EDITORIAL

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Evidence of smoke and atherosclerotic fire

THE EPIDEMIOLOGIC LITERATURE persuasively suggests that the circulating C-reactive protein (CRP) level is a uniquely powerful indicator of risk in patients with coronary artery disease, according to a review in this issue by Patel, Robbins, and Topol.[1]

See related articles, pages 521–534 and 535–537

The CRP level, in some settings, may be an even more powerful predictor of adverse outcome than traditional risk factors such as total cholesterol or low-density lipoprotein (LDL) levels. Patel et al propose that measurement of CRP levels using a sensitive assay should become part of our routine assessment of cardiovascular risk.

In coronary disease, CRP may not simply reflect systemic inflammation

Unlike trials of lipid-lowering drugs, however, no interventional studies have yet demonstrated that CRP levels can be lowered with anti-atherosclerotic therapy; that patients with elevated CRP levels have better outcomes if treated more aggressively (eg, striving for extremely low LDL levels); or that targeting control of the CRP level can modulate vascular lesions more effectively than targeting the more traditional markers for vascular disease. It is not known whether the small but statistically significant elevations in CRP levels play a direct role in the progression of vascular disease, or whether CRP levels are a surrogate marker for an underlying process that both fosters progression of coronary artery disease and elevates CRP (the cytokine interleukin-1 can increase levels of both CRP and angiotensin-converting enzyme).

The data summarized by Patel et al are persuasive in linking CRP levels with risk of adverse outcomes in patients with coronary artery disease; however, I believe it is premature to extend the clinical use of the highly sensitive CRP assay (hsCRP) as a test for the presence of coronary artery disease or for monitoring of therapy.

DOES A SLIGHTLY ELEVATED CRP INDICATE ATHEROSCLEROSIS IS A SYSTEMIC INFLAMMATORY STATE?

Patel et al assert that the slightly higher CRP levels in coronary patients who suffer poor outcomes represent a systemic inflammatory state. This explanation stems in part from recognition that significantly elevated CRP levels in other diseases such as bacterial infection and rheumatoid arthritis are a well-defined component of the acute-phase response which accompanies inflammation.

Others disagree. Our current understanding of the role CRP plays in the classic acute-phase response owes much to the seminal work of Kushner.[2] But as Kushner himself argues in a separate article in this issue,[3] factors other than inflammation may also influence CRP levels. Gabay and Kushner notes that the levels of CRP that have correlated with a poorer cardiovascular outcome are within a range generally considered normal, and significantly below the level detected in patients with active rheumatoid arthritis or pneumococcal pneumonia. The CRP level may be a surrogate marker for a systemic vascular process, perhaps vascular aging, but not necessarily inflammation.

Others have discussed the interplay between components of the immune system and aging. Levels of interleukin-6, a proinflammatory cytokine that activates macrophages and stimulates the hepatic production of CRP, rise with age and synchronously with age-related decreases in estrogen and testosterone.[4] Thus, the cytokine profile changes with aging. Does it change more in patients with more extensive vascular disease?

SHOULD WE BROADEN THE DEFINITION OF INFLAMMATION?

Should we move our focus away from inflammation per se as the cause for the elevated CRP? This would not negate the predictive power of the CRP level in determining the prognosis of patients with coronary artery disease.

Alternatively, should we broaden our definition of inflammation from the time-honored one that includes pain, redness, swelling, heat, and loss of function? Is atherosclerotic coronary artery disease a unique biological situation? I believe the answers are yes to the first question and no to the second.

The traditional hallmarks of inflammation are caused largely by the reaction to cytokines of the small blood vessels and nerves that feed or drain the inflamed tissue: vasodilatation with hyperemia and increased vascular permeability with resultant edema. When the target of "inflammation" is a specialized anatomic structure such as a muscular artery or airway, the response to inflammatory cytokines may be different.

For example, it is now generally accepted that asthma is a chronic inflammatory disease that targets the muscular airways, causing muscular constriction and subsequent remodeling. Remodeling of the myocardium following infarction may also be considered a part of the inflammatory response to ischemic injury, just as healing or loss of function (counterproductive healing) has traditionally been considered part of the inflammatory response. Corticosteroids, complement antagonists, and modulators of the eicosanoid biochemical cascade (leukotriene and prostaglandin inhibitors, fish oil supplements) have been used in both asthma and myocardial infarction with variable success.

For many years it has been known that the pathophysiologic processes of atherosclerosis share many components with the typical inflammatory response. Mononuclear cells accumulate within the involved blood vessels and acquire the characteristics of activated tissue macrophages. Oxidation occurs—a byproduct of activated inflammatory cells—and oxidized LDL has been increasingly implicated as a primary player in the evolution of atherosclerotic lesions. Large blood vessels in animals unable to efficiently eradicate herpes viruses manifest arteritis, which may result in vascular injury akin to chronic atherosclerotic damage.[5] Chlamydial antigens can be found in atherosclerotic aneurysms. Whether these types of indolent vascular infections with localized inflammation play a role in human disease or contribute to slight elevations in CRP is unknown.

UNSTABLE PLAQUES MAY REPRESENT A LOCAL INFLAMMATORY RESPONSE

It is now accepted that clinical outcome is not related solely to the size of the atherosclerotic lesion, but rather that the nature of the plaque is of equal or greater importance.

The determinants of plaque instability continue to be elucidated. Incriminated candidates include soluble inflammatory mediators, activated platelets, and monoclonal T cells that seem to specifically accumulate in unstable plaques.[6] These T cells are phenotypically similar to those found in the synovial fluid of patients with rheumatoid arthritis, and express cytokines capable of activating macrophages and perpetuating a chronic regional inflammatory response. The finding of clonality of T cells within specific atherosclerotic lesions, if confirmed in other laboratories, may provide further evidence that a local inflammatory response is part of the atherosclerotic process. Conceivably, this may help identify infections associated with the atherosclerotic process or other antigens that initiate it.

Risk stratification does not equal diagnosis

LEARNING HOW TO PUT OUT FIRES

High-dose dietary fish oil supplementation and statin drugs both have a salubrious effect in patients with coronary artery disease, beyond their expected hypocholesterolemic effects. Whether they in some way modulate the inflammatory aspect of atherosclerotic plaque, however, remains to be established.

Whether to use an hsCRP assay to screen all patients depends on the clinician's philosophy on how to treat patients with well-defined coronary artery disease risk, and on the evidence supporting hsCRP assay to direct treat-

ment and affect outcome. We do not yet have the benefit of outcome data.

If you believe that identified risk factors such as LDL level represent a continuum of risk, with no arbitrary "safe" level, then you should aggressively treat all patients who have an unacceptable *absolute* risk for coronary artery disease. Testing is warranted if you would recommend treatment for a patient whose *absolute* risk is marginal as assessed by traditional means, but whose *relative* risk is increased when assessed by a test such as the hsCRP (as the case-controlled Women's Health Study[7] demonstrated).

Definitive demonstration that this strategy is correct waits a prospective interventional trial. Whether particularly aggressive treatment similar to strategies proposed for secondary (as opposed to primary) prevention is warranted based on an elevated hsCRP is unknown at present.

As when any clinical test is put to a new task, the operating characteristics of the test (predictive value, sensitivity, and specificity) must be defined. Since we already know from clinical experience that patients exhibit transiently elevated CRP levels in response to many stimuli,[2] Bayes' theorem must be invoked as we anticipate wide utilization of this test and attempt to use the results to direct therapy.

It may turn out that the hsCRP assay will help in risk stratification and choice of therapy. It is unlikely in my mind that the hsCRP assay will prove to be the gold standard diagnostic test for atherosclerotic disease; the evidence to date does not support its use for this purpose. Stratifying the risk for complications of coronary artery disease is not equivalent to diagnosing coronary artery disease in a given patient.

Successful use of the CRP level as a prognostic indicator in patients with coronary artery disease may or may not be a "simple" reflection of systemic inflammation as a contributor to the atherosclerotic process. Whether the smoke of the CRP reflects a systemic fire of atherosclerosis or is associated with the regional inflammation or even a related but noninflammatory vasculopathic process remains to be determined. Nonetheless, recognition of the regional fire within the coronary plaque will spur years of inquiry in the laboratory and in the clinic.

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