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Effects of Systemic Inflammation on Endothelium-Dependent Vasodilation

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Abstract

The importance of inflammation in the pathogenesis of atherosclerosis is well established. The vascular endothelium contributes to and is affected by the inflammatory process. For example, a variety of cytokines have the ability to "activate" the endothelium and thereby promote expression of adhesion molecules and chemotactic factors that accelerate the inflammatory process and direct accumulation of leukocytes to specific sites in the arterial tree. In experimental systems, activation of endothelial cells is also associated with a loss of the biologic activity of endothelium-derived nitric oxide, an effect that accelerates the inflammatory process and also promotes local thrombosis and impairs local control of vasomotor tone. Consistent with these experimental studies, recent studies have provided evidence that inflammation is associated with an impairment of nitric oxide-dependent responses in human subjects. This article will review the experimental and clinical studies that support the relevance of inflammation to nitric oxide bioactivity in human atherosclerosis.

It is now well recognized that atherosclerosis is an inflammatory disease (Ross 1999). Systemic risk factors induce a state of inflammation that contributes to all stages of atherosclerosis from the initiating events in lesion formation to the latest phase when plaques rupture, thrombose, and produce clinical syndromes such as myocardial infarction or stroke (Libby et al. 2002). The importance of inflammation in atherosclerosis is supported by recent studies showing that elevated levels of inflammatory markers identify individuals with increased risk for cardiovascular events (Pearson et al. 2003). In particular, the acute phase reactant C-reactive protein (CRP) shows promise as a clinically useful marker of cardiovascular risk (Ridker 2003).

The vascular endothelium is both affected by and contributes to the inflammatory process that leads to atherosclerosis. For example, proinflammatory factors "activate" endothelial cells to promote an atherogenic phenotype. The activated endothelium, in turn, expresses adhesion molecules and chemotactic factors that accelerate and localize the inflammatory process. An important consequence of endothelial activation is loss of the biologic activity of endothelium-derived nitric oxide. Investigators have argued that a broad alteration of endothelial function, including loss of nitric oxide under proinflammatory conditions, might be a critical mechanism that links systemic states of inflammation to atherosclerosis (Vallance et al. 1997). This article will review the recent studies that support the relevance of systemic inflammation to nitric oxide bioactivity in human subjects.

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The Endothelium as a Regulator of Vascular Homeostasis

The endothelium regulates vasomotor tone, blood fluidity, growth of vascular smooth muscle cells, and local inflammation by elaborating a number of paracrine factors, including nitric oxide (Widlansky et al. 2003a). Endothelium-derived nitric oxide is a potent vasodilator and acts to inhibit platelet activity, vascular smooth muscle cell growth, and adhesion of leukocytes to the endothelial surface. The endothelium produces other vasodilators, including prostacyclin and endothelium-derived hyper-polarizing factor, and vasoconstrictors, including endothelin, angiotensin II, and vasoconstrictor prostaglandins. The endothelium controls fibrinolysis by producing tissue plasminogen activator and plasminogen activator inhibitor 1 and is the source of coagulation factors such as von Willebrand factor and thrombo-modulin. Under normal conditions, the endothelium maintains a vasodilator, antithrombotic, and anti-inflammatory state. However, classic and recently recognized cardiovascular disease risk factors are associated with a loss of the biologic activity of endothelium-derived nitric oxide and increased expression of prothrombotic factors, proinflammatory adhesion molecules, cytokines, and chemotactic factors. These profound changes in endothelial phenotype are believed to contribute to all phases of atherosclerosis (Widlansky et al. 2003a).

Given its relevance to atherosclerosis, there is great interest in evaluating endothelial function in human subjects, and many studies have focused on responses that depend on the availability of endothelium-derived nitric oxide (Vita, 2002). Endothelium-dependent vasodilation may be assessed invasively by examining the changes in arterial diameter or flow during infusion of agonists such as acetylcholine or brady-kinin that stimulate production of nitric oxide by the endothelium. Shear stress is another potent stimulus for endothelial nitric oxide production, and noninvasive approaches to assess endothelium-dependent dilation include assessment of brachial artery flow-mediated dilation by ultrasound (Corretti et al. 2002) and measurement of flow-mediated changes in pulse amplitude in the fingertip (Kuvin et al. 2003b). Other noninvasive methods to assess endothelial function include measurement of pulse wave velocity and other indicators of arterial stiffness, which are influenced, in part, by vasomotor tone and nitric oxide availability (Oliver and Webb 2003). Another approach involves assessment of reactive hyperemia after limb occlusion. This response occurs after a period of tissue ischemia and reflects, in large part, the local vasodilator effects of factors such as adenosine and acidosis. However, there is growing appreciation that nitric oxide contributes to the hyperemic response and that reactive hyperemia is blunted in the setting of risk factors (Mitchell et al. 2004). Another recently recognized manifestation of endothelial dysfunction is a decrease in circulating endothelial progenitor cells in human subjects, possibly reflecting decreased capacity for endothelial repair (Hill et al. 2003).

There now is strong evidence that endothelial dysfunction is clinically relevant. Patients with endothelial vasomotor dysfunction in the coronary or peripheral circulation have increased risk for future cardiovascular events, including myocardial infarction, stroke, and cardiovascular disease (Widlansky et al. 2003a). In addition, a variety of interventions have been shown to both improve endothelial function and reduce cardiovascular risk, suggesting that endothelial dysfunction contributes to the pathogenesis of cardiovascular disease. In this regard, statin therapy, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, smoking cessation, exercise, and weight loss have all been shown to improve endothelium-dependent vasodilation and reduce cardiovascular risk.

Experimental Studies of Endothelial Activation by Proinflammatory Factors

A number of relevant factors have been shown to activate endothelial cells, for example, oxidized low-density lipoprotein (ox-LDL), lipopolysaccharide, interleukin (IL) 1, tumor necrosis factor α (TNF-α), CRP, and other factors stimulate endothelial expression of adhesion

molecules, monocyte chemotactic factor 1, tissue factor, plasminogen activator inhibitor 1, cyclooxygenase (COX) 2, and other factors that contribute to inflammation in the vascular wall. Expression of many of these factors depends on activation of the nuclear factor-κB (NF-κB) pathway. Some NF-κB-dependent factors such as IL-1 have the ability to further activate NF-κB and amplify the inflammatory response (Monaco and Paleolog 2004).

An important consequence of endothelial activation is a decrease in the bioavailability of endothelium-derived nitric oxide. In cell culture, proinflammatory factors such as TNF-α, CRP, and ox-LDL downregulate expression of endothelial nitric oxide synthase (eNOS) and thus decrease nitric oxide production (Vallance et al. 1997, Verma et al. 2002). This effect appears to be mediated via a decrease in the stability of eNOS messenger RNA (Verma et al. 2002). Whereas it is clear that cytokines such as TNF-α activate endothelial cells, recent studies have raised the possibility that the reported effects of the acute phase reactant CRP might be attributable to contaminants in commercially available preparations. Thus, CRP could be a marker of systemic inflammation rather than an active participant in vascular wall pathology (Pepys 2005). In addition to decreasing eNOS protein, cytokine exposure also has the potential to decrease the bioavailability of nitric oxide by increasing the production of reactive oxygen species in endothelial cells that can react with and reduce the activity of nitric oxide. Reactive oxygen species can also decrease the production or effects of nitric oxide via oxidative modification of eNOS or guanylyl cyclase (Stocker and Keaney 2004).

A number of studies have made it clear that traditional risk factors induce a proinflammatory state. In addition, however, there has been considerable interest in the possibility that novel risk factors, including certain chronic infections, might also impair endothelial function and contribute to the development of atherosclerosis (Vallance et al. 1997), for example, serologic evidence of prior infection with *Chlamydia pneumoniae*, cytomegalovirus, and other pathogens is associated with increased risk for cardiovascular disease (Epstein et al. 2000). Interestingly, net infectious burden also correlates with the severity of endothelial dysfunction in patients with and without angiographically apparent coronary artery disease (CAD) (Prasad et al. 2002). Chronic infections might alter endothelial function by stimulating a systemic inflammatory response or by directly invading endothelial cells and altering their function.

Human Studies of Systemic Inflammation and Endothelial Dysfunction

The growing body of experimental studies linking inflammation to endothelial activation and loss of nitric oxide bioactivity has promoted investigators to seek evidence that systemic inflammation or infection leads to endothelial dysfunction in human subjects. Such studies have taken several forms. For example, investigators have examined changes in endothelial function after acute administration of proinflammatory factors to healthy subjects. Alternatively, investigators have completed observational studies designed to demonstrate a correlation between circulating markers of inflammation or infection and endothelial dysfunction. Finally, recent intervention studies have examined the potential benefits of interventions designed to reduce systemic inflammation or infection.

Several studies have examined the effects of acute proinflammatory stimuli. Hingorani et al. (2000) made measurements of vascular function immediately before and after *Salmonella typhi* vaccination, which produces an acute inflammatory response and increased circulating levels of inflammatory cytokines. Vaccination was associated with short-term impairment of endothelium-dependent dilation in conduit and resistance vessels that paralleled the inflammatory response. A subsequent study from the same group demonstrated that high-dose aspirin treatment prevents the development of endothelial dysfunction under these conditions (Kharbanda et al. 2002). Another study showed that 1-h exposure to TNF-α, IL-1β, or endotoxin impairs endothelial function in hand veins of healthy subjects (Bhagat et al. 1996). Endothelial

dysfunction is also produced by intra-arterial endotoxin infusion, and this impairment can be prevented by pretreatment with a statin (Pleiner et al. 2004).

Another line of investigation that relates inflammatory mechanisms to endothelial dysfunction is provided by studies of transplant arteriopathy. In this situation, the previously normal donor vasculature is exposed to a chronic immune response beginning at a fixed point in time. Studies in heart transplant patients have shown that endothelial dysfunction develops in the donor coronary arteries in the 1 to 2 years after heart transplant, and the severity of endothelial dysfunction under these conditions predicts the subsequent development of graft atherosclerosis (Davis et al. 1996). Overall, these studies showing impairment of endothelial function in previously normal arteries provide strong evidence that proinflammatory states lead to a loss of the bioactivity of endothelium-derived nitric oxide in humans. However, these studies do not address the relevance of these mechanisms for patients with risk factors or ordinary CAD.

Many studies have correlated serum markers of inflammation or infection with endothelial function in patients and have yielded mixed results. As outlined in Table 1, a number of relatively small studies in selected patient populations have shown correlations between serum levels of CRP or soluble adhesion molecules and endothelium-dependent vasodilation. In contrast, several larger studies have failed to observe a significant relationship between serum markers of inflammation and endothelium-dependent vasodilation. For example in a study of 218 patients undergoing coronary angiography, Prasad et al. (2002) found no correlation between CRP and endothelium-dependent responses to acetylcholine in the coronary circulation. Similarly, Verma et al. (2004) observed no correlation between CRP and brachial artery flow-mediated dilation in a group of 1154 healthy and relatively young male fire-fighters. These studies argue against a specific pathogenic role for CRP as an inducer of endothelial dysfunction but do not address the importance of other potential proinflammatory stimuli.

Vita et al. (2004) recently examined the question of whether circulating markers of inflammation and endothelial activation correlate with vascular function, with the use of the well-characterized Framingham Heart Study Offspring cohort. In that study, the investigators measured brachial artery flow-mediated dilation and reactive hyperemia in the forearm and serum levels of CRP, IL-6, soluble intercellular adhesion molecule 1 (sICAM-1), and monocyte chemotactic protein 1 in 2701 participants. Three of these markers (CRP, IL-6, and sICAM-1) were inversely related to flow-mediated dilation and reactive hyperemia, but this relation was lost or markedly weakened after adjustment for traditional risk factors. These findings suggest that systemic inflammation and endothelial activation relate to the vasomotor function of the endothelium but provide evidence that much of this relationship is accounted for by the proinflammatory effects of traditional risk factors. The findings argue against an important role for chronic infection or other proinflammatory states in the pathogenesis of vascular dysfunction, at least in the relatively low-risk, community-based Framingham cohort.

Whereas large-scale studies such as the Framingham Heart Study have excellent statistical power to adjust for potential confounders, they are limited to examination of associations between vascular function and markers of inflammation. Stronger evidence for a causal relationship between chronic inflammation or infection and vascular dysfunction in humans with atherosclerosis would be provided by intervention studies showing that specific anti-inflammatory drugs or interventions reversed endothelial dysfunction. Several studies along these lines have been reported. Anti-inflammatory therapies, including nonselective and selective COX inhibitors, have been reported to improve endothelial function in patients with risk factors and established atherosclerosis. For example, aspirin (Husain et al. 1998) and the selective COX-2 inhibitor celecoxib (Widlansky et al. 2003b) have both been shown to improve endothelium-dependent dilation. It is well established that cholesterol-lowering therapy also

reduces systemic markers of inflammation, including CRP (Ballantyne et al. 2003). On this basis, investigators have argued that the beneficial effects of statins on endothelial function in patients might also be attributable to pleiotropic anti-inflammatory effects (Bonetti et al. 2003). More specific interventions, including drugs that bind TNF-α, have also been shown to improve endothelial function in patients with heart failure (Fichtlscherer et al. 2001) or rheumatoid arthritis, (Hurlimann et al. 2002), and it would be interesting to observe the effects of these or more specific interventions in patients with atherosclerosis.

If inflammation due to chronic infection is important for endothelial dysfunction in atherosclerosis, antibiotic treatment might have a beneficial effect. Several studies have examined this possibility by studying the effects of therapy directed against *C pneumoniae* on endothelial function and systemic inflammation. In general, these studies have failed to demonstrate beneficial effects (Kuvin et al. 2003a), and these findings are consistent with recent clinical trials that failed to demonstrate a benefit of antimicrobial therapy for secondary prevention (Anderson 2005). However, it remains possible that infectious agents might contribute to systemic inflammation by inducing a chronic inflammatory response, even after the inciting organisms have been cleared, and under these conditions, antimicrobial therapy would likely have no effect (Epstein et al. 2000).

Summary and Conclusions

The importance of systemic inflammation and endothelial dysfunction in the pathogenesis and clinical expression of atherosclerosis is now well accepted. There also is convincing experimental evidence to suggest that proinflammatory factors activate endothelial cells and reduce the bioavailability of endothelium-derived nitric oxide. Human studies have shown that acute inflammatory responses in healthy subjects blunt endothelial function and that nonspecific therapy directed against inflammation may reverse endothelial dysfunction in patients with atherosclerosis. In addition, more specific interventions such as anti-TNF-α therapy reverse endothelial dysfunction in other disease states, including heart failure and rheumatoid arthritis. However, despite suggestive findings in small studies of selected groups of patients, the available association studies have provided mixed information and indicate relatively modest or no correlation between endothelial function and serum CRP and other systemic markers after adjustment for traditional risk factors. These findings emphasize the difficulties of attempting to draw conclusions about events in the vascular wall by measuring markers in circulating blood and the importance of traditional risk factors as causes of systemic inflammation.

Ultimately, this body of work supports the possibility that anti-inflammatory therapy might have promise as a new approach for the treatment or prevention of atherosclerotic cardiovascular disease. Many other interventions that reverse endothelial dysfunction have been shown to reduce cardiovascular risk and prevent recurrent events. An anti-inflammatory strategy that restores normal endothelial function might have similar beneficial effects. Given the many different and redundant factors that contribute to the inflammatory response, interventions that inhibit upstream activators of inflammation, such as NF-κB, might have particular promise. However, it is clear that much more work needs to be done to identify the best approaches and then to put those approaches into practice.

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Table 1

Selected observational studies of endothelial function and markers of inflammation

Reference	Study population	Inflammatory marker	Assessment of endothelial function	Results
Fichtlscherer et al. (2000)	60 Men with CAD	CRP, TNF-α, and sICAM-1	FBF acetylcholine	Inverse correlation between CRP and endothelial function and no correlation with other markers
Sinisalo et al. (2000)	31 Men with CAD	CRP, antibodies to ox-LDL, and CD4 and CD8 counts	FBF acetylcholine	Inverse correlations between endothelial function and CRP, ox-LDL, and CD4 count
Tomai et al. (2001)	54 Patients with CAD	CRP	Coronary cold pressor test	Correlation between CRP and severity of cold-induced constriction
Brevetti et al. (2001)	31 Patients with PAD, 14 controls	sICAM-1 and sVCAM-1	Brachial artery FMD	Inverse correlation between sICAM-1 and sVCAM-1 and FMD
Tan et al. (2002)	80 Patients with type II diabetes and hypercholesterolemia	CRP	Brachial artery FMD	Inverse correlation between FMD and CRP
Holmlund et al. (2002)	59 Healthy subjects	CRP, ICAM-1, VCAM-1, and E selectin	FBF methacholine and nitroprusside	Inverse correlation between endothelial function and sICAM-1 and no relation with VCAM-1, E selectin, or CRP
Prasad et al. (2002)	218 Patients referred for catheterization	CRP and antibodies to infectious agents	Coronary acetylcholine	No relation between endothelial function and CRP and strong inverse correlation with pathogen antibodies
Brevetti et al. (2003)	88 Patients with PAD	CRP and fibrinogen	Brachial artery FMD	Inverse correlation between CRP, fibrinogen, and FMD
Witte et al. (2003)	166 Healthy subjects	sICAM-1 and CRP	Brachial artery FMD	Inverse correlation between sICAM-1, CRP, and FMD
Teragawa et al. (2004)	46 Patients with normal coronary angiography	CRP	Intracoronary artery acetylcholine	Inverse correlation between CRP and endothelial function in

Reference	Study population	Inflammatory marker	Assessment of endothelial function	Results
				coronary microcirculation
Vita et al. (2004)	2701 Community-based subjects	CRP, IL-6, MCP-1, and sICAM-1	Brachial artery FMD and reactive hyperemia	Inverse correlation between CRP, IL-6, ICAM-1, and FMD and reactive hyperemia, and weakened after adjustment for risk factors
Verma et al. (2004)	1154 Male firemen	CRP	Brachial artery FMD	No correlation between CRP and FMD

FBF indicates forearm blood flow measured with venous occlusion plethysmography; PAD, peripheral arterial disease; sVCAM-1, soluble vascular adhesion molecule 1; FMD, flow-mediated dilation; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular adhesion molecule 1; MCP-1, monocyte chemotactic protein 1.