Shouldering the Risk Factor Burden
Infection, Atherosclerosis, and the Vascular Endothelium
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The healthy endothelium maintains vascular homeostasis via production of paracrine factors that promote vasodilation and inhibit thrombosis, inflammation, and cellular proliferation in the blood vessel. Atherosclerosis is associated with a loss of the biological activity of endothelium-derived nitric oxide and other alterations of endothelial phenotype that may contribute to plaque rupture and subsequent thrombosis and vasospasm. Indeed, the severity of impairment of endothelium-dependent vasodilation in the coronary circulation predicts the risk for future cardiovascular disease events. The ability to reverse endothelial dysfunction is a common property of otherwise diverse interventions that have been proven to reduce cardiovascular risk, including lipid lowering therapy, angiotensin converting enzyme inhibition, smoking cessation, and exercise. These observations support the concepts that endothelial dysfunction contributes to the clinical expression of cardiovascular disease and is a clinically useful surrogate for cardiovascular disease risk.

In addition to its role in advanced disease, there is strong evidence that endothelial dysfunction is important in the early stages of atherogenesis. For example, pharmacological inhibition of nitric oxide synthesis promotes atherogenesis, and the endothelial nitric oxide synthase null mouse is more susceptible to lesion formation than its wild type counterpart. Endothelial dysfunction is present in patients with coronary risk factors before the development of coronary atherosclerosis, as detected by angiography or intracoronary ultrasound. Endothelium-dependent flow-mediated dilation is impaired in young children with hypercholesterolemia before any clinical evidence of disease is seen. In general, the degree of endothelial dysfunction correlates with the number and severity of coronary risk factors. Thus, measurement of endothelial function may serve as an index of the cumulative effects of risk factors on the vasculature.

Traditional risk factors account for not more than half of cardiovascular disease risk. For this reason, cardiovascular epidemiologists and vascular biologists have attempted to identify other factors that can account for the remaining attributable risk. Recent studies suggest that certain chronic infections increase the risk for cardiovascular disease, and that such infections may be considered novel and potentially modifiable risk factors. Infection of cultured endothelial cells with cytomegalovirus and other pathogens induces expression of tissue factor, cytokines, and adhesion molecules, and evokes other phenotypic changes that tend to promote atherothrombosis. In animal models of atherosclerosis and restenosis, recurrent infection has been shown to worsen lesion severity. Epidemiological studies have shown increased cardiovascular disease in patients with serological evidence of prior infection with intracellular pathogens including cytomegalovirus, Chlamydia pneumoniae, Helicobacter pylori, herpes simplex virus, hepatitis A virus, and others. A number of these organisms have been detected in human atherosclerotic lesions, although the possibility remains that such findings reflect an increased susceptibility of atherosclerotic vessels to colonization rather than a pathogenic relationship. Cross-sectional epidemiological studies indicate that patients with coronary artery disease are more likely to have serological evidence of prior infection. Finally, there have been prospective studies indicating increased risk for cardiovascular events in patients with serological evidence of prior infection, particularly those with evidence of multiple infections. Severe periodontal disease, which is associated with recurrent bacteremia and chronic inflammation, has also been associated with increased coronary and carotid atherosclerosis and cardiovascular disease risk. Recent evidence suggest that Porphyromonas gingivalis, the principal organism believed to be responsible for adult periodontitis, accelerates atherogenesis in heterozygous apolipoprotein E-deficient mice.

A number of potential mechanisms have been proposed to explain how chronic infections might promote atherogenesis. First, it is possible that certain organisms can directly invade cells in the vascular wall, leading to a local inflammatory reaction that stimulates atherogenesis. Alternatively, chronic infection elsewhere in the body may lead to a systemic inflammatory state with an increase in circulating cytokines, acute phase reactants, leukocytes, and other factors that activate endothelial cells and promote atherogenesis. This possibility fits well with the growing recognition of the importance of systemic inflammation in atherogenesis.
between infection and cardiovascular disease is stronger when one considers the aggregate number of infecting organisms rather than single organisms. Furthermore, prior infection is particularly important when C-reactive protein is elevated, suggesting a systemic inflammatory state. Recent data suggest that toll-like receptors for bacterial endotoxin, especially TLR-4, are expressed on macrophages in murine and human atheroma. The expression of this receptor can be upregulated by oxidized low-density lipoprotein, and may thereby offer a mechanistic tie between atherogenic lipoproteins and the infection-inflammation axis in atherosclerosis.

Another intriguing possibility is the concept of “molecular mimicry,” where an autoimmune response is induced because of cross-reactivity between antigens that are common to host cells and the pathogen. An important corollary of the infection hypothesis of atherosclerosis is the possibility that antimicrobial therapy will reduce cardiovascular disease risk, and this possibility is currently under investigation in regard to C pneumoniae. If the overall pathogen load or an autoimmune mechanism is important, however, antimicrobial therapy directed against a single pathogen will likely prove to be ineffective.

There are only limited data about the effect of chronic infection and inflammation on endothelial dysfunction in human subjects. Hingorani and colleagues demonstrated reduced brachial artery flow-mediated dilation and impairment of endothelium-dependent vasodilation of forearm resistance vessels after Salmonella typhi vaccination in healthy subjects. Several other studies suggest that elevated levels of C-reactive protein are associated with impaired endothelium-dependent vasodilation in the forearm microcirculation of patients with coronary artery disease. Interestingly, there is evidence that endothelial function may improve in parallel with spontaneous reduction in C-reactive protein over time. A very recent study demonstrated an improvement in brachial artery flow-mediated dilation and decreased serum E-selectin and von Willebrand factor after 5-weeks of azithromycin treatment in patients with positive C pneumoniae titers. Although these findings suggest that endothelial dysfunction may relate to chronic infection, interpretation is complicated by the possibility that azithromycin may have anti-inflammatory properties that are distinct from its antimicrobial properties.

In the current issue of Circulation, Prasad and colleagues provide further information about the relations between chronic infection, atherosclerosis, and endothelial dysfunction. These investigators measured serum IgG antibodies against 5 infectious agents (cytomegalovirus, herpes simplex virus-1, hepatitis A virus, C pneumoniae, and H pylori) and C-reactive protein in 375 patients undergoing coronary angiography. For individual pathogens, only the presence of antibodies against hepatitis A was an independent predictor of the presence of coronary artery disease on angiography; however, the total number of pathogens ("pathogen burden") was a stronger and independent predictor of the presence and extent of coronary atherosclerosis. Furthermore, pathogen burden correlated inversely with endothelial vasomotor function as assessed by intracoronary acetylcholine infusion. Interestingly, this relationship with endothelial dysfunction persisted in a subset of 86 patients with angiographically normal coronary arteries. There was a significant interaction between pathogen burden and serum C-reactive protein, with a markedly increased likelihood of having coronary artery disease in patients with 4 to 5 positive titers and elevated C-reactive protein levels (>0.5 mg/dL) compared with patients with only 0 to 1 positive titers and low C-reactive protein levels. In contrast to prior studies, there was no correlation between C-reactive protein levels and endothelial dysfunction.

The strengths of the study include the careful and well-developed methodology for the study of endothelial function in the coronary circulation and the relatively large sample size for a study of this type. As acknowledged by the authors, the study had several limitations. Most importantly, the study was cross-sectional in nature, precluding any conclusions about a causal relationship. For example, it seems quite plausible that the presence of multiple infections could reflect other unmeasured risk factors that increase cardiovascular disease risk. Persistent effects of concurrent medications, which were stopped for 48 hours before catheterization, may have also confounded the interpretation of the results. Finally, the most severely diseased subjects did not undergo a study of endothelial function, which may have biased the outcome. Despite these limitations, the study provides further evidence for a relationship between prior infection and extent of atherosclerosis and offers interesting new information about the potential relation between chronic infection and endothelial dysfunction.

The work by Prasad and colleagues suggests that chronic infection may be added to the list of factors that induce endothelial dysfunction and contribute to the development and clinical expression of atherosclerosis. Furthermore, the study results are consistent with the notion that the number and severity of risk factors are particularly important for quantifying risk. The ability of the endothelium to resist the "burden" of risk factors may be determined by genetic,
dietary, and other environmental factors, and may itself contribute to overall cardiovascular disease risk (Figure). Assessment of endothelial function may therefore provide clinically useful information for the assessment of cardiovascular disease risk and the evaluation of potential therapies for cardiovascular disease.

References
11. Epstein SE. The multiple mechanisms by which infection may contribute to atherosclerosis development and course. Circ Res. 2002;90:2–4.

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