Tissue Angiotensin and Pathobiology of Vascular Disease
A Unifying Hypothesis
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Abstract—There is increasing evidence that direct pathobiological events in the vessel wall play an important role in vascular disease. An important mechanism involves the perturbation of the homeostatic balance between NO and reactive oxygen species. Increased reactive oxygen species can inactivate NO and produce peroxynitrite. Angiotensin II is a potent mediator of oxidative stress and stimulates the release of cytokines and the expression of leukocyte adhesion molecules that mediate vessel wall inflammation. Inflammatory cells release enzymes (including ACE) that generate angiotensin II. Thus, a local positive-feedback mechanism could be established in the vessel wall for oxidative stress, inflammation, and endothelial dysfunction. Angiotensin II also acts as a direct growth factor for vascular smooth muscle cells and can stimulate the local production of metalloproteinases and plasminogen activator inhibitor. Taken together, angiotensin II can promote vasoconstriction, inflammation, thrombosis, and vascular remodeling. In this article, we propose a model that unifies the interrelationship among cardiovascular risk factors, angiotensin II, and the pathobiological mechanisms contributing to cardiovascular disease. This model may also explain the beneficial effects of ACE inhibitors on cardiovascular events beyond blood pressure reduction. (Hypertension. 2001;37:1047-1052.)

Key Words: cardiovascular diseases ■ endothelium-derived factor ■ molecular biology ■ risk factors ■ vasculature

Scientific discoveries are inaugurated by a growing sense . . . that an existing paradigm has ceased to function adequately in the exploration of an aspect of nature to which that paradigm itself had previously led the way.

—Thomas Kuhn

The Structure of Scientific Revolutions, 1970

Since its discovery a century ago, the role of the renin-angiotensin system as an endocrine system involved in blood pressure and fluid electrolyte regulation has been well established.1 Disorders of this system contribute importantly to the pathophysiology of hypertension, renal disease, and congestive heart failure. The recent discoveries of the tissue actions of angiotensin II (Ang II) have revolutionized our thinking of the role of this peptide in cardiovascular disease. Evidence indicates that Ang II is more than a hormone that exerts hemodynamic and renal actions but that it is also a local, biologically active mediator that has direct effects on endothelial and smooth muscle cells.2 It plays a key role in the initiation and amplification of pathobiological events that lead to vascular disease. Indeed, recent clinical trials of ACE inhibitors have consistently documented the salutary effects of this class of agents in treating and preventing cardiovascular disease, with impressive reductions in coronary and cerebral vascular events despite a modest effect on blood pressure lowering.3–5 These data suggest that ACE inhibitors may also exert direct actions on the blood vessel beyond their hemodynamic effects. The present article reviews the evidence for the direct tissue actions of Ang II, the cellular signaling pathways, and the interactions of Ang II with other local mediators. It is hypothesized that these tissue effects are important in the process of vascular disease and may mediate the additional nonhemodynamic actions of ACE inhibitors in treating cardiovascular conditions, such as coronary artery disease.

Endothelium, Oxidative Stress, and Vascular Disease

To understand the effect of Ang II on vascular pathobiology, we must first examine the role of the endothelium. Ang II is synthesized by and has a key action on the endothelium: it exerts direct influence on endothelial function. The endothelium is well recognized as having a pivotal role in maintaining normal vascular function and structure.6 The endothelium presents a thromboresistant surface to blood and forms a macromolecular barrier between blood and the vessel wall. Endothelial cells produce factors that regulate vessel tone, coagulation, cell growth and death, and leukocyte migration. Vascular tone is maintained by a balance between vasodilators, such as NO, and vasoconstrictors, such as Ang II. Under the influence of the endothelium and other factors, vascular smooth muscle cells are also capable of releasing cytokines
and growth-regulatory factors that can influence vascular cellular phenotype and growth.

The association between endothelial dysfunction and vascular disease is well established. Endothelial dysfunction may result in increased vasoconstrictor activity. It may induce alterations in local mediators (eg, cytokines, chemokines, and adhesion molecules) such that they favor inflammation. Endothelial dysfunction may also create an imbalance between tissue-type plasminogen activator (tPA) and plasminogen activator inhibitor type 1 (PAI-1) that can predispose to thrombosis.

A key determinant of endothelial biology is the cell redox state, and a key molecule that mediates endothelial function is NO. Evidence indicates that a homeostatic balance between NO and reactive oxygen species (ROS), such as superoxide anion and hydrogen peroxide, regulates cell redox and is necessary for normal endothelial function. The impairment in the capacity of the vessel to dilate in the presence of endothelial dysfunction reflects, at least in part, increased oxidative stress due to an enhanced catabolism of NO caused by increased generation of superoxide anion. In addition to being a vasodilator, NO is an endogenous inhibitor of vascular smooth muscle cell growth and migration, of the expression of proinflammatory molecules,9,10 with the activity of the transcription factor nuclear factor (NF)-κB, and of the expression of proinflammatory molecules.9,10 With an imbalance between NO and ROS, there is a propensity for vasospasm, smooth muscle cell proliferation, prothrombosis, and pro-inflammatory and pro-oxidant states.

The well-established cardiovascular risk factors, such as dyslipidemia, elevated blood pressure, diabetes, and smoking, can initiate endothelial dysfunction by altering the cell redox state (oxidative stress) in the vessel wall.11–16 Dyslipidemia is associated with increased generation of superoxide anions and enhanced oxidation of LDL cholesterol within the vessel wall.12,13 In patients with diabetes, potentiation of atherogeneic alterations in local mediators (eg, cytokines, chemokines, and metalloproteinases). Therefore, Ang II is a pleiotropic factor that mediates the expression of VCAM and the release of the cytokines interleukin-6 and tumor necrosis factor-α.23 This proinflammatory action of Ang II on the vessel wall interacts synergistically with those of other cardiovascular risk factors, such as dyslipidemia and diabetes.

Ang II is also involved in vascular remodeling, acting as a bifunctional growth factor that induces increased expression of autocrine growth factors (eg, platelet-derived growth factor, basic fibroblast growth factor, insulin-like growth factor-1; and TGF-β, transforming growth factor-β).

### Direct Vascular Effects of Ang II

The Table lists the direct vascular effects of Ang II. Ang II is a major mediator of oxidative stress and reduced NO activity. Ang II induces monocyte chemotactic protein-1 mRNA expression in monocytes and vascular smooth muscle cells, an effect that is inhibited by coadministration of an intracellular antioxidant.20 Ang II induces endothelial dysfunction and activates the expression of the proinflammatory phenotype of human vascular smooth muscle cells.21 It activates NF-κB and stimulates the expression of VCAM and the release of the cytokines interleukin-6 and tumor necrosis factor-α.23 This proinflammatory action of Ang II on the vessel wall interacts synergistically with those of other cardiovascular risk factors, such as dyslipidemia and diabetes.

Ang II also affects vascular remodeling, acting as a bifunctional growth factor that induces increased expression of autocrine growth factors (eg, platelet-derived growth factor, basic fibroblast growth factor, insulin-like growth factor, and transforming growth factor-β) in vascular smooth muscle cells.24 Other mechanisms whereby Ang II may promote vascular remodeling and formation of vascular lesions are the modulation of vascular cell migration, decreased vascular smooth muscle apoptosis, and altered extracellular matrix composition.27,28 Indeed, Ang II can stimulate the synthesis and release of matrix glycoproteins and metalloproteinases. Therefore, Ang II is a pleiotropic local mediator of vascular remodeling and lesion formation.

Ang II can also upset the balance between the fibrinolytic and coagulation systems via its effect on the endothelium. Ang II induces the formation of PAI-1, an effect that is mediated by specific angiotensin receptors on endothelial cells.
Independent of its stimulation of PAI-1 synthesis via Ang II production, tissue ACE also downregulates tPA production via degradation of bradykinin, which is a potent stimulator of tPA production in the endothelium. These actions of tissue ACE/Ang II on the fibrinolytic system can enhance the development of a prothrombotic state.

Evidence for Increased Tissue Production of Ang II: A Vicious Cycle

High levels of ACE expression and Ang II have been shown in experimental and human vascular lesions. Indeed, ACE, Ang II, and its receptor are colocalized in areas of inflammation in human atherosclerotic lesions. Recent data indicate that inflammatory cells can release enzymes that generate Ang II, including ACE from monocytes/macrophages, cathepsin G from neutrophils, and chymase from mast cells. Furthermore, we have reported that as the macrophage becomes activated with modified LDL, its ACE expression increases significantly. This creates a positive-feedback mechanism (Figure 1) for local Ang II formation. Tissue ACE and Ang II produced within an atherosclerotic lesion contribute to high local levels of Ang II, which activate Ang II receptors on different cell types, leading to progressive lesion formation via proliferation of smooth muscle cells, formation of foam cells, and facilitation of thrombosis. Of note, we have reported a marked accumulation of tissue ACE and Ang II in the inflamed shoulder regions of vulnerable plaques that are prone to rupture. It is attractive to hypothesize that the increased production of ACE and Ang II contributes to this process of acute ischemic complication. In addition to its effects on inflammation and vascular contraction, local Ang II stimulates metalloproteinases, which can break down the extracellular matrix, weakening this vulnerable region that is subject to increased circumferential stress and thus enhancing the probability of rupture.

Integrated Model of Tissue Angiotensin and Vascular Pathobiology

The effects of many of the biologically active mediators produced in the vessel wall are long term, reflecting the progressive nature of vascular disease. In the present article, we propose a model that integrates the complex interrelationship of tissue ACE and Ang II with the various biologically active mediators, cardiovascular risk factors, and the pathobiological mechanisms that contribute to the vascular disease process (Figure 2). In this paradigm, a common mechanism by which cardiovascular risk factors initiate the disease process is oxidative stress, leading to endothelial dysfunction and vascular inflammation. The latter pathways increase local ACE and Ang II production. Thus, a positive-feedback mechanism involving increased tissue Ang II and decreased NO production and in which Ang II acts as a direct mediator of increased tissue Ang II formation with subsequent induction of oxidative stress and inflammation. Activation of tissue ACE promotes release of cytokines and growth factors that increase vessel wall inflammation. Inflammatory cells, in turn, release enzymes and other substances that generate Ang II.
as well as an amplifier exists in vascular pathology. Through its activation of oxidative stress, local Ang II magnifies endothelial dysfunction and smooth muscle phenotypic alterations induced by cardiovascular risk factors and serves as a vicious positive-amplification mechanism for decreased NO, increased ROS, and the activation of other biologically active mediators for vascular disease. Thus, through its direct tissue effects, increased tissue Ang II activates various pathobiological processes that lead to vascular complications.

**Tissue ACE as a Therapeutic Target**
 Therapeutic strategies for cardiovascular disease would include antioxidants, anti-inflammatory agents, agents that enhance NO activity, and agents that reduce Ang II. In this context, an important therapeutic target is tissue ACE, which has multiple actions. Inhibition of tissue ACE not only reduces Ang II, oxidative stress, and Ang II–induced inflammatory states but also increases bradykinin formation; this increases NO and prostacyclin, which also exert anti-inflammatory, antithrombotic, and vasorelaxant actions.

Evidence from experimental and clinical trials supports the role of direct vascular effects of tissue ACE inhibition. The Trial on Reversing Endothelial Dysfunction (TREND study) demonstrated that 6 months of treatment with the tissue ACE inhibitor quinapril normalized endothelial function in patients with coronary artery disease, as evidenced by a reversal of the paradoxical vasoconstriction caused by intracoronary administration of acetylcholine. In another study, improvement in forearm vasodilation was noted after 6 months of treatment with lisinopril in patients with hyperlipidemia. Enalaprilat has also been shown to improve acetylcholine- and bradykinin-mediated epicardial and microvascular dilation in patients with coronary artery disease and/or its risk factors. The effects of ACE inhibitors on endothelium-dependent vasodilation appear to exhibit some differences among the agents. The differential effects of various ACE inhibitors may be related to their pharmacokinetic properties, such as the affinity of binding to tissue ACE, their dissociation constants from the enzyme, and their lipophilicity.

ACE inhibition has emerged as an important therapeutic modality for cardiovascular disease. In addition to hypertension and congestive heart failure, ACE inhibitors are now shown to be effective in the treatment of coronary heart disease. Studies of ACE inhibitor administration in post-myocardial infarction (MI) patients with left ventricular dysfunction demonstrated that ACE inhibitor treatment was associated with significant reductions in the risk of recurrent MI. The risk reduction was ~24% in the Studies of Left Ventricular Dysfunction (SOLVD) and Survival and Ventricular Enlargement (SAVE) trials and ~37% in the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) study; also, there was a 25% reduction in sudden death in the Trandolapril Cardiac Evaluation (TRACE). Several long-term clinical trials were initiated to evaluate the potential clinical benefits of ACE inhibition in patients with coronary artery disease without left ventricular dysfunction; these trials were as follows: the Quinapril Ischemic Events Trial (QUIET), Heart Outcomes Prevention Evaluation (HOPE), Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), Prevention of Events With Angiotensin-Converting Enzyme Inhibition (PEACE), and the European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA). Of these, the QUIET and HOPE studies have been completed. Results of the QUIET study were neutral with respect to the effect on cardiac ischemic end points of ACE inhibition initiated within 72 hours of revascularization. This outcome may have been due, in part, to its being a small study (1750 patients) of relatively brief duration (3 years) that enrolled a relatively lower-risk patient population (ie, normal LDL cholesterol and normal body mass index).

The recently completed HOPE study that evaluated ramipril provides compelling data regarding the beneficial effects of ACE inhibition on cardiovascular morbidity and mortality. The study followed 9297 high-risk patients who had evidence of vascular disease or diabetes plus 1 other cardiovascular risk factor but who did not have a low ejection fraction or heart failure. The planned 5-year treatment period was terminated early because of the significant, and much greater than anticipated, effect of ACE inhibition on the composite primary outcome of MI, stroke, or death from cardiovascular causes (22% greater reduction with ramipril compared with placebo), as well as significantly greater reductions in the individual end points (MI 20%, stroke 31%, and death from cardiovascular causes 25%). In addition, significant reductions in all-cause mortality (relative risk [RR] 0.84), need for revascularization procedures (RR 0.84), cardiac arrest (RR 0.63), heart failure (RR 0.77), worsening angina (RR 0.89), and new diagnosis of diabetes (RR 0.68) or complications related to diabetes (RR, 0.84) were observed. ACE inhibitor treatment demonstrated beneficial effects within 1 year, which were significant at 2 years. The favorable effects of treatment were noted in all subgroups, including those with/without diabetes, hypertension, microalbuminuria, coronary artery disease, or history of MI; men and women; and those older younther than 65 years. The findings from the HOPE study indicate that a broad spectrum of patients potentially can derive additional benefit from ACE inhibitor treatment. The blood pressure–lowering effect of ACE inhibition was modest and could not account completely for the risk reductions observed in the HOPE study. As the investigators noted, “it is likely that angiotensin-converting enzyme inhibitors exert additional direct mechanisms on the heart or the vasculature that are important.”

The studies assessing the effect of ACE inhibitors on clinical outcomes in patients with coronary artery disease support the body of experimental evidence indicating that locally generated vasoactive mediator substances such as NO and Ang II are important determinants in the progression of vascular disease and that restoring the local balance of these mediators is an important therapeutic goal. As a therapeutic strategy, inhibiting tissue ACE appears to be an effective target for preventing premature death, MI, and stroke in patients at high risk for vascular disease. In summary, advances in renin-angiotensin research have improved our understanding of the role of this system in cardiovascular
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pathobiology and have validated its importance as a target for pharmacological inhibition.

References

11. Heitzer T, Yla-Herttuala S, Luoma J, Kurz S, Munzel T, Just H, Dzau VJ. Tissue Angiotensin and Cardiovascular Disease


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