Editorial

Novel Inflammatory Markers of Coronary Risk

Theory Versus Practice

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For practitioners committed to coronary risk reduction, recent clinical trial data pose a considerable challenge. Specifically, in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a primary prevention trial, treatment with lovastatin among an apparently healthy group of individuals without traditional coronary risk factors resulted in significant reductions in future cardiovascular events. Application of the results of that trial and of the West of Scotland primary prevention trial of pravastatin suggests that tens of millions of Americans without manifest atherosclerosis could benefit from lipid-lowering therapy.

Such a blanket approach, however, may be unwise from medical as well as economic perspectives. Unnecessary exposure to pharmacological agents, even those as safe as the statins, will ultimately subject some asymptomatic and low-risk individuals to unwanted side effects. Furthermore, economic constraints dictate that primary prevention strategies with even modest cost must be limited to those individuals who are likely to gain the greatest benefit. Even when an inexpensive preventive therapy such as low-dose aspirin is proven effective, behavioral barriers on the parts of both physicians and patients must be overcome if long-term compliance is to be achieved. All of these considerations highlight the need for better methods to stratify risk of atherosclerotic events in apparently healthy populations.

New Approaches to Coronary Risk Assessment

Clinical strategies designed to improve risk prediction have taken several forms. Imaging techniques including carotid ultrasound, MRI, and electron beam computed tomography (EBCT) all hold promise for identifying “vulnerable plaques” and detecting silent atheroma. However, prospective studies demonstrating the clinical utility of these approaches are limited. For example, a recent study of coronary calcification detected by EBCT has shown that this method does not accurately predict future coronary events, even in high-risk patients. The cost of these noninvasive imaging modalities may also prohibit their application for widespread screening application.

Proconvative testing of endothelium-dependent vasodilation has a firm pathophysiological foundation and may also furnish information regarding an asymptomatic individual’s risk for future coronary events. However, as in the case of imaging modalities, the specificity of this approach is uncertain, and practical barriers preclude its utility for screening in outpatient clinic settings. Similarly, although the rapid progress in identifying genetic polymorphisms that correlate with coronary risk holds great promise, we have much work to do before we will know how to apply these data in practice.

By contrast, several serum markers have recently come to the fore as potential solutions to the challenge of detecting high-risk individuals for primary prevention. Indeed, because of their low cost and simplicity for outpatient use, the identification of a simple blood test, or a battery of such tests, has become a major initiative in preventive cardiology. In this issue of Circulation, Xu and colleagues furnish new evidence that antibodies to heat-shock protein 65 (hsp65) are associated with increased risk of atherosclerotic events in a free-living population. What can we learn from such studies about the pathophysiology of atherosclerosis and its complications? What criteria should we use in deciding how and when to apply these new techniques to our clinical practice?

Markers of Inflammation and Stress Furnish Insight Into Pathophysiology

Serum markers of inflammation provide an avenue of insight into the pathophysiology of atherosclerosis and its complications. High-sensitivity testing for C-reactive protein (hs-CRP), a nonspecific marker of low-grade systemic inflammation, has received much attention, and several studies now support a strong link between baseline elevations of hs-CRP and future risk of coronary events. “Distal” indicators of inflammation likewise predict coronary risk (Figure 1). Examples include the soluble forms of leukocyte adhesion molecules, such as intercellular adhesion molecule-1 (sICAM-1). These distal markers may reflect the consequences of elevated levels of proinflammatory cytokines. For example, interleukin-6 (IL-6) probably provokes the augmented expression of the C-reactive protein (CRP) gene in the liver. Cytokines such as tumor necrosis factor-α (TNF-α) or IL-1 isoforms can in turn stimulate the expression of IL-6 and of the leukocyte adhesion molecules, such as ICAM-1 (Figure 1).

The source of these cytokines remains unclear. Increased levels of cytokines might arise from atheroma themselves,
binding to proteins critical to cellular function, these molecular “chaperones” can stabilize them and increase their resistance to denaturation (for example, by heat). Whatever their function, the expression of hsps does reflect cellular trauma, a process that in turn appears to activate vascular endothelium and smooth muscle cells, as well as regulate macrophage TNF-α and matrix metalloproteinase expression.13,14 Furthermore, cytokines and oxidized LDLs can induce adhesion molecules such as ICAM-1 and hsp60.15 A body of work from the laboratories of Xu and Wick has implicated hsp65 as an antigen involved in instigating the chronic immune response characteristic of human atherosclerosis. Specifically, previous cross-sectional data from this group have shown a direct relationship between antibodies against hsp65 and carotid wall atherosclerosis.16 In the present follow-up study, these antibodies are sustained among those with the most severe degrees of underlying atherosclerosis and were demonstrated to predict 5-year mortality.6 These new data furnish additional support for the inflammatory hypothesis of atherogenesis and of the acute coronary syndromes.

**Should We Use Novel Inflammatory Markers of Coronary Risk in the Clinic Today?**

Although studies of serum markers of inflammation provide substantial insight into the pathophysiology of atherosclerosis, the clinical utility of measuring these markers remains uncertain. In general, we advocate a cautious approach for several reasons.5 First, for a novel inflammatory marker to have a clinical role, there must be a widely available diagnostic test with reproducible assay characteristics appropriate for patient-related purposes. Of the major inflammatory markers, only CRP has an established World Health Organization standard, and high-sensitivity assays for this parameter appear to provide reliable results. Second, there must be a consistent series of prospective studies that indicate that baseline elevations of a given inflammatory marker predict future coronary events. In this regard, prospective data remain limited for the cellular adhesion molecules and for various hsps. In contrast, a remarkably consistent series of prospective data is available for both hs-CRP and fibrinogen.

Third, to be of clinical use, markers of inflammation must be

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**Figure 1.** Pathways by which vascular and extravascular sources of inflammation result in circulating levels of serum markers that provide a reflection of the underlying inflammatory response. Inflammation, systemic or local, either in the blood vessel itself or elsewhere, triggers the production of multipotent proinflammatory cytokines we denote here as “primary” (eg, IL-1β or TNF-α). These primary cytokines can directly elicit production by endothelial and other cells of adhesion molecules, coagulants, and other mediators that may be released in soluble form into circulating blood. Primary cytokines also stimulate production of “messenger” cytokines, IL-6, which induces expression of hepatic genes encoding acute-phase reactants found in blood, including CRP and serum amyloid-A (SAA). Thus, these markers in serum can provide a window on the inflammatory status of the individual, otherwise inaccessible in the intact subject.

Reflecting their quantity (atherosclerotic burden) or quality (the degree of inflammatory activity within these lesions), the cytokines might also derive from nonvascular sources and reflect inflammatory states such as chronic infections that may accelerate atherogenesis and its manifestations.11 Both vascular and extravascular sources of inflammatory cytokines may prove important to various degrees in different individuals. Regardless of the source of the inflammatory cytokines, emerging work on serum inflammatory markers supports the notion of a “pathway” of inflammatory activation related to acute coronary events (Figure 1). The inflammation (vascular or extravascular) begets cytokines (local and systemic), which in turn elicit the expression of acute-phase reactants such as hs-CRP and fibrinogen and of other effector molecules in the inflammatory response, such as adhesion molecules for leukocytes (Figure 1). Indeed, prospective epidemiological studies have now shown that measurements of serum inflammatory markers at each level of this pathway are associated with increased coronary risk (Figure 2).

Where do hsps fit into this schema? Cells that are stressed by thermal and other injuries augment their synthesis of a series of molecules known as hsps or chaperonins.12 By

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**Figure 2.** Relative risks of future myocardial infarction for apparently healthy middle aged men according to baseline plasma concentrations of fibrinogen, sICAM-1, IL-6, hs-CRP, and the combination of hs-CRP with the total cholesterol–to–HDL cholesterol ratio (TC:HDL). Data derive from participants in the Physicians Health Study.5,7,8,10 For consistency, risks are computed for men in top vs bottom quartiles for each parameter.
shown to add substantially to our ability to predict risk beyond that achievable by use of traditional risk factors such as those incorporated into the Framingham risk algorithms or the European guidelines. Although some studies suggest that inflammatory markers may well improve risk-prediction models, we believe more data are needed before firm clinical recommendations can be made. Finally, whether inflammation per se represents a modifiable risk factor is currently uncertain, although preliminary data suggest that several common preventive therapies may work in part through anti-inflammatory targets.

As evidenced by the current study from Xu and colleagues concerning hsps, we are in a rapidly expanding phase of knowledge with respect to novel markers of vascular inflammation. Although extraordinarily valuable as research tools, we must await completion of prospective evaluations of various panels of these peripheral markers before implementing their use in daily practice. In all likelihood, a combination of genetic markers (reflecting heredity) and serum markers (reflecting the net interaction between heredity and the environment) will ultimately afford a solution to the current challenges posed in primary prevention.

References

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