Endothelial Function, Fibrinolysis, and Angiotensin-Converting Enzyme Inhibition

DOUGLAS E. VAUGHAN, M.D.
Departments of Medicine and Pharmacology, Vanderbilt University and Veterans Affairs Medical Centers, Nashville, Tennessee, USA

Summary: Experimental and clinical studies with angiotensin-converting enzyme (ACE) inhibitors have suggested that these agents may reduce the risk of atherothrombotic events. Recent studies have identified the role of angiotensin II and ACE in the regulation of fibrinolysis. There is now substantial evidence that the renin-angiotensin system (RAS) plays an important role in the regulation of vascular fibrinolytic balance. This recently recognized relationship may contribute to the vasculoprotective effects of ACE inhibitors.

Key words: angiotensin-converting enzyme, fibrinolysis, plasminogen activator inhibitor type 1, tissue-type plasminogen activator

The Fibrinolytic System

The plasminogen activator, or fibrinolytic system, constitutes one of the primary endogenous mechanisms for preventing intravascular thrombosis, which is implicated importantly in the pathogenesis of myocardial infarction (MI) and other acute coronary syndromes. Fibrinolysis depends on a balance between plasminogen activators [urokinase and tissue-type plasminogen activator (TPA)] and plasminogen activator inhibitor type 1 (PAI-1), the major physiologic inhibitor of urokinase and TPA in plasma. This balance is maintained through processes that appear to be mediated largely by the endothelium. Plasminogen activators convert plasminogen to the active enzyme, plasmin, which is a protease that lyases fibrin clots. One important mechanism for regulating plasmin generation involves the formation of complexes between PAI-1 and the plasminogen activators, which prevents the conversion of plasminogen to plasmin.1, 2 Because both TPA and PAI-1 are synthesized primarily by endothelial cells (and smooth muscle cells), the endothelium is thought to play a prominent role in maintaining vascular fibrinolytic balance.

Modest excesses or deficiencies in the fibrinolytic proteins can be associated with clinical consequences. Increased levels of PAI-1 have been associated with an increased risk of thrombosis in animal and clinical studies.3–6 In one clinical study, low TPA activity and higher PAI-1 levels were observed in survivors of MI compared with healthy age-matched controls.4 In another study, low TPA activity and increased PAI-1 concentrations were the only hemostatic variables associated with recurrent MI in a group of men with early coronary heart disease.5 Imbalance of the fibrinolytic proteins can also have pathogenic consequences within the vascular wall. In vascular tissue, plasmin activates matrix metalloproteinases, which are crucial in remodeling following vascular injury through degradation of collagen and other glycoproteins that accumulate in plaques.7 Several groups have reported increased deposition of PAI-1 in and around atherosclerotic plaques, which in turn reduces vascular plasmin activation and, subsequently, metalloproteinase activity. This reduction in plasmin activation is also associated with reduced activation of transforming growth factor-beta, which is important in suppressing the proliferation and migration of smooth muscle cells that contribute to atherosclerotic lesions.8

Address for reprints:
Dr. Douglas E. Vaughan
Vanderbilt University School of Medicine
Division of Cardiology, Room 315, MRB II
2220 Pierce Ave.
Nashville, TN 37232-6300, USA

Regulatory Role of Endothelium in Fibrinolytic Balance and Role of the Renin-Angiotensin System

The role of the renin-angiotensin system (RAS) in regulating fibrinolysis was suggested by findings in two major clinical studies of angiotensin-converting enzyme (ACE) inhibitor therapy: the Survival and Ventricular Enlargement (SAVE) trial9 and the Studies of Left Ventricular Dysfunction (SOLVD).10 In both these studies, ACE inhibition significant-
Angiotensin-Converting Enzyme (ACE) inhibition and fibrinolytic balance have been the subject of extensive investigations in recent years. The angiotensin-converting enzyme (ACE) is a key component of the renin-angiotensin system (RAS), which plays a vital role in regulating blood pressure, fluid balance, and electrolyte homeostasis. ACE catalyzes the conversion of angiotensin I to angiotensin II, thereby enhancing the vasoconstrictor and aldosterone-stimulating effects of angiotensin I. In turn, angiotensin II is a potent stimulator of tissue-type plasminogen activator (TPA) production in endothelial cells, leading to increased fibrinolytic activity.

The imbalance between the fibrinolytic and prothrombotic systems can contribute to the development of cardiovascular diseases. Angiotensin II has been shown to bind to endothelial cells and to stimulate dose-dependent production of TPA in cultured rat vascular smooth muscle cells, cultured bovine aortic cells, and human endothelial cells, thus demonstrating a potential link between the RAS and thrombosis. In other studies, ACE inhibition increased plasminogen activator activity in cultured bovine aortic endothelial cells and decreased vascular PAI-1 expression in normal and balloon-injured rat aorta.

Several clinical investigations, including recent studies designed to assess the effect of ACE inhibition on fibrinolytic factors, have provided additional evidence for the link between the RAS and the fibrinolytic system; these are reviewed below.

### Angiotensin-Converting Enzyme and Fibrinolytic Balance

As suggested by the findings regarding ACE inhibition in cultured cells and in clinical studies, ACE occupies an important position in regulating the balance of fibrinolytic elements. It converts angiotensin I to angiotensin II, which is associated with stimulation of PAI-1 production. Through an independent and parallel pathway, ACE is also important in downregulating TPA production via degradation of bradykinin, a highly potent stimulator of TPA production in endothelial cells. In vivo, intra-arterial administration of bradykinin results in a dose-dependent increase in plasma TPA levels. In human subjects with hypertension, graded doses of bradykinin were associated with dose-dependent increases in plasma TPA levels during concomitant ACE inhibitor administration, but had no effect on TPA in the absence of ACE inhibitor administration. This finding confirms earlier reports that bradykinin is an extremely potent stimulus for the release of TPA in vivo. It also highlights the importance of the RAS in regulating vascular fibrinolytic balance.

### Angiotensin-Converting Enzyme Inhibition and Fibrinolytic Balance

In addition to the experimental studies mentioned, clinical investigations have shown that ACE inhibition is associated with alterations in fibrinolysis. In the first study to demonstrate an effect of ACE inhibition on endogenous fibrinolysis, Wright et al. administered captopril 75 mg/day or placebo to 15 patients beginning 8 weeks after uncomplicated MI and compared effects on fibrinolytic variables in these patients and 12 matched control subjects. The fibrinolytic variables assessed were PAI-1 antigen levels, TPA antigen levels, and PAI-1 activity. After the placebo treatment period, patients post MI had significantly higher TPA antigen and PAI-1 antigen levels and significantly greater PAI-1 activity than did controls. However, 4 weeks of ACE inhibition resulted in significant reductions in TPA antigen levels and PAI-1 activity in the 15 patients and a nonsignificant reduction in levels of PAI-1 antigen (Fig. 3).
More recently, we\textsuperscript{21} have assessed the effect of short-term ACE inhibition on fibrinolytic variables in a subset of 120 patients from the Healing and Early Afterload Reducing Therapy (HEART) study of patients with acute anterior MI and systolic blood pressure >100 mmHg. In this double-blind, placebo-controlled trial, patients were randomized to ramipril 0.625 or 1.25 mg/day titrated to 10 mg/day or placebo for 14 days. Subsequently, subjects in the placebo-treatment arm were crossed over into the high-dose ramipril arm of the study. Baseline PAI-1 activity and PAI-1 antigen and TPA antigen levels were comparable in the three groups; the ratio of PAI-1 to TPA, a measure intended as an index of fibrinolytic balance, was normal in each of the treatment groups as well. After 14 days, PAI-1 antigen levels were approximately 44% lower, and PAI-1 activity levels an average of 22% lower, in the patients treated with the ACE inhibitor (combined groups) than in placebo-treated patients (Fig. 4). In contrast, plasma TPA levels were not significantly different between the ACE inhibitor-treated patients and placebo-treated patients. Given
the significant reduction in PAI-1 activity and antigen levels, it is safe to say that ACE inhibition preserved normal fibrinolytic balance in these patients post MI. No other drugs besides ACE inhibitors have been shown to have such an impact on the plasma fibrinolytic balance during the recovery phase of acute MI. These results may help explain the beneficial effects of ACE inhibition on rates of MI and ischemic events in previous randomized trials.

**Conclusion**

There is accumulating evidence that the RAS interacts with the fibrinolytic system at the level of the endothelium. In fibrinolysis, both angiotensin II and ACE may be considered prothrombotic: angiotensin II because it induces PAI-1 expression, and ACE because it mediates the formation of angiotensin II and the degradation of bradykinin. Increased PAI-1 levels are associated with an increased risk of thrombotic events in humans. In experimental models, ACE inhibition is associated with reductions in PAI-1 expression in both cultured cells and tissue. These beneficial changes in fibrinolytic variables may be attributed to ACE inhibition’s dual effects of inhibiting angiotensin II formation (and thus limiting the production of PAI-1) and blocking bradykinin degradation (and thereby enhancing the production of TPA by bradykinin). These mechanisms may contribute to the vasculoprotective effects of ACE inhibitors.

**References**