further clarification.

More research is required to establish the quantifiable risks of elevated CRP and the long term outcomes associated with decreased CRP levels in treated subjects. Measurement of CRP during a routine cardiac evaluation could reveal an underlying inflammation. Against a background of co-exist-
ing CV risk factors this becomes an invaluable tool in primary and secondary prevention. CRP level is an invaluable tool in secondary prevention of CHD; this should be part of routine blood work in every patient with established disease.

References