IRVING KUSHNER, MD*
Professor of Medicine and Pathology, Division of Rheumatology, Department of Medicine, Case Western Reserve University at MetroHealth Medical Center, Cleveland

C-reactive protein elevation can be caused by conditions other than inflammation and may reflect biologic aging

THE ARTICLE BY Patel et al[1] in this issue summarizes the emerging data indicating that inflammatory processes participate in the pathogenesis of coronary artery disease. Much of this evidence is very persuasive. Among these data is the striking finding that minor elevations in C-reactive protein (CRP) concentration, such as those found in the upper quintile of apparently normal populations, predict coronary events. While generally taken as further support for the presence of underlying inflammation, it is not at all clear that this interpretation is correct. CRP elevation is indeed a sensitive test for inflammation, but there is a solid body of information indicating that it is not a specific test for inflammation.

WHAT IS INFLAMMATION?

Classically defined as the localized response to tissue injury (a definition with some weaknesses),[2] inflammation is ordinarily recognized by detecting functional or cellular elements of that response, such as enhanced capillary permeability or accumulation of phagocytic cells at affected sites. As our understanding of the molecular mechanisms involved in inflammation has expanded, there has been a regrettable tendency to conclude that inflammation is present when inflammatory mediators such as inducible nitric oxide, interleukin-1 beta (IL-1 beta), and tumor necrosis factor alpha (TNF-alpha) are found in increased concentration, or when the transcription factor called nuclear factor kappa B (NF-kappaB) is found to be activated.

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Such conclusions are treacherous, since these molecules are multifunctional and play many roles unrelated to inflammation, including regulation of cell growth, metabolic pathways, ovulatory events, embryonic development and implantation, angiogenesis, hematopoiesis, bone turnover, and neuronal and glial growth and differentiation.[2] We do not regard walking as an inflammatory process just because mechanical stresses and pressures cause local release of inflammatory mediators in joints.[3,4]

MODEST CRP ELEVATIONS ARE NOT SPECIFIC FOR INFLAMMATION

A minimal acute phase response occurs in many non-inflammatory conditions

Since the cytokines responsible for the acute-phase response[5] are known to have many functions unrelated to inflammation, it should not be surprising that a minimal acute-phase response does not necessarily indicate an inflammatory state and that modest CRP elevation is not specific for inflammation. As pointed out by Macy et al,[6] the meaning of CRP concentrations in the upper portion of the reference range is not well understood at this time.

This subject has been only scantily studied thus far, but we already know that a substantial number of conditions that are not apparently inflammatory, as we ordinarily understand that term,[2] are associated with a minimal acute-phase response. These include obesity, diabetes mellitus, uremia, hypertension, marked physical exertion, oral hormone replacement therapy, sleep disturbance, chronic fatigue, notably high or low levels of alcohol consumption, low levels of physical activity, and depression.[7–15] In addition, CRP levels have recently been shown to be influenced by genetic factors.[16]

One can only speculate about how many other physiologic, pharmacologic, or pathophysiologic states not ordinarily regarded as inflammatory may involve increased cytokine production with consequent minimal acute-phase changes. Indeed, a weak relationship between attendance at religious services and IL-6 levels has been reported.[17]

Of particular interest is the emerging evidence that the cytokines responsible for acute-phase protein induction play significant roles in neuropsychologic function and dysfunction. Of special relevance, depression, a recognized risk factor for coronary artery disease,[18] is accompanied by a minimal acute-phase response.[19] Is it possible that detecting modest CRP elevation is merely an indirect way of detecting the presence of the risk factor *depression*, thus explaining the epidemiologic correlation of CRP and coronary artery disease?

Given that a number of noninflammatory processes can elicit modest CRP responses, we still need to explain why such elevations predict coronary events. In confronting this issue we should be aware that such predictive capability is not limited to CRP elevation and to coronary events. Minor acute-phase changes of many kinds bear a poor prognosis for many conditions,[8,20–23] including diabetes, peripheral vascular disease, uremia, ischemic stroke, and cataracts,[24–26] as well as for both cardiovascular and noncardiovascular mortality in the elderly.[27]

CRP predicts poor outcomes of many kinds

Is there a process, commonly regarded as noninflammatory, that predisposes to poor prognoses and to death and is capable of inducing a modest acute-phase response? The answer is yes: biologic aging.

MODEST CRP ELEVATION MAY BE A MARKER OF BIOLOGIC AGING

Aging may be defined as the accumulation of diverse adverse changes that increase the risk of death and is the major risk factor for disease after age 28 in developed countries.[28] Blood levels of at least some inflammation-associated cytokines and acute-phase reactants have long been known to increase with age.[29–32] Elevated circulating levels of IL-6 predict onset of disability in older persons.[33] The frailty and late-stage cachexia that may occur in the elderly are accompanied by and may be due to elevated blood levels of inflammatory cytokines.[32,34] Indeed, it has recently been shown that aging is accompanied by a profile of gene expression that characterizes an inflammatory response and oxidative stress.[35]

Since a minimal acute-phase response appears to be bad news across the board, identifying individuals who are "further down the road" in a nonspecific way, these data suggest that a minimal acute-phase response may be a marker for biologic aging. At present, it is unclear to what extent inflammatory cytokines may themselves contribute to the phenotypic changes that accompany aging.[31]

The molecular mechanisms implicated in biologic aging could readily give rise to a minimal acute-phase response. A leading theory of aging is that reactive oxygen species, generated by normal metabolism and by formation of advanced glycation end products (AGEs), cause cumulative tissue damage over a lifetime.[36] The transcription factor NF-kappaB, which participates in the transcriptional induction of a vast array of inflammation-associated cytokines and acute-phase reactants, may be a general sensor of such oxidative stress.[37,38] More specifically, binding of AGEs to their cognate cellular receptor, RAGE, leads to activation of NF-kappaB and induction of inflammatory cytokines.[39,40] NF-kappaB activation by such stimuli would clearly result in at least a minimal acute-phase response.

SUMMARY

Epidemiologic studies have revealed that minimal acute-phase changes predict poor prognoses in many conditions and predict disability and mortality in the elderly. These findings have usually been interpreted to indicate that inflammatory processes of some kind play a role in these situations. In fact, a minimal acute-phase response does not necessarily establish the existence of an inflammatory process but may also reflect a variety of noninflammatory states, including obesity, sleep disturbance, depression, chronic fatigue, and low levels of physical activity. I propose that a minimal acute-phase response may also be a marker of biologic aging, a condition known to predispose to poor prognoses and to death.

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***ADDRESS:** Irving Kushner, MD, Case Western Reserve University at MetroHealth Medical Center, 2500 MetroHealth Drive, Cleveland, OH 44109; e-mail ixk2@po.cwru.edu.*