Abstract—Angiotensin-converting enzyme (ACE) inhibition significantly decreases plasminogen activator inhibitor-1 (PAI-1) without altering tissue plasminogen activator (tPA) during activation of the renin-angiotensin-aldosterone system in humans. Because ACE inhibitors and angiotensin II type 1 (AT1) receptor antagonists differ in their effects on angiotensin II formation and bradykinin degradation, the present study compared the effect of equivalent hypotensive doses of an ACE inhibitor and AT1 antagonist on fibrinolytic balance. Plasma PAI-1 antigen, tPA antigen, plasma renin activity, and aldosterone were measured in 25 normotensive subjects (19 white, 6 black; 14 men, 11 women; mean age 38.5±1.8 years; mean body mass index 25.3±0.7 kg/m2) during low salt intake alone (10 mmol Na/d), low salt intake + quinapril (40 mg PO bid), and low salt intake + losartan (50 mg PO bid). Compared with low salt alone (systolic blood pressure [BP] 118.8±2.2 mm Hg), both quinapril (106.3±2.5 mm Hg, P<0.001) and losartan (105.4±2.8 mm Hg, P<0.001) reduced BP. No statistical difference was found between quinapril and losartan in their BP lowering effect. Losartan (P=0.009), but not quinapril, lowered heart rate. Both drugs significantly lowered aldosterone (P<0.001 versus low salt alone for each); however, this effect was significantly greater for quinapril than for losartan (P<0.001 for quinapril versus losartan). Treatment with quinapril, but not with losartan, was associated with a decrease in both PAI-1 antigen (P=0.03) and activity (P=0.018). PAI-1 activity was lower during treatment with quinapril than with losartan (P=0.015). The average PAI-1 antigen concentration was 13.0±2.0 ng/mL during low salt alone, 10.5±1.6 ng/mL during quinapril treatment, and 12.3±2.1 ng/mL during losartan treatment. In contrast, plasma tPA antigen concentrations were reduced during treatment with losartan (P=0.03) but not with quinapril. This study provides the first evidence that ACE inhibitors and AT1 antagonists differ in their effects on fibrinolytic balance under conditions of activation of the renin-angiotensin-aldosterone system. Further studies are needed to address the mechanism for the contrasting effects of these 2 classes of drugs on fibrinolysis and to define the clinical significance of these differences. (Hypertension. 1999;34:285-290.)

Key Words: angiotensin II n renin n plasminogen activators

Activation of the renin-angiotensin-aldosterone system (RAAS) has been associated with an increased risk of ischemic cardiovascular events independent of effects on blood pressure (BP).1,2 Conversely, interruption of the RAAS with an angiotensin-converting enzyme (ACE) inhibitor decreases progression of atherosclerosis in animal models3,4 and appears to reduce the risk of recurrent myocardial infarction (MI) in patients with left ventricular dysfunction.5,6

The mechanisms through which activation of the RAAS increases or ACE inhibition decreases the risk of ischemic cardiovascular events in selected populations is not known. One possible explanation involves an interaction between the RAAS and the fibrinolytic system. Accumulating data suggest that angiotensin (Ang) II modulates fibrinolysis. For example, Ang II increases expression of plasminogen activator inhibitor-1 (PAI-1) in cultured endothelial and vascular smooth muscle cells.7,8 PAI-1 is the major physiological inhibitor of fibrinolysis in vivo.9 Increased PAI-1 expression has been demonstrated in atherosclerotic lesions.10,11 Elevated concentrations of PAI-1 are seen in young survivors of acute MI versus age-matched controls12 and appear to be a risk factor for recurrent MI.13 In endothelial cells, the effect of Ang II on PAI-1 expression is mediated through its hexapeptide metabolite, Ang IV.8 Thus, the effect of Ang II on endothelial PAI-1 expression is not blocked by either Ang II type 1 receptor (AT1) or Ang II type 2 receptor (AT2) antagonists and inhibition of the conversion of Ang II to Ang IV blocks the effect of Ang II on PAI-1 expression.8 In contrast, AT1 antagonism blocks the effect of Ang II on PAI-1 expression in vascular smooth muscle cells.14

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In humans, our group and others\textsuperscript{15–20} have demonstrated that activation of the RAAS by salt depletion increases peak plasma PAI-1 concentrations, whereas ACE inhibition significantly decreases plasma PAI-1 without consistently decreasing tissue plasminogen activator (tPA) concentrations. In contrast, the effect of AT\textsubscript{1} antagonism on fibrinolysis has not been extensively studied in humans.\textsuperscript{21} ACE inhibitors and AT\textsubscript{1} antagonists differ in their effects on the RAAS. For example, Ang II concentrations increase versus baseline during AT\textsubscript{1} antagonism, but not ACE inhibition.\textsuperscript{22} If the effect of endogenous Ang II on circulating PAI-1 concentrations in intact humans is mediated through a non–AT\textsubscript{1} and non–AT\textsubscript{2} receptor, then PAI-1 concentrations would be expected to increase, rather than decrease, during AT\textsubscript{1} antagonism. Furthermore, in addition to inhibiting the formation of Ang II, ACE inhibitors block the degradation of bradykinin.\textsuperscript{23} AT\textsubscript{1} antagonists do not alter the metabolism of bradykinin when given short-term.\textsuperscript{24} Bradykinin is a potent stimulus to tPA release in the human vasculature.\textsuperscript{25} For these reasons, ACE inhibitors and AT\textsubscript{1} antagonists might be expected to differ in their effects on the balance between PAI-1 and tPA. Thus, the purpose of the present study was to compare the effect of equivalent hypotensive doses of the ACE inhibitor, quinapril, and the AT\textsubscript{1} antagonist, losartan, on fibrinolytic balance in the setting of activation of the RAAS.

**Methods**

All subjects underwent a complete history and physical examination before the investigation. Subjects with significant cardiovascular, renal, endocrine (including diabetes), or pulmonary disease, or who were taking vasoactive medications were excluded. Written informed consent was obtained, and the study protocol was approved by the Vanderbilt University Institutional Review Board. Figure 1 illustrates the study protocol. Beginning on day 1 of the protocol, subjects were provided with a low sodium (10 mmol/d), caffeine- and alcohol-free diet for 6 days. On the fifth diet day, subjects were asked to collect all of their urine for 24 hours. On the sixth diet day, subjects were asked to report to the Vanderbilt University General Clinical Research Center at 7:00AM in the fasting state. A catheter was placed in an antecubital vein for blood drawing. BP and heart rate were measured at 8:00 AM and every 2 hours thereafter until 2:00 PM. Each measurement was made after the subject had been seated for 30 minutes. Following each measurement of BP, blood was drawn for measurement of PAI-1 antigen and tPA. Blood was drawn during the morning because PAI-1 concentrations peak during this period.\textsuperscript{26} Blood for measurement of plasma renin activity (PRA) and serum aldosterone was drawn at 8:00 AM and 10:00 AM. Blood for measurement of fasting glucose and insulin concentrations was drawn at 8:00 AM. A light lunch was provided after the noon blood draw.

At the end of the first study day, subjects were allowed to resume their usual diet. Four days later, they were randomized to treatment with either quinapril (10 mg BID) or losartan (12.5 mg BID). The dose of each medication was doubled every 2 days during the first week to a final dose of 40 mg BID for quinapril and 50 mg BID for losartan. All medications were administered in identical-appearing capsules in a double-blind fashion. Subjects were maintained on the medication for an additional 10 days after titration. During the last 6 days of medication, subjects were again provided a 10 mmol sodium per day diet. On the sixth day of diet, hemodynamic measurements, blood sampling, and urine collection were repeated. After the second study day, subjects were again allowed to resume their usual diet. After 2 weeks, they were crossed-over to the opposite treatment, and the protocol was repeated.

**Laboratory Analysis**

Blood samples were collected on ice and centrifuged immediately at 0°C for 20 minutes. All plasma or serum was separated and stored at −70°C until the time of assay. Blood for measurement of PAI-1 and tPA was collected in standard vacutainer tubes containing 0.105 mol/L sodium citrate (Becton Dickinson). PAI-1 activity levels were measured using an assay based on the methods of Verheijen et al.\textsuperscript{27} which use standardized commercial kits (Biopool, Inc), with results expressed as units/mL. Antigen levels were determined using a 2-site enzyme-linked immunosorbent assay (Biopool AB) as previously described.\textsuperscript{28} In our laboratory, the coefficients of variation for repeated measures of tPA antigen and PAI-1 antigen are 5.9% and 8.1%, respectively. Blood for PRA was collected in tubes containing EDTA. PRA was measured by radioimmunoassay for Ang I formation at pH 7.4 and 37°C.\textsuperscript{29} Serum aldosterone was assayed with a commercially available radioimmunoassay kit (Diagnostic Corporation). The intra-assay and interassay coefficients of variation were 6% and 10%, respectively. Plasma glucose concentrations were measured with a colorimetric assay (Johnson and Johnson Clinical Diagnostics). Serum insulin was measured by immunoassay (Tosoh Medics, Inc).

**Statistics**

Data are presented as mean±SEM. Ordinary graphing techniques were used to assess for outliers. Of PAI-1 antigen concentrations (6/100 samples collected during low salt alone, 5/96 during quinapril, 6/100 during losartan), 5.7% were greater than 2 SD from the mean for that subject and excluded as outliers. These values were replaced by the mean for that subject on the given study day. No outliers existed among the values measured for any other variable, including PAI-1 activity. Data were analyzed with a General Linear Model in which the between-subject variable was renin status (upright PRA≤2.4 versus >2.4 ng Ang I · mL\textsuperscript{−1} · h\textsuperscript{−1} during salt depletion) and the within-subject variables were treatment and time. F statistics and P values derived from the General Linear Model analysis are presented in the text, unless otherwise specified. Post hoc comparisons were made using a paired t test. A 2-tailed P value of <0.05 was the criterion for statistical significance.

**Results**

**Subject Characteristics**

The study was comprised of 25 normotensive subjects (14 men, 11 women; 19 white, 6 black). Based on previous studies of ACE inhibition in normotensive subjects, this sample size was calculated to give a power of 0.85 to detect a 5 ng/mL difference in PAI-1 antigen concentration between groups (α=0.05) given an SD of 8 ng/mL. The mean age was 38.5±1.8 years, and the mean body mass index was 25.3±0.7 kg/m\textsuperscript{2}. The mean serum cholesterol was 4.84±0.18 mmol/L (187±7 mg/dL), whereas the mean serum triglyceride concentration was 1.46±0.19 mmol/L (129±17 mg/dL). Four
subjects (2 black and 2 white) had upright PRAs \( \leq 2.4 \) ng Ang I \( \cdot \) mL\(^{-1}\) \cdot h\(^{-1}\) during low salt intake. One subject (a white male) withdrew from the study prior to his third study arm (quinapril), and his data are excluded from analysis for that arm.

Data for mean 24-hour urinary sodium excretion are provided in Table 1. Twenty-four hour urinary sodium excretion was significantly greater during quinapril than during either baseline \((P = 0.01)\) or losartan \((P = 0.01)\). There were no differences between treatment arms in urinary potassium excretion.

### Hemodynamic Response

BP decreased significantly during the quinapril arm (effect of drug for systolic pressure \( F = 21.4, P < 0.001 \); for diastolic pressure \( F = 30.6, P < 0.001 \)) and losartan arm (effect of drug for systolic pressure \( F = 19.8, P < 0.001 \); for diastolic pressure \( F = 11.0, P = 0.003 \)) of the study versus salt depletion alone (Table 1). There was no significant difference in systolic \((F = 0.2, P = 0.68)\) or diastolic \((F = 1.6, P = 0.21)\) BP between quinapril and losartan treatments. Heart rate decreased significantly versus baseline during losartan treatment, but not quinapril treatment (Table 1). However, heart rate was not significantly different between the 2 drug treatment arms \((P = 0.14)\).

### Endocrine Response

PRA increased significantly versus baseline in response to both quinapril \((F = 11.8, P = 0.003)\) and losartan \((F = 9.6, P = 0.005)\) (Figure 2 and Table 2). No significant difference in PRA was found between the 2 drug treatments \((F = 1.1, P = 0.3)\). Aldosterone decreased significantly during treatment with both quinapril \((F = 27.7, P < 0.001)\) and losartan \((F = 7.3, P = 0.017)\); however, serum aldosterone decreased to a significantly greater extent during quinapril treatment than during losartan treatment \((F = 21.1, P < 0.001)\). This effect was seen in 23 of the 24 subjects who completed both the quinapril and losartan treatment arms. During treatment with either quinapril or losartan, there was a weak, but significant, correlation between serum aldosterone concentration and plasma PAI-1 antigen \((R = 0.37, P < 0.001)\). No differences were found between treatment arms in fasting plasma glucose concentrations or serum insulin concentrations (Table 1). The glucose-insulin ratio, an index of insulin sensitivity, tended to increase during both losartan and quinapril treatments versus low salt alone, but this effect was not significant during either drug treatment \((P = 0.06)\) for quinapril versus low salt alone, \(P = 0.07\) for losartan versus low salt alone.

### Fibrinolytic Parameters

Plasma PAI-1 antigen \((F = 5.4, P = 0.03)\) and activity \((F = 6.6, P = 0.018)\) were significantly lower during ACE inhibition with quinapril than during salt depletion alone. This effect was greatest 6 hours following quinapril when PAI-1 antigen concentrations were 18% lower \((95\%\) confidence interval, 0.7% to 35%) than at the same time during low salt alone. There was no significant effect of losartan on PAI-1 antigen \((F = 0.04, P = 0.8)\) or activity \((F = 0.07, P = 0.8)\). PAI-1 activity \((F = 7.1, P = 0.015)\), but not PAI-1 antigen \((F = 4.1, P = 0.05)\), was significantly lower during quinapril than during losartan. In contrast, plasma tPA antigen was significantly reduced versus baseline during losartan treatment \((F = 5.5, P = 0.03)\), but not during quinapril treatment \((F = 1.3, P = 0.3)\).

### Discussion

The present study is the first to compare the effects of ACE inhibition and AT\(_1\) antagonism on fibrinolytic balance under conditions of controlled activation of the RAAS. The data

### Table 1. Urinary Electrolyte Excretion and Insulin Sensitivity During Each Treatment Arm

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low Salt Diet Alone</th>
<th>Quinapril</th>
<th>Losartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mm Hg</td>
<td>118.8±2.2</td>
<td>106.3±2.5†</td>
<td>105.4±2.8†</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>78.2±1.0</td>
<td>67.0±1.2‡</td>
<td>68.8±1.7‡</td>
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<tr>
<td>Heart rate, bpm</td>
<td>77.7±2.3</td>
<td>74.9±2.7</td>
<td>72.9±2.7†</td>
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<tr>
<td>24-Hour urine volume, mL</td>
<td>2374±120</td>
<td>2313±177</td>
<td>2157±159</td>
</tr>
<tr>
<td>24-Hour urine sodium, mmol/d</td>
<td>11.5±1.4</td>
<td>16.1±1.9§</td>
<td>11.5±2.0</td>
</tr>
<tr>
<td>24-Hour urine potassium, mmol/d</td>
<td>70.7±3.9</td>
<td>66.6±4.5</td>
<td>64.9±3.8</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.71±0.08</td>
<td>4.71±0.10</td>
<td>4.77±0.10</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L</td>
<td>40.4±3.5</td>
<td>36.1±4.1</td>
<td>39.3±4.4</td>
</tr>
<tr>
<td>Glucose/insulin, ( \times 10^3 )</td>
<td>0.13±0.1</td>
<td>0.17±0.02</td>
<td>0.16±0.02</td>
</tr>
</tbody>
</table>

*\( P < 0.05 \), †\( P < 0.01 \), ‡\( P < 0.001 \) vs low-salt diet alone by paired t test. §\( P < 0.05 \) vs losartan.

![Figure 2. Effect of quinapril and losartan on (A) plasma renin activity and (B) aldosterone level vs low salt diet alone. Data are presented as the average of 2 time points. *\( P < 0.01 \), ††††\( P = 0.005 \) vs baseline, ‡‡‡‡\( P < 0.0001 \) vs losartan by paired t test.]
suggest that, at equivalent hypotensive doses, an ACE inhibitor and AT₁ antagonist differ in their effects on fibrinolytic balance.

Quinapril significantly lowered both PAI-1 antigen and activity during salt depletion in the normotensive subjects studied. A similar effect of ACE inhibition on PAI-1 has been observed in at least 6 studies,15–18,20,31 but not in others.32–36 With respect to the effect of ACE inhibition on fibrinolytic balance, one explanation for the conflicting findings is that studies have differed widely in design. The effect of ACE inhibition on fibrinolytic balance may depend on the ACE inhibitor used, the population studied (eg, post-MI, hypertensive, or normotensive), and the state of activation of the RAAS.37 Indeed, the relatively modest 18% reduction in PAI-1 antigen during ACE inhibition in the present study versus the 44% reduction observed in post-MI patients15 and PAI-1 antigen during ACE inhibition in the present study presented as the average of 4 time points. * P < 0.05 vs low-salt diet alone by paired t test.

### Figure 3.

The mechanism for the dissimilar effects of ACE inhibition and AT₁ antagonism on PAI-1 observed in the present study requires further investigation. Quinapril and losartan were administered at equivalent hypotensive doses, suggesting that differences in potency do not account for the distinct effects of the 2 drugs on fibrinolysis. Nevertheless, the study design does not allow us to exclude the possibility that the potency of these drugs with respect to effects on fibrinolysis differs from their potency as hypotensive agents. This possibility can only be addressed with a dose ranging study.

One explanation for the divergent effects of ACE inhibition and AT₁ antagonism on PAI-1 is the hypothesis that Ang II increases PAI-1 expression in humans through its hexapeptide metabolite, Ang IV, and the Ang II type 4 receptor (AT₄), which has been observed in vitro in endothelial cells.8 However, if this were the case, one would expect to measure increased PAI-1 antigen concentrations during AT₁ antagonism, when Ang II, and presumably, Ang IV are increased and the AT₄ receptor is not blocked. On the other hand, down-regulation of the AT₁ receptor by its ligand, if it occurs, could attenuate such an effect.

Alternatively, the differential effects of ACE inhibition and AT₁ inhibition on PAI-1 antigen concentrations could have resulted from different effects of the 2 drugs on insulin sensitivity. Insulin resistance is associated with increased PAI-1 concentrations.28 ACE inhibitors have been shown to improve insulin sensitivity in diabetes, whereas losartan has been reported to have neutral effects on insulin sensitivity.39,40 The similar effects of quinapril and losartan on the fasting glucose-insulin ratio in the present study make it unlikely that metabolic factors underlie the different effects of the drugs on fibrinolysis; however, the effect of the drugs on proinsulin, which increases endothelial PAI-1 expression in vivo,41 was not measured.

The dissimilar effects of quinapril and losartan on PAI-1 concentrations also could have resulted from different effects of the 2 drugs on serum aldosterone concentrations. We have observed previously16 and again in the present study, that PAI-1 concentrations correlate with serum aldosterone concentrations. In vitro, aldosterone interacts synergistically with Ang II to increase PAI-1 expression.22 An unexpected finding of the present study is that aldosterone concentrations were significantly lower during ACE inhibition with quinapril then during AT₁ antagonism with losartan. This conflicts with data from Goldberg et al,22 which showed no difference in the
TABLE 2. Continued

<table>
<thead>
<tr>
<th></th>
<th>Losartan</th>
<th></th>
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<td></td>
<td>0800</td>
<td>1000</td>
<td>1200</td>
<td>1400</td>
</tr>
<tr>
<td>12.5 ± 2.0</td>
<td>12.2 ± 1.9</td>
<td>11.6 ± 2.3</td>
<td>12.8 ± 2.6</td>
<td>$\dagger$</td>
</tr>
<tr>
<td>13.7 ± 1.3</td>
<td>15.4 ± 1.8</td>
<td>12.2 ± 1.4</td>
<td>13.3 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>6.6 ± 0.53</td>
<td>5.91 ± 0.54$^*$</td>
<td>5.78 ± 0.59</td>
<td>5.75 ± 0.55</td>
<td></td>
</tr>
<tr>
<td>23.2 ± 5.4$^\dagger$</td>
<td>27.5 ± 7.6$^*$</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>37.4 ± 3.3</td>
<td>43.2 ± 3.8$^</td>
<td></td>
<td>$</td>
<td>ND</td>
</tr>
</tbody>
</table>

aldosterone response to chronic enalapril versus losartan treatment in salt-replete hypertensive subjects. However, a number of other investigators have reported similar responses to losartan and placebo on serum aldosterone.43–45

In the present study, salt depletion may have accentuated a difference between the effect of ACE inhibition and AT1 antagonism on aldosterone. PRA was markedly elevated during both quinapril and losartan treatment. Although losartan has been shown to block the effects of short-term Ang II administration on aldosterone in salt-deplete subjects,46 it is possible that chronically elevated levels of Ang II offset the effect of AT1 antagonism on aldosterone. Further studies are needed to determine whether ACE inhibitors and AT1 antagonists differ in their effect on aldosterone and fibrinolysis in hypertensive and post-MI patients, in whom the RAAS may be less activated, and to determine whether aldosterone antagonism, either alone or in combination with AT1 antagonism, lowers PAI-1 concentrations.

The effect of ACE inhibition on tPA is even more controversial than the effect of ACE inhibition on PAI-1, with studies reporting increased,47 decreased,17,31,34 and unchanged15,16,20,32,33,35,36 tPA antigen during ACE inhibition. This controversy stems, in part, from the fact that tPA exists in several forms in blood, including free active tPA and tPA bound to PAI-1 and other inhibitors.48,49 Because tPA/PAI-1 complexes are cleared more slowly from the blood than complexes of active tPA, total tPA antigen tends to rise and fall in parallel with PAI-1.50 In this regard, unchanged circulating tPA antigen concentrations in the face of falling PAI-1 antigen concentrations, as observed in the present study during ACE inhibition, might suggest concurrent increased tPA synthesis. Hornig et al51 have reported a significant increase in tPA release across the forearm during intrabrachial administration of an ACE inhibitor. One possible mechanism for the preservation of circulating tPA concentrations during systemic ACE inhibition and the increase in vascular tPA production during local ACE inhibition relates to the effects of ACE inhibitors on bradykinin,23 a potent stimulus to tPA release both in animal models52 and humans.25

In contrast to the lack of effect of losartan on PAI-1 antigen or activity, tPA antigen decreased significantly during losartan treatment. The mechanism for this effect is not clear from the present study. However, tPA is regulated by a number of neurohumoral substances in addition to bradykinin.52 In particular, catecholamines are potent agonists for the release of tPA.53 In the present study, heart rate decreased during losartan therapy versus during salt depletion alone. It is possible that decreased sympathetic activity during losartan treatment may have resulted in decreased tPA antigen, but this hypothesis remains to be tested.

In summary, this study provides evidence of different effects of ACE inhibition and AT1 antagonism on fibrinolytic balance under conditions of activation of the RAAS. It raises the possibility that ACE inhibitors and AT1 antagonists could differ in the extent to which they modify the progression of vascular disease. Further studies are needed to clarify the roles of Ang IV, aldosterone, and bradykinin in the contrasting effects of these 2 classes of drugs on fibrinolysis and to define the clinical significance of these differences.

Acknowledgments

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Comparative Effect of Angiotensin-Converting Enzyme Inhibition and Angiotensin II Type 1 Receptor Antagonism on Plasma Fibrinolytic Balance in Humans

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