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EDITORIAL COMMENT

The Yin and Yang of Arterial Inflammation*

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The recent wave of enthusiasm for including inflammation as one of the primary pathophysiologic processes in cardiovascular disease has substantial merit (1). Arterial inflammation is central to plaque progression and plaque rupture. Among clinical markers of inflammation, C-reactive protein (CRP), a complex pentameric protein largely of hepatic origin, is the current gold standard (2,3). In a variety of clinical situations, the elevation of CRP predicts adverse outcomes, including mortality (4,5). Beyond its "biomarker" role, CRP probably actively participates in atherothrombosis. For example, CRP opsonization of low-density lipoprotein (LDL) cholesterol mediates LDL uptake by macrophages.

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Although CRP has caught our attention, many other pro-inflammatory factors also indicate patient risk and participate in the atherosclerotic process, including interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, interferon gamma, monocyte chemoattractant protein-1, cell adhesion molecules, nuclear factor kappa B, CD 40, lipoprotein-associated phospholipase A₂, myeloperoxidase, nitrotyrosine, and matrix metalloproteinase-9 (6). The list of offenders grows larger almost weekly.

Although inflammation plays an important part in the pathogenesis of atherothrombotic syndromes, not all inflammatory mediators are evil. Analogous to the thrombotic cascade, inflammatory pathways have counterbalancing factors to keep the system in check. The inflammatory cascade maintains a delicate balance of pro- and anti-inflammatory molecules that regulate homeostatic functioning. Control of heart rate with a balance of sympathetic and parasympathetic tone and regulation of intravascular volume by a balance of salt-retaining and -wasting mechanisms provide other examples of a basic biological principal: physiological regulation involves a balance of stimulating and repressing forces. Our concepts of arterial inflammation should now expand to both sides of the equation. Although the focus of this editorial comment is coronary atherosclerosis, the same patterns of pro- and anti-inflammatory cytokine balance

occur in congestive heart failure, peripheral arterial disease, and stroke (7).

Genetic determinants affect levels of high-sensitivity CRP as well as other inflammatory moieties (8). Beyond genetics, environmental factors may influence CRP levels as well as levels of other inflammatory markers and mediators (9). Obesity, in particular abdominal adiposity, is a powerful modulator of CRP levels. Adipocytes produce IL-6 in abundance and lead to CRP production by the liver; subcutaneous fat contains messenger ribonucleic acid (mRNA) for CRP as well (10). Exercise and weight loss result in lower CRP levels (11). Smoking and hormone replacement therapy raise CRP levels, whereas light-to-moderate alcohol intake is associated with lower CRP levels. Potentially, in patients with periodontitis, antimicrobial periodontal treatment may lower levels of inflammatory markers, including CRP. Statins, niacin, peroxisome proliferator-activated receptor gamma and alpha agonists, and antiplatelet therapy are just some of the medications that have been shown to lower CRP and diminish its pro-inflammatory effects (12). In the "big picture," factors that lower CRP are generally associated with cardiovascular benefit and factors that raise CRP are largely detrimental. Along with other potential inflammatory mediators, the interplay of these pro- and anti-inflammatory factors may determine the state of vascular health (Fig. 1).

In this issue of the *Journal*, Fichtlscherer et al. (13) have provided evidence to link pro- and anti-inflammatory modulators directly to endothelial function. Using plethysmography to assess forearm blood flow in patients with coronary artery disease, they demonstrated an association between impaired endothelial function and elevated CRP. In addition, their data suggest that higher IL-10 levels preserved endothelial vasodilation in response to acetylcholine, even in the setting of elevated CRP levels. These findings build upon a substantial body of prior work suggesting that elevated IL-10 levels are beneficial in patients with acute coronary syndromes, particularly in those with elevated CRP levels (6,14,15).

Interleukin-1, IL-6, IL-12, and IL-18 are all pro-inflammatory cytokines, whereas IL-10 is an anti-inflammatory cytokine (16). Interleukin-10 has several anti-inflammatory properties, including the ability to inhibit production of TNF-alpha, IL-8, tissue factor, and matrix metalloproteinase-9 (17). Low levels of IL-10 are associated with the metabolic syndrome in obese women, although obesity itself is associated with elevation in CRP, IL-6, and also IL-10. Furthermore, various interactions between interleukins and CRP may occur. For example, human coronary artery smooth muscle cells are capable of producing CRP and can be stimulated to do so by IL-1-beta, IL-6, and TNF-alpha. Particularly relevant to the study by Fichtlscherer et al. (13), human recombinant CRP induces expression of IL-18 by endothelial cells, an effect inhibited by treatment with IL-10. Blood pressure, in part a reflection of the state of the endo-

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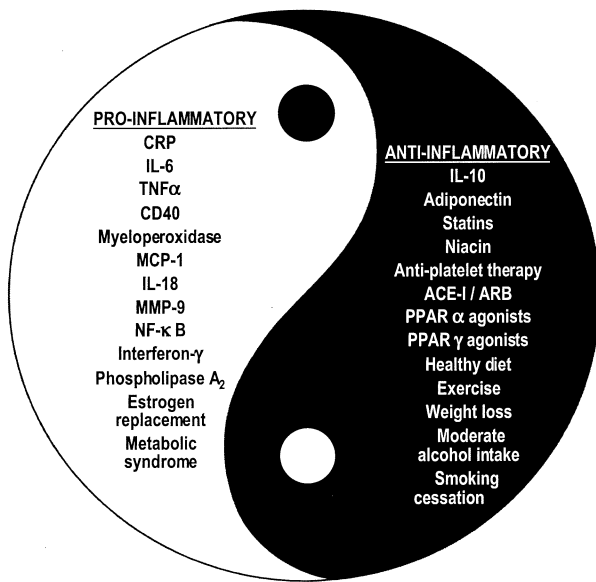


Figure 1. The balance of pro- and anti-inflammatory mediators may determine vascular health or illness. The list of inflammatory molecules, in particular those that are pro-inflammatory, are rapidly expanding. Some of the more prominent ones are listed. ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CRP = C-reactive protein; IL = interleukin; MCP = monocyte chemoattractant protein; MMP = matrix metalloproteinase; NF = nuclear factor; PPAR = peroxisome proliferator-activated receptor; TNF = tumor necrosis factor.

thelium, may also modulate the production of inflammatory molecules and vice versa. Inflammatory mediators may contribute to blood pressure elevation, but blood pressure elevation also leads to production of cytokines and cell adhesion molecules. In fact, CRP, at clinically relevant concentrations, has been found to potentiate the effects of angiotensin II by up-regulating the expression of angiotensin receptors on vascular smooth muscles. C-reactive protein also has been shown to reduce endothelial nitric oxide (NO) synthase expression and prostacyclin release in cultured human cells. In particular, CRP inhibits basal and stimulated NO release by endothelial cells, apparently through a posttranscriptional effect on endothelial NO mRNA stability. The incubation of human saphenous vein endothelial cells with CRP decreased endothelial release of NO and increased endothelin-1 production. Because NO and prostacyclin are both potent vasodilators and endothelin-1 is a powerful vasoconstrictor, their modulation by CRP could alter vascular tone. Furthermore, CRP, at least in the setting of acute coronary syndromes, has been shown to sensitize endothelial cells to destruction by cytotoxic CD4⁺ T cells. In addition to these effects on the endothelium, CRP directs the recruitment of monocytes into the intima. In summary, the connection between inflammation and endothelial dysfunction suggested by Fichtlscherer et al. (18) has a cogent biological basis.

In the study by Fichtlscherer et al. (13), a large percentage of patients were receiving aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and statins. Whether the relationship they described between CRP and IL-10 would be greater or lesser in a population not

receiving such therapy is unknown. Aspirin pretreatment blunts the effects of inflammation on endothelial dysfunction, and statin therapy may reverse endothelial dysfunction through both lipid-lowering and anti-inflammatory pathways. Good medical therapy in general has been shown to lower CRP with a corresponding improvement in endothelial function as measured by brachial flow-mediated dilation.

Endothelial dysfunction is not irreversible; therapies that lower CRP and presumably decrease vascular inflammation have already been demonstrated to restore endothelial health. Nevertheless, even with current state of the art medical therapy, there are still patients who display an ongoing elevation of inflammatory markers and all that is implied by such markers, including endothelial dysfunction.

The work by Fichtlscherer et al. (13) adds further support to a strategy of multi-marker testing. On a population level, high-sensitivity CRP (or any surrogate or pathogenic marker) is useful, but for any given individual the incremental risk conferred by CRP elevation is relatively modest. The Fichtlscherer et al. (13) findings may help to explain why some patients with elevated CRP do not experience adverse clinical events; perhaps these individuals have elevated IL-10 or other counterbalancing factors. Adiponectin, a cytokine produced by adipose tissue, may be another counter-regulatory moiety; adiponectin levels tend to move in a direction opposite to CRP (10). Low levels of adiponectin also correlate with higher levels of IL-6 and phospholipase A₂. In the future, point-of-care testing of a panel of inflammatory markers may help to stratify risk more precisely in both inpatient and outpatient settings. However, substantial further investigation will be required to sort out the patterns of inflammatory marker expression that have true predictive value. Parallel developments in single nucleotide polymorphism and haplotype analysis are likely to complement these advances. Sophisticated noninvasive imaging, such as high-resolution magnetic resonance imaging, will probably further refine our ability to detect risk and allow correlation between abnormal levels of markers and arterial pathology. Already, higher levels of soluble CD40 ligand have been correlated with intra-plaque lipid accumulation in carotid atheroma as assessed by high-resolution magnetic resonance imaging (19). Future studies will uncover additional associations between inflammatory marker levels and in vivo plaque characterization.

Although current efforts have been directed at suppressing inflammation and lowering CRP in particular, raising IL-10 might provide logical complementary or perhaps even superior therapy (1), although unopposed anti-inflammatory activity, such as the blockade of TNF- α , has not proven beneficial in patients with heart disease (20). Perhaps Mother Nature has outwitted us once again, with counter-regulatory factors that negate any benefit of opposing just one particular cytokine. Similarly, human recombinant IL-10 has not been particularly effective in rheumatoid arthritis and has even been shown to produce some pro-

inflammatory effects resulting from the up-regulation of Fc gamma receptor expression on macrophages (21). Our initial simplistic attempts to alter just one particular element of the inflammatory cascade are unlikely to have the desired effect. As our understanding of the regulation of physiologic processes deepens, the beauty and complexity of counter-regulatory pathways recalls the ancient Chinese concept of the natural balance of Yin and Yang, light and dark, positive and negative, male and female. Ultimately, only a better understanding of the Yin and Yang of arterial inflammation will enhance our ability to prognosticate risk and effectively design therapy directed to an individual's specific risk profile.

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