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Scientific Update™

Angiotensin-Converting Enzyme Inhibition and Endothelial Dysfunction: The Taming of the Hostile Endothelium

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Reported and discussed by:
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Endothelial cells are metabolically active and play a dynamic role in the regulation of normal vascular biology, in the repair of the arterial wall following injury, and in the pathogenesis of atherosclerosis. The endothelium releases numerous substances that not only affect vascular tone, but also influence antithrombotic, anti-inflammatory, and growth inhibitory functions. Thus, endothelial dysfunction is a frequently observed and early event in the atherosclerotic process. Endothelial dysfunction (and its related nitric oxide and bradykinin deficiency and angiotensin II excess) in the clinical settings of coronary artery disease, hypertension, and congestive heart failure, may be dramatically improved with the use of angiotensin-converting enzyme (ACE) inhibitors. In particular, administration of agents which have a high affinity for tissue ACE (e.g. quinapril) may effect important changes in the functional integrity of the endothelium.

In presentations at a satellite symposium at the 70th Scientific Session of the American Heart Association, the importance of the endothelium in coronary artery disease and hypertension was discussed. The role of ACE inhibitors in the treatment of congestive heart failure patients with endothelial dysfunction was elucidated in an abstract presentation.

The role of endothelium in the atherosclerotic process

Previously, the endothelium was regarded as a relatively inert, semipermeable barrier lining the vasculature. However, in the last two decades, it has become clear that the endothelium is not just a passive barrier between the blood and vessel wall. It is, in fact, a metabolically active lining of cells that interact with cellular and soluble factors present in the blood, as well as in other layers of the vessel wall.

Functional integrity of the endothelium is crucial for the maintenance of blood flow and antithrombotic capacity because the endothelium produces mediators regulating vascular growth, platelet function, and coagulation. In addition, it alters vasomotor tone by synthesizing and metabolizing vasoactive substances including an endothelium-derived hyperpolarizing factor (EDHF), prostacyclin, and most notably, endothelium-derived relaxing factor (EDRF), which has been identified as nitric oxide (NO). NO, which is formed from L-arginine by the action of the enzyme nitric oxide synthase, inhibits platelet aggregation and adhesion, modulates smooth muscle cell proliferation, attenuates the generation of endothelin, and modulates leukocyte and monocyte adhesion to the endothelium.[1]

The healthy endothelium maintains vasodilation by continuously releasing NO at low levels, and by releasing NO in response to a variety of physical and chemical stimuli, the most important being shear-stress. In contrast, many endothelial substances cause vasoconstriction, including angiotensin II, endothelin, and, indirectly, superoxide O_2^-.

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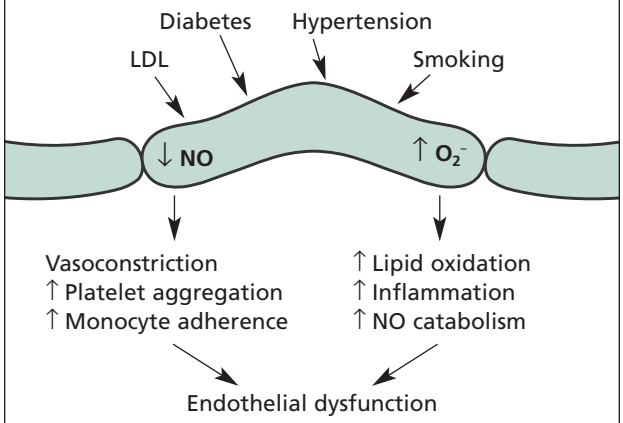
Figure 1: Schematic diagram of endothelial dysfunction



Angiotensin II produces vasoconstriction directly and also indirectly by releasing endothelin, the most potent endothelial vasoconstrictor. Adequate basal levels of NO also prevent: platelet adhesion and the release of platelet-derived growth factor, expression of leukocyte adhesion molecules or chemo-attractants, and oxidation of low-density lipoproteins (LDL) by scavenging reactive oxygen substances (figure 1).

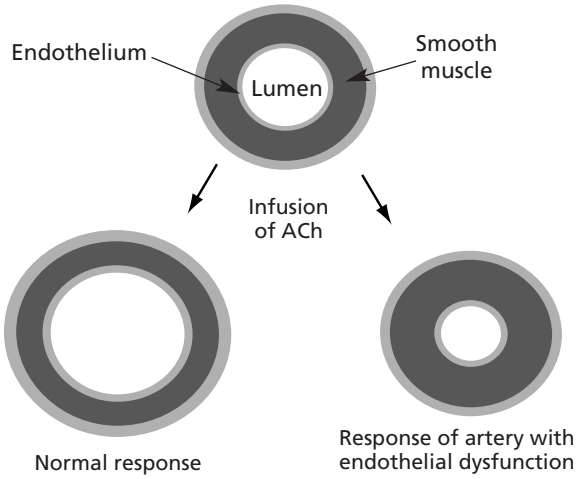
Although the complications of atherosclerosis usually occur in middle and old age, atherogenesis is a decades-long process. A key early event in atherogenesis is dysfunction of the endothelial cell layer. This involves decreased availability of NO in the arterial wall and is associated with cigarette smoking, hypertension, hypercholesterolemia, and diabetes.

Assessment of endothelial function

In vivo study of endothelial function can be demonstrated by both pharmacologic and physiologic stimuli. For example, infusion of acetylcholine (ACh) and subsequent assessment of coronary artery diameter angiographically can provide invasive assessment of endothelial function. ACh is an endothelium-dependent, muscarinic, cholinergic agonist that causes normal vessels to dilate through the release of NO.

However, atherosclerotic vessels constrict in response to ACh, since its direct vasoconstrictor effect in muscarinic receptors in smooth muscle cells overrides the decreased NO effect in atherosclerotic vessels (figure 2). Ludmer et al[2] were the first to recognize the paradoxical vasoconstriction induced by ACh in atherosclerotic human coronary arteries. These

Figure 2: Acetylcholine (ACh) and endothelial response



Stylized representations of endothelial responses. After a coronary artery is infused with acetylcholine, the artery dilates in the absence of disease, reflecting normal endothelial cell function (left). In contrast, arteries constrict in the presence of hypercholesterolemia and/or atherosclerosis, reflecting endothelial cell dysfunction (right).

authors demonstrated that ACh produced dose-dependent dilatation in normal arteries but constriction of prestenotic, stenotic, and post-stenotic segments of coronary arteries in the presence of atherosclerosis. Zeiher et al[3] extended these findings by demonstrating progressive impairment in endothelial vasodilation in patients with mild atherosclerosis and in those with hyperlipidemia without overt angiographic disease. Others have also shown abnormal vasoconstriction in response to ACh in individuals with angiographically normal coronary arteries but with one or more risk factors for atherosclerosis, including diabetes, hypertension, cigarette smoking, and hyperlipidemia (Vita et al,[4] Seiler et al[5]).

Endothelial function can also be studied with physiologic stimulation, either invasively or noninvasively. For example, Gordon et al[6] demonstrated that angiographically normal arteries dilated during supine bicycle exercise; however, arteries with irregularities or stenoses generally constricted in response to exercise or in response to ACh.

Impact of the renin-angiotensin system on endothelium

The renin-angiotensin system (RAS) affects the vasculature through the actions of ACE, largely via the consequences of angiotensin II production and bradykinin degradation.

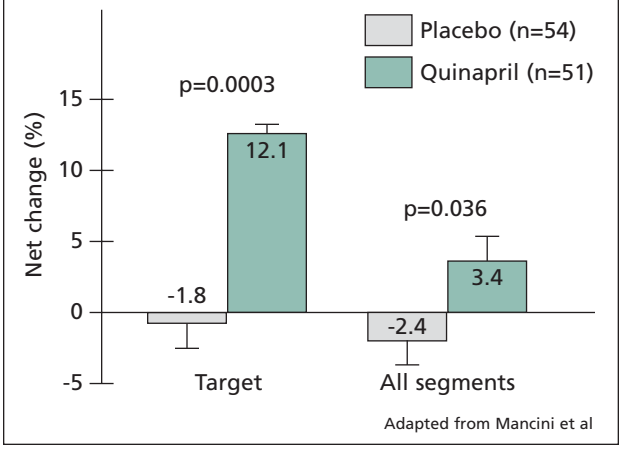
Angiotensin II in the vascular wall causes a decrease in production and/or release of NO which can contribute to endothelial dysfunction. Angiotensin II also appears to increase the oxidation of LDL and induces production of plasminogen activator inhibitor-1 (PAI-1), the most potent endothelial t-PA inhibitor. Increased levels of angiotensin II could therefore lead to increased risk for thrombosis. ACE also degrades bradykinin, which normally serves as an important stimulus for NO production. Bradykinin is also a stimulus for tPA release, which helps to maintain the normal equilibrium between fibrinolysis and thrombosis.

Quinapril improves endothelial dysfunction

Since ACE inhibition prevents the degradation of bradykinin and inhibits angiotensin II (leading to less vasoconstriction and an increase in NO levels), ACE inhibitors should improve endothelial function.

This is supported by the results of the Trial on Reversing Endothelial Dysfunction (TREND), a six-month randomized, double-blind study assessing the impact of quinapril on endothelial function.[7] In patients undergoing percutaneous transluminal coronary angioplasty (PTCA) for significant stenosis in one or two arteries, the researchers identified an adjacent artery with endothelial dysfunction as the "target" artery for the study. Endothelial dysfunction was defined as vasoconstriction in response to acetylcholine during a baseline angiogram. Twelve to seventy-two hours after PTCA, patients were randomized to receive either placebo or quinapril (40 mg per day). Patients with potentially confounding conditions such as hyperlipidemia treated with lipid-lowering therapy, or poorly controlled hypertension, were excluded. After six months, the response to ACh infusion was assessed angiographically. While the placebo group showed no change in the vasoconstrictor response to acetylcholine, the quinapril group demonstrated a marked improvement (figure 3).

Figure 3: Net change (%±SE) in target and all segment response at an acetylcholine dose of 10^{-4} mol/L after 6 months in the TREND study



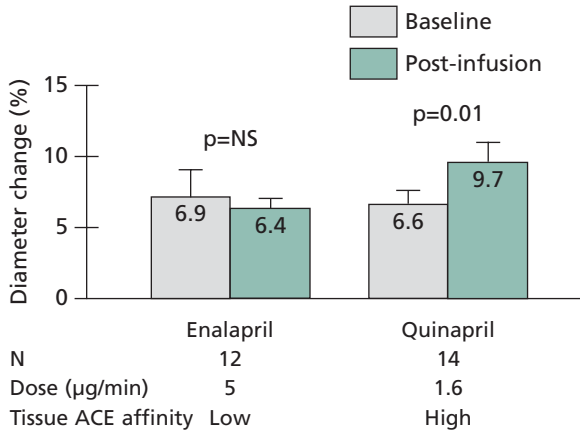
TREND suggests that the benefits of ACE inhibition are due to attenuation of the contractile and super oxide-generating effects of angiotensin II and to the enhancement of endothelial cell release of NO, secondary to diminished breakdown of bradykinin. The improvement noted in endothelial dysfunction in TREND with an ACE inhibitor (quinapril) that has a high affinity for tissue ACE is consistent with trials of lipid-lowering therapy that also show improvement in endothelial function as compared to placebo (Treasure et al,[8] Anderson et al[9]).

More recently, noninvasive assessment of endothelial dysfunction has been demonstrated with high-resolution ultrasound measurement of brachial artery flow vasodilation. There is evidence that brachial artery dilation is impaired by the same risk factors that attenuate coronary vasodilation and a correlation between brachial and coronary vasodilator responses has been described.

In the recently completed Brachial Artery Normalization of Forearm Flow Function (BANFF), 88 patients with established coronary artery disease underwent high-resolution ultrasound to assess brachial artery dilation in response to reactive hyperemia. Patients received a total of three drugs in a crossover design, with each drug administered for eight weeks, and with a two week washout period between treatments. BANFF evaluated the effects of the ACE inhibitors quinapril and enalapril, the direct angiotensin blocker losartan, and the calcium channel blocker, amlodipine, on flow-mediated vasodilation of the brachial artery. Preliminary data suggest a more dramatic change from baseline in brachial artery flow-mediated vasodilation in patients who had received eight weeks of quinapril treatment. In contrast, there was no change in vasodilation with enalapril and amlodipine, and a more modest effect with losartan. This suggests that ACE inhibitors and other antihypertensive agents may differ in their impact upon endothelial dysfunction.

ACE inhibition with quinapril also appears to improve endothelial function in patients with congestive heart failure (CHF). Recent data suggest that endothelium-dependent dilation of blood vessels is impaired in CHF and could potentially be improved with ACE inhibition. Drexler and

Figure 4: Radial artery diameter change (%) as measured by high-resolution ultrasound at baseline and 8 minutes after wrist occlusion (representing flow-dependent, endothelium-mediated dilation)



Adapted from Hornig et al

colleagues have previously demonstrated that ACE inhibition improves flow-dependent, endothelium-mediated dilation due to an increased availability of NO.[10,11]

Most recently, Hornig et al evaluated the effects of quinapril (1.6 µg/min: high affinity to tissue ACE) and enalapril (5 µg/min: low affinity to tissue ACE) on flow-dependent, endothelium-mediated dilation in 26 patients with CHF. Radial artery diameter was measured by high resolution ultrasound. Following eight minutes of wrist occlusion, the changes in radial artery diameter were significantly increased compared to baseline in the quinapril, but not in the enalapril-treated patients (figure 4). Thus, despite a higher dose of enalapril, quinapril (with a higher affinity to tissue ACE) showed greater dilation. After increasing the dose of enalapril further and to the point of a systemic effect (change in blood pressure), there was still no improvement in radial artery diameter as compared to baseline in the enalapril group.

Summary

Endothelial dysfunction is an early and frequent manifestation of atherosclerotic heart disease. Administration of ACE inhibitors, particularly those with higher affinity for tissue ACE (e.g., quinapril) appears to be an effective means of altering endothelial dysfunction. Whether treatment specifically targeted at endothelial dysfunction in patients with coronary artery disease, hypertension, and congestive heart failure translates into a better long-term clinical outcome awaits large-scale trial results.

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