C-Reactive Protein—Undervalued, Underutilized

Tissue injury or infection leads to an increase in the serum concentration of a number of analytes, and to a decrease in the serum concentration of several others *[1, 2]*. The change in concentration is referred to as the acute-phase response. Serum analytes that increase in concentration include C-reactive protein (CRP), serum amyloid A, fibrinogen, haptoglobin, ceruloplasmin, copper, interleukin-6, polypeptide-specific antigen, neopterin, and ferritin *[3–6]*. Analytes that decrease in concentration include transferrin and iron *[6]*.

CRP is a noteworthy member of this group because of the speed and degree to which its concentration increases after a variety of inflammatory states or injuries to tissues—including myocardial injury or infarction *[2]*. CRP was discovered in 1930 by William Tillet and Thomas Francis at the Rockefeller Institute *[7]*. They extracted a protein from the sera of patients with pneumococcal pneumonia that coprecipitated with the C polysaccharide derived from the cell wall of the pneumococcus. Because the reaction between the protein and the polysaccharide was so specific they named the protein C-reactive protein.

The original test was a simple precipitin test, usually in a microcapillary tube, in which the height of the precipitant defined the amount of CRP present. The test lacked analytical sensitivity and remained that way for 50 years. Not until the early 1980s did analytically sensitive and specific immunoassays become commercially available. The new assays were widely adopted in Europe, but not in the US.

The test for CRP is a simple and effective screening test for occult bacterial infection or tissue injury *[1]*. CRP is synthesized rapidly by hepatocytes in response to cytokines released into the circulation by activated leukocytes. The cytokine-induced change in the concentration of CRP in serum is often quite large —reaching values that are 10 to 100 times greater than basal concentrations in healthy subjects.

The article in this issue of *Clinical Chemistry* by Dahler-Eriksen et al., which evaluates the technical performance and robustness of a near-patient test for CRP, highlights the reliability and potential utility of measuring CRP in a general practice setting *[8]*. The authors found the technical performance of the near-patient test to be satisfactory. There was essentially no difference in technical performance between technical and nontechnical staff, or for clinics with frequent or nonfrequent use of the test kit. Before introducing the test in daily routine, however, the authors recommend a further evaluation of the clinical effectiveness of the test in a near-patient setting.

The above caveat does not apply to the measurement of CRP in a hospital setting. There is abundant data attesting to its clinical effectiveness in this setting. For example, in studies of mortality after myocardial infarction, only the peak concentration of CRP and not of cardiac enzymes was predictive of death as late as 24 months after infarction *[9, 10]*. And in a study of patients treated for infective endocarditis, serial measurements of CRP were useful to monitor response to antimicrobial therapy and to detect complications *[11]*. The erythrocyte sedimentation rate was found to have no value.

CRP is particularly useful in monitoring recovery from an operative procedure *[12–14]*. Normally, CRP concentrations begin to increase within 4 to 6 h after surgery, and peak in 48 to 72 h at concentrations approaching 25–35 mg/L. In uncomplicated cases serum CRP concentrations return to normal by the 7th postoperative day. But if the postoperative course is complicated by inflammation or sepsis, from any cause, then CRP concentrations remain increased and may even rise to higher concentrations.

Recently, CRP was identified as a risk indicator for coronary heart disease (CHD). In two independent studies, baseline concentrations of CRP predicted the risk of future myocardial infarction *[15, 16]*. The positive association between CRP concentrations and CHD risk supports the hypothesis that there is an inflammatory component to atherosclerosis *[17]*. The CRP concentrations associated with risk assessment, however, are within the generally accepted reference range for the test. Thus, an isolated CRP concentration cannot be used to assess risk for an individual because many factors other than atherosclerosis can alter CRP concentrations. One study of the within- and between-subject variability of CRP concentrations found that within-subject variability accounted for 14% of the total variance *[18]*. On the basis of that finding, the authors suggest that triplicate sampling of CRP is required to establish an individual reference point for risk evaluation. A second study reported the CV of within-subject variability to be 42% and the CV of between-subject variability to be 118% *[19]*. These authors conclude that CRP values appear to be relatively tightly regulated, and that individuals appear to have consistent, and consistently different, CRP values.

The newly discovered association of atherosclerosis and inflammation could bring together in one unifying hypothesis several disparate risk factors or indicators for CHD. Increased serum concentrations of CRP, fibrinogen, ferritin, and white blood cell count *[20]* are each associated with an increase in the risk of developing CHD, yet each also participates in the acute-phase response. Does each act independently as a risk factor for CHD, or is each just an indicator of an underlying inflammatory state? This is a challenging research frontier in laboratory medicine. We need a better understanding of when and to what degree a serum constituent is signaling an acute-phase response vs when it is abnormal in its own right.

Finally, we require more research on the biology of the acute-phase response—specifically, research focused on gaining a better understanding of how cells communicate with one another when responding to viruses, bacteria, or neoplastic cells so that we can intercept and comprehend the messages being sent.

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