Current Perspective

Are ACE Inhibitors a “Magic Bullet” Against Oxidative Stress?

Thomas Münzel, MD; John F. Keaney, Jr, MD

The recently published Heart Outcomes Prevention Evaluation (HOPE) study,1,2 as well as the Study to Evaluate Carotid Ultrasound Changes in Patients Treated With Ramipril and Vitamin E (SECURE),3 demonstrated that treatment with an ACE inhibitor but not vitamin E had beneficial effects on the prognosis and progression of atherosclerosis. In these studies, long-term ACE inhibition significantly reduced the rate of death, myocardial infarction, and stroke and reduced the intima-to-media ratio of carotid arteries in patients at high risk for cardiovascular events. It is likely that these findings will have wide-ranging implications for the treatment of cardiovascular disease, and the contrasting results with respect to ACE inhibitors and vitamin E provide an opportunity to revisit the role of oxidative stress in vascular disease.

LDL Oxidation and Cardiovascular Disease

A surprising finding of these studies was the ineffectiveness of vitamin E in preventing the clinical manifestations of coronary artery disease and the progression of atherosclerosis. A wealth of previous experimental and epidemiological data suggested that excess LDL oxidation was, in part, responsible for the development of atherosclerosis.4 Because vitamin E can inhibit LDL oxidation ex vivo, a logical strategy to reduce oxidative stress would include the administration of antioxidants such as vitamin E. This approach carries considerable risk if the antioxidant is not active against all oxidants relevant to atherosclerosis. Although vitamin E effectively scavenges lipid peroxyl radicals, it has limited activity against other oxidants such as superoxide, peroxynitrite, and hypochlorous acid that have been implicated in atherosclerosis. Another risk with an antioxidant strategy relates to putative cellular compartments or “microwodomains” in the vascular wall that do not contain appreciable amounts of the antioxidant. The sum total of these effects would be continued oxidation even in the presence of the antioxidant. Experimental evidence from both animals and patients suggests that lipid peroxidation does proceed in the vascular wall even in the presence of vitamin E.5 Attempts to increase the effectiveness of vitamin E with higher doses have met with worsening atherosclerosis and vascular function in experimental models,6 perhaps because of the well-described requirement for coantioxidants to achieve optimal vitamin E antioxidant activity.7 Thus, a single-agent antioxidant strategy may not completely reduce vascular oxidative stress and may leave other important processes, such as smooth muscle proliferation and impaired vascular function, untouched (the Figure).

Some might argue that combination antioxidant therapy should circumvent the shortcomings of vitamin E supplementation outlined above. In this regard, it has been proposed that ascorbic acid (vitamin C) can regenerate vitamin E from its oxidized form in LDL ex vivo.8 The relevance of these findings for lipid peroxidation in vivo, however, is not clear owing, in part, to the relative paucity of data comparing the effectiveness of combination therapy with vitamin E alone. A study of vascular injury in pigs suggested that the combination of vitamins C and E was more effective than either vitamin alone in promoting “positive” vascular remodeling.9 However, in cholesterol-fed rabbits, neither vitamin E or its combination with vitamin C is effective in limiting atherosclerosis.10 The only clinical study demonstrating reduced atherosclerosis by combining vitamins E and C compared with vitamin E alone was the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) trial11; however, this result was restricted to men (The overall results were not reported), and there was no additional antioxidant activity afforded by combination therapy compared with either vitamin alone.12 Thus, there currently is no evidence that the combination of vitamins C and E will provide any enhancement of vitamin E antioxidant activity that will refute the results of the HOPE and SECURE trials.

ACE Inhibitors: Cardiovascular Pharmacology

At first glance, it may seem strange that ACE inhibitors and vitamin E would be assessed for the prevention of cardiovascular disease within the same trial. Traditionally, the vascular action of ACE inhibitors has been associated with their inhibition of angiotensin II formation. Angiotensin II causes vasoconstriction via stimulation of smooth muscle AT₁ receptor.13 Angiotensin has also been shown to be a strong stimulus for the expression of preproendothelin within endothelial cells14 and smooth muscle cells.15 Part of the angiotensin II–induced vasoconstriction is due to stimulation of the

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release of endothelin-1 from endothelial cells and smooth muscle cells.

By inhibiting angiotensin II formation, ACE inhibition may also beneficially influence inflammatory processes within the vascular wall. Angiotensin II facilitates recruitment of monocytes and macrophages into the vessel wall by stimulating smooth muscle cell production of monocyte attractant protein-1 and expression of vascular cell adhesion molecule-1.\(^{17}\) In addition, angiotensin II is a well-characterized mitogen for vascular smooth muscle cells and may stimulate the accumulation of extracellular matrix either directly or indirectly through the production of the transforming growth factor-B.\(^{18}\)

Another important aspect of ACE inhibitors relates to the fact that the ACE and the endothelial kininase II are one in the same.\(^{19}\) Inhibition of kininase II leads to increased formation of bradykinin, which stimulates the bradykinin B\(_2\) receptor, inducing the release of vasodilator substances such as nitric oxide (NO), endothelium-derived hyperpolarizing factor, and prostacyclin.\(^{19}\) The production of NO, endothelium-derived hyperpolarizing factor, and prostacyclin causes vascular smooth muscle cell relaxation through distinct mechanisms such as generation of cGMP, activation of BkCa channels, and generation of cAMP, respectively. Although stimulation of the bradykinin B\(_2\) receptor is subject to a rapid tachyphylaxis, recent in vitro studies indicate that this phenomenon is prevented by ACE inhibition.\(^{20}\) The action of ACE inhibitors to increase endothelial NO and prostacyclin production may, in part, explain the vasodilator, antithrombotic, and antiproliferative effects of ACE inhibitors.

**ACE Inhibitors and Oxidative Stress**

In addition to the aforementioned activity of ACE inhibitors to reduce levels of angiotensin II and increase bradykinin, emerging evidence suggests that ACE inhibitors have important implications for vascular oxidative stress. In this regard, all the major cell types of the vascular wall (endothelium, smooth muscle, and fibroblasts) contain enzyme systems that use NADH and/or NADPH as substrates for the production of superoxide anion,\(^{21}\) and these systems are activated in response to angiotensin II.\(^{22}\) Therefore, in conditions in which the local and/or systemic renin angiotensin system is activated, one would expect superoxide production to be increased. Experimental and clinical evidence supports this contention. For example, activation of the renin-angiotensin system in experimental animals produces hypertension that is associated with increased vascular superoxide.\(^{23}\) Likewise, experimental models of atherosclerosis demonstrate activation of the local renin-angiotensin system, along with evidence of increased vascular NADH/NADPH oxidase activity.\(^{24}\) In patients, ACE activity in atherosclerotic plaques\(^{25}\) is increased, and the vascular NAD(P)H oxidase activity increases as a function of risk factors for coronary artery disease.\(^{26}\) Thus, both experimental and clinical studies have provided functional evidence for stimulation of the renin-angiotensin system and simultaneously for activation of an NAD(P)H oxidase in the arterial wall.

Activation of NAD(P)H oxidase and increased superoxide within the vascular wall have important implications for both the progression of atherosclerosis and the development of clinical events. Superoxide combines with NO in a diffusion limited reaction (\(k = 1.9 \times 10^{10} \text{ mol} \cdot \text{L}^{-1} \cdot \text{s}^{-1}\)) that is \(\approx 10\) times faster than the dismutation of superoxide by the superoxide dismutase.\(^{27}\) This reaction produces peroxynitrite, a compound with limited NO-like bioactivity, thereby “shunting” NO away from its typical targets such as vasodilation and inhibition of platelets. This latter effect may be important for precipitating vascular events because impaired NO bioactivity is predictive of atherosclerotic disease activity.\(^{29}\) In addition to reducing NO bioactivity, peroxynitrite formation also promotes lipid and protein oxidation in atherosclerotic lesions.\(^{30}\) Thus, excess vascular superoxide has the dual effect of reducing the bioactivity of NO and promoting vascular oxidative stress.

Increased NAD(P)H oxidase–derived superoxide has important implications for vascular disease that extend beyond its interaction with NO. Superoxide is subject to dismutation by superoxide dismutase producing hydrogen peroxide (H\(_2\)O\(_2\)), an agent typically associated with lipid and protein oxidation in the presence of transition metals. Consistent with this notion, high concentrations of H\(_2\)O\(_2\) induce necrosis or apoptosis in a number of cell types. More recently, however, it has become clear that H\(_2\)O\(_2\) elicits specific responses in a number of vascular cells.\(^{31}\) For example, H\(_2\)O\(_2\) stimulates smooth muscle cell proliferation and inhibits the proliferation of endothelial cells.\(^{32}\) Endothelial cells respond to H\(_2\)O\(_2\) with increased endothelin-1 expression\(^{33}\) and activation of proapoptotic signals.\(^{34}\) With respect to NAD(P)H oxidase, a number of receptor-mediated phenotypic responses are due to activation of this enzyme. For example, both hypertension\(^{23}\) and smooth muscle cell hypertrophy\(^{35}\) in response to angiotensin II require NAD(P)H oxidase activation. Similarly, stimulation of the receptor for advanced glycation end products (RAGE) induces NAD(P)H oxidase–dependent adhesion molecule expression and tissue factor production.\(^{36}\) As outlined above, a common feature of NAD(P)H oxidase activation in vascular cells is a “maladaptive” phenotype (eg,
proliferation and inflammation) that is associated with the promotion of vascular disease.

**ACE Inhibition as an Antioxidant Strategy**

On the basis of the link between ACE action and vascular NAD(P)H oxidase activity, we propose that ACE inhibitors represent a novel antioxidant strategy that targets oxidative stress at its source. As seen in the Figure, ACE inhibition limits the stimulation of vascular NAD(P)H oxidase, thereby preventing the increased superoxide flux associated with activation of the renin-angiotensin system. This maneuver should have a number of important downstream effects that benefit the vasculature. Because superoxide reacts with NO, ACE inhibition should improve NO bioactivity, and this prediction has been realized in patients with coronary artery disease and some experimental models of hypertension. Because NO is known to inhibit the activity of NAD(P)H oxidase, another predictable effect of ACE inhibitors would be to reduce the ambient levels of superoxide in the vascular wall. ACE inhibition should also inhibit lipid peroxidation through reduced formation of peroxynitrite; this notion is consistent with observations that angiotensin II induces lipid peroxidation in experimental animals. Because superoxide is the principal source of H$_2$O$_2$, ACE inhibitors should limit smooth muscle proliferation, and this prediction is consistent with observations that ACE inhibition limits the progression of carotid intimal thickening as described in the SECURE study. Because ACE inhibitors will limit the production of H$_2$O$_2$, the formation of H$_2$O$_2$-derived oxidants such as hydroxyl radical and hypochlorous acid (HOCl) should also be reduced by ACE inhibitors, although this has not been tested experimentally. Finally, because ACE inhibitors limit the production of oxidants at the source, issues of compartmentalization and scavenging efficiency are not a consideration.

Although our scheme (the Figure) is an attractive means to conceptualize the results of the HOPE and SECURE studies, we are not so naive as to believe it is complete. Our level of understanding of the vascular NAD(P)H oxidase isoforms and their regulation is relatively immature at this point, and our proposed scheme is likely to become more complex with further investigation. Already there is evidence that vascular isoforms of NAD(P)H oxidase may be activated through a variety of pathways, including receptor tyrosine kinases, cytokines, thrombin, and mechanical forces (reviewed in Reference 21), and we are only beginning to understand how these stimuli alter the clinical expression of vascular disease. Nevertheless, even in the face of further investigation, we predict that angiotensin II will play a central role in vascular disease judging from the beneficial effects of ACE inhibition and angiotensin II receptor blockade in a number of animal models and clinical studies.

In summary, ACE inhibitors ameliorate vasoconstriction, increase the bioactivity of NO, and can inhibit vascular superoxide production at its source. In contrast, antioxidant therapy with vitamin E is limited to scavenging lipid-soluble oxidants and may therefore be considered a more "symptomatic" rather than a causal treatment for vascular oxidative stress. Such marked differences in the targets for these 2 treatment strategies may easily explain why antioxidants have failed so far to successfully influence morbidity and prognosis in patients with cardiovascular disease and why ACE inhibitors may represent a "magic bullet" against vascular oxidative stress, as has been suggested by the results of the HOPE and SECURE trials.

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