Effect of Activation and Inhibition of the Renin-Angiotensin System on Plasma PAI-1

Nancy J. Brown, Mehmet A. Agirbasli, Gordon H. Williams, W. Reid Litchfield, Douglas E. Vaughan

Abstract—Increased plasma renin activity (PRA) has been associated with an increased risk of myocardial infarction (MI), whereas angiotensin-converting enzyme (ACE) inhibition appears to reduce the risk of recurrent MI in patients with left ventricular dysfunction. These observations may be partially explained by an interaction between the renin-angiotensin system (RAS) and fibrinolytic system. To test this hypothesis, we examined the effect of salt depletion on tissue-type plasminogen activator (tPA) antigen and plasminogen activator inhibitor-1 (PAI-1) activity and antigen in normotensive subjects in the presence and absence of quinapril (40 mg BID). Under low (10 mmol/d) and high (200 mmol/d) salt conditions there was significant diurnal variation in PAI-1 antigen and activity and tPA antigen. Morning (8 AM through 2 PM) PAI-1 antigen levels were significantly higher during low salt intake compared with high salt intake conditions (ANOVA, F=5.8, P=0.048). PAI-1 antigen correlated with aldosterone (r=0.56, P<10^-7) during low salt intake. ACE inhibition significantly decreased 24-hour (ANOVA for 24 hours, F=6.7, P=0.04) and morning (F=24, P=0.002) PAI-1 antigen and PAI-1 activity (F=6.48, P=0.038) but did not alter tPA antigen. Thus, the mean morning PAI-1 antigen concentration was significantly higher during low salt intake than during either high salt intake or low salt intake and concomitant ACE inhibition (22.7±4.6 versus 16.1±3.3 and 16.3±3.7 ng/mL, respectively; P<0.05). This study provides evidence of a direct functional link between the RAS and fibrinolytic system in humans. The data suggest that ACE inhibition has the potential to reduce the incidence of thrombotic cardiovascular events by blunting the morning peak in PAI-1. (Hypertension. 1998;32:965-971.)

Key Words: renin ■ angiotensin II ■ plasminogen activator inhibitor 1 ■ fibrinolysis ■ tissue plasminogen activator ■ sodium ■ quinapril

A ctivation of the renin-angiotensin system (RAS) has been associated with an increased risk of ischemic cardiovascular events independent of effects on blood pressure. Retrospective and prospective epidemiologic studies have provided evidence that hypertensive subjects with an increased renin-sodium profile are at increased risk for both myocardial infarction and stroke.14,15 Similarly, activation of the RAS by diuretic use or low salt intake has been associated with an increased risk of myocardial infarction (MI).14,16 Conversely, interruption of the RAS with an angiotensin-converting enzyme (ACE) inhibitor decreases progression of atherosclerosis in animal models17,18 and appears to reduce the risk of recurrent MI in patients with left ventricular dysfunction.17,18 The mechanisms through which activation of the RAS increases or ACE inhibition reduces the risk of ischemic cardiovascular events in selected populations are not known. One possible explanation involves an interaction between the RAS and fibrinolytic system. Accumulating data suggest that angiotensin II (Ang II) modulates fibrinolysis. For example, Ang II and its hexapeptide metabolite Ang IV stimulate plasminogen activator inhibitor-1 (PAI-1) expression in cultured endothelial cells in a dose-dependent manner.9 Infusion of exogenous Ang II has been shown to increase PAI-1 antigen selectively in both normotensive and hypertensive subjects.10 These findings may be of clinical significance because PAI-1 is the major inhibitor of tissue plasminogen activator (tPA) in vivo.31 Increased PAI-1 expression has been observed in atherosclerotic plaques in humans12 and may contribute to the progression of vascular disease. Elevated PAI-1 levels are observed in insulin-resistant states13 and appear to be a risk factor for recurrent MI.14 ACE inhibitors not only block the formation of Ang II but also prevent the degradation of bradykinin.15,16 We have previously proposed that the prothrombotic effects of Ang II may be balanced by the antithrombotic effects of bradykinin.17 Bradykinin is a potent stimulus for tPA secretion in ACE-pretreated bovine aorta endothelial cells, in animal models, and in humans.15,19 Thus, ACE inhibitors would be expected to favorably alter fibrinolytic balance by decreasing Ang II and increasing bradykinin.

The purpose of the present study was to test the hypothesis that activation of the RAS increases PAI-1 and that ACE
inhibition blocks this effect and favorably alters fibrinolytic balance. Salt depletion was used to stimulate the RAS. Fibrinolytic and RAS parameters were measured throughout the day because of the known diurnal variation in these 2 systems.

Methods
All subjects underwent a complete history and physical examination before investigation. Subjects with cardiovascular, renal, endocrine, or pulmonary disease were excluded. Written informed consent was obtained, and the study protocol was approved by the Vanderbilt Institutional Review Board. The study protocol is outlined in Figure 1. Beginning on day 1 of the protocol, each subject was provided with either a low (10 mmol/d) or a high (200 mmol/d) salt, caffeine-free, and alcohol-free diet for 5 days. The order of diets was randomized. On the morning of the 5th day of diet, subjects were asked to report to the Vanderbilt General Clinical Research Center at 7 AM. A catheter was placed in an antecubital vein. Beginning at 8 AM and every 3 hours thereafter for 24 hours, blood was drawn through the catheter for measurement of PAI-1 and tPA antigen and activity, as well as plasma renin activity (PRA), aldosterone, catecholamine, and cortisol concentrations after the subject had been recumbent for at least 30 minutes. In addition, blood was obtained for measurement of PRA, catecholamines, and fibrinolytic variables at 11:30 AM after the subject had been standing for 30 minutes. Subjects were allowed to ambulate between blood draws. They slept from approximately 11 PM through 6 AM. Blood pressure and heart rate were measured every 8 hours, after subjects had been supine for at least 30 minutes. Subjects were asked to collect all of their urine for the 24-hour study period for measurement of sodium, creatinine, and volume. At the end of the study day, subjects were switched to the opposite diet. On the 5th day of the second diet, blood sampling and urine collection were repeated.

Four days after completion of the second diet period, subjects were treated with quinapril at an initial dose of 5 mg PO BID. The dose was increased every 3 days through 10, 20, and 40 mg PO BID. After titration, subjects were maintained on the 40-mg BID dose of quinapril for an additional 14 days. They were then provided a caffeine-free, and alcohol-free diet for the last 5 days of quinapril treatment. On the 5th day of the diet, blood sampling and urine collection were repeated. One subject completed the quinapril phase of the study before the diet phase.

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 evacuated 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. with standardized commercial kits (Biopool AB), with results expressed as units per milliliter. Antigen levels were determined using a 2-site enzyme-linked immunosorbent assay (Biopool AB) as previously described. In our laboratory, the coefficients of variation for repeated measures of tPA antigen and PAI-1 antigen are 5.9% and 8.1%, respectively. The PAI-1 and tPA mass ratio was determined by dividing plasma concentrations (ng/mL) by the molecular weights of the 2 proteins, with a value of 70 000 g/mol used for tPA, and a value of 50 000 g/mol for PAI-1. Blood for measurement of PRA was collected in tubes containing EDTA. PRA was measured in samples drawn from 8 AM through 8 PM by radioimmunoassay for Ang I formation at pH 7.4 and 37°C. Serum aldosterone and cortisol levels were assayed using commercially available radioimmunoassay kits. For aldosterone (Diagnostic Corp) the intra-assay and interassay coefficients of variation were 6% and 10%, respectively. For cortisol (Incstar Corp), the intra-assay and interassay coefficients of variation were 4.5% and 6.7%, respectively. Catecholamines were collected in tubes containing reduced glutathione and measured by high-performance liquid chromatography, as previously described. Plasma samples from blood collected at 8 AM, 11 AM, 11:30 AM, and 11 PM were assayed for catecholamines.

Statistical Analysis
Data are presented as mean±SEM (Figures 2, 3 and 4). To examine the effect of diurnal variation, the day was divided into 3 periods: period 1 (8 AM through 2 PM), period 2 (5 PM through 11 PM), and period 3 (2 AM through 8 AM). (Mean values for samples drawn during each of these periods are presented in Table 2.) Data were analyzed using repeated-measures ANOVA (SPSS for Windows, Release 6, SPSS) in which the between-subject variable was renin status (upright PRA <2.4 versus ≥2.4 ng Ang I/mL per hour during salt depletion), and the within-subject variables were time of day (with repeated samples within each time of day), salt intake (low versus high salt), and drug (ACE inhibition versus control). When
analysis showed an effect of time of day, a separate ANOVA was repeated for each of the 3 time periods. Post hoc comparisons were made using a paired t test. A 2-tailed value of P, 0.05 was the criterion for statistical significance.

Results

Subject Characteristics
Nine normotensive men (8 white, 1 black) were studied. The mean age was 29.2 ± 1.7 years, and the mean body mass index was 26.5 ± 1.2 kg/m². Mean serum cholesterol concentration was 4.21 ± 0.52 mmol/L (162.7 ± 20.2 mg/dL), whereas the mean serum triglyceride concentration was 2.29 ± 0.61 mmol/L (203.0 ± 53.8 mg/dL). Six of the 9 subjects demonstrated low renin as defined by previously published criteria (upright PRA under salt-depleted conditions, <2.4 ng Ang I/mL per hour).24 The mean 24-hour urinary sodium excretion on each study day is provided in Table 1.

Hemodynamic Response
There was no effect of salt intake or ACE inhibition on blood pressure in these normotensive subjects (Table 1). Heart rate was significantly lower during ACE inhibition than during low salt intake alone.

Endocrine Response
There was no difference in PRA measured from 8 AM through 2 PM and PRA measured from 5 PM through 8 PM (Table 2). Low sodium intake was associated with significantly higher PRA compared with high sodium intake (F = 17.4, P = 0.003; Figure 2A). This was most pronounced for upright PRA (3.4 ± 1.0 during low salt intake versus 1.3 ± 0.6 during high salt intake, P = 0.007 by paired Student’s t test). ACE inhibition was associated with a marked increase in PRA compared with low salt intake alone (F = 20.5, P = 0.002; mean shown in Table 2). There was significant diurnal variation in serum aldosterone concentrations during low salt (F = 21.6, P < 0.001), high salt (F = 12.2, P = 0.001), and ACE inhibition (F = 6.7, P = 0.009), such that a nadir occurred during the 5 PM – 11 PM period (period 2). Low salt intake was associated with increased aldosterone compared with high salt intake (F = 32.4, P = 0.001; Figure 2B). ACE inhibition decreased the aldosterone level (F = 21.5, P = 0.002) under low salt conditions, but the aldosterone level remained significantly higher than under high salt conditions (F = 31.6, P = 0.001).

There was significant diurnal variation in serum cortisol during low salt intake (F = 23.4, P = 0.001), high salt intake

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low Salt</th>
<th>High Salt</th>
<th>Low Salt + Quinapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-Hour urinary sodium, mmol</td>
<td>24.3 ± 4.3*</td>
<td>205.5 ± 18.0</td>
<td>34.7 ± 5.7*</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>88.6 ± 2.2</td>
<td>85.6 ± 2.4</td>
<td>86.7 ± 3.7</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71.9 ± 3.6</td>
<td>67.7 ± 3.1</td>
<td>63.2 ± 3.4‡</td>
</tr>
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</table>

MAP indicates mean arterial pressure.
*P < 0.05 vs high salt; † P < 0.05 vs low salt.

Figure 3. Effects of salt intake and ACE inhibition on cortisol (A) and catecholamines (B). Open bars indicate low salt; solid bars, high salt; and hatched bars, low salt + quinapril. * P < 0.05, ** P < 0.01, ***P < 0.005 vs low salt. † P < 0.05, ‡ P < 0.005 vs high salt.

Figure 4. Effects of salt intake (A) and ACE inhibition (B) during low salt intake on PAI-1 antigen concentration. * P < 0.05, ** P < 0.001 vs low salt alone.
There was significant diurnal variation in PAI-1 antigen under low (effect of time of day, F = 6.48, P = 0.010) conditions, such that levels were lowest during the period from 5 PM through 11 PM (period 2; Figure 4, Table 2). Treatment with quinapril attenuated this diurnal variation in PAI-1 antigen (time of day, F = 2.65, P = 0.106) and activity (F = 3.32, P = 0.066). There was significant diurnal variation in tPA antigen under all 3 study conditions: low salt (F = 11.66, P = 0.001), high salt (F = 9.68, P = 0.002), and during quinapril (F = 5.80, P = 0.005). There was significant diurnal variation in the molar ratio of PAI-1 to tPA antigen under low salt conditions alone (F = 4.6, P = 0.029) but not under high salt conditions or during treatment with quinapril.

Salt intake had no significant effect on PAI-1 antigen, PAI-1 activity, or tPA antigen, measured over the entire 24-hour period (Figure 4). However, compared with low salt intake, high salt intake was associated with a decrease in PAI-1 antigen during the period from 8 AM through 2 PM (period 1, F = 5.76, P = 0.048). tPA antigen tended to be lower during the period 2 high salt intake compared with low salt intake, but this difference did not reach significance (F = 4.1, P = 0.08).

ACE inhibition significantly decreased PAI-1 antigen levels measured over the entire 24-hour period (26%, F = 6.68, \( P = 0.035 \)) under low salt conditions (Figure 4). This effect was most pronounced during the morning hours when PAI-1 antigen levels were highest (F = 24, \( P = 0.002 \) for drug effect from 8 AM through 2 PM) but was also seen during period 3 (F = 11.4, \( P = 0.012 \)). ACE inhibition also significantly lowered PAI-1 activity (F = 6.48, \( P = 0.038 \) for the full 24-hour period and F = 7.42, \( P = 0.03 \) for period 1). There was a significant interaction between the subjects’ renin status and the effect of ACE inhibition on PAI-1 antigen (F = 24.0, \( P = 0.002 \) for interaction) and PAI-1 activity (F = 12.2, \( P = 0.01 \)). There was no effect of ACE inhibition on tPA antigen (Table 2) during salt depletion. For this reason, the PAI-1:tPA molar ratio (Table 2) was significantly lower during period 1 with ACE inhibition than during low salt alone (F = 11.1, \( P = 0.013 \)). In addition, the PAI-1:tPA ratio was significantly lower during ACE inhibition than during high salt intake during period 3 (F = 12.0, \( P = 0.011 \)).

To determine the relationship between activation of the RAS and PAI-1 antigen, the correlation between serum aldosterone and PAI-1 antigen levels was determined. In addition, because of the diurnal variation in PAI-1, the relationship between PAI-1 antigen and cortisol or catecholamine levels was also determined. There was a significant positive correlation between PAI-1 antigen and PRA \((r = 0.28, t = 3.02, P = 0.003)\) measured under both low and high salt intakes. In the presence of quinapril, the relationship between PAI-1 and PRA was no longer significant \((r = 0.25, t = 1.85, P = 0.069)\). There was a highly significant correlation between PAI-1 antigen levels and serum aldosterone under low salt conditions [PAI-1 antigen = 0.41(aldosterone) + 7.4; \( r = 0.56, P = 7.0 \times 10^{-8} \), Figure 5] that remained significant during ACE inhibition [PAI-1 antigen = 0.36(aldosterone) + 8.5; \( r = 0.26, P = 0.019 \)]. In contrast, there was no correlation between PAI-1 and aldosterone under high salt conditions \((r = 0.10, t = 0.89, P = 0.38)\). PAI-1 antigen also correlated with serum cortisol levels under both high \((r = 0.28, t = 2.6, P = 0.01)\) and low salt intake \((r = 0.26, t = 2.3, P = 0.029)\).
Discussion

Recent in vitro and in vivo studies have identified an interaction between the RAS and fibrinolytic system. Although previous studies have determined the effect of exogenous Ang II on PAI-1 antigen levels, this is the first study to examine the effect of activation of the endogenous RAS on plasma fibrinolytic balance in healthy human subjects. The data suggest that activation of the RAS results in increased PAI-1 antigen during the morning hours and that interruption of the RAS with the ACE inhibitor quinapril significantly lowers PAI-1 antigen and activity without lowering tPA antigen.

In this study, activation of the RAS during low salt intake was documented by significant increases in PRA and serum aldosterone concentrations. Under these conditions, PAI-1 antigen was increased compared with during high salt intake during the period from 8 AM through 2 PM. This is consistent with data from an uncontrolled study that showed that patients with ischemic heart disease who were treated with diuretics had significantly higher levels of PAI-1 antigen compared with patients who did not receive diuretics. The correlation between PAI-1 antigen and serum aldosterone concentrations observed in this study further supports an interaction between the RAS and fibrinolytic system.

As other investigators have reported, we observed marked diurnal variation in PAI-1 antigen and activity, with a nadir occurring during the 5 PM–11 PM time period. tPA antigen, which reflects tPA:PAI-1 complex as well as free tPA, followed a similar pattern. This diurnal pattern of variation in PAI-1 antigen and activity may have clinical significance in that it mirrors the pattern of variation in time of occurrence of MI reported by several investigators. Furthermore, it has recently been reported that the thrombolytic efficacy of intravenous tPA is reduced when administered during the morning hours, coincident with the diurnal peak in PAI-1.

The pattern of diurnal variation in PAI-1 antigen and activity observed in this study closely mimicked the pattern of diurnal variation in aldosterone. Aldosterone secretion is influenced by Ang II, adrenocorticotropic hormone, and potassium. The sensitivity of the adrenal cortex to Ang II varies with sodium intake such that under conditions of salt depletion, Ang II is the major determinant of aldosterone. The highly statistically significant correlation between serum aldosterone and PAI-1 antigen under low salt conditions and the lack of such a correlation under high salt conditions (when aldosterone levels are independent of Ang II) supports the hypothesis that Ang II regulates vascular PAI-1 levels.

There was also a significant correlation between serum cortisol concentrations and PAI-1 antigen under both high and low salt conditions in this study. This contrasts with data from Chandler et al who concluded that cortisol was not responsible for circadian variation in PAI-1 activity; however, in this earlier study, subjects were not studied under controlled salt conditions, and there was wide interindividual variation in the time of peak and trough PAI-1 activity. One possible explanation for the observed correlation between cortisol and PAI-1 antigen is that glucocorticoids increase PAI-1 synthesis. Dexamethasone has been shown to increase PAI-1 expression directly or to enhance the response to interleukin-1 in both rat and human hepatocyte cell lines. Furthermore, a glucocorticoid responsive element has been localized to the region −330 to +75 of the PAI-1 gene. Data from the present study suggest that there may be an interactive effect of glucocorticoids and Ang II on PAI-1 synthesis, in that ACE inhibition abolished the correlation between cortisol and PAI-1. This potential mechanistic interaction remains to be examined in vitro.

ACE inhibitors have been shown to reduce progression of atherosclerosis in several animal models and to reduce the vascular expression of PAI-1 in normal and balloon-injured vessels. Two large-scale clinical trials of ACE inhibitor therapy administered to patients with left ventricular dysfunction, Survival and Ventricular Enlargement Trial (SAVE) and Studies on Left Ventricular Enlargement (SOLVD) trials, both reported similar reductions in the rate of ischemic cardiovascular events. The present study suggests a mechanism whereby ACE inhibitors could alter the incidence of ischemic cardiovascular events in the setting of an activated RAS. Specifically, ACE inhibition significantly lowered both PAI-1 antigen and activity during salt depletion. This is consistent with data from the Healing and After-load Reducing Therapy (HEART) study, which showed a 44% decrease in PAI-1 antigen and a 22% decrease in PAI-1 activity after 2 weeks of treatment with the ACE inhibitor ramipril after MI. In addition, recent studies have reported a relationship between the insertion/deletion polymorphism of the ACE gene and PAI-1 levels, further supporting a functional link between the RAS and fibrinolytic systems. Whether the effect of ACE inhibition on PAI-1 results from decreased Ang II or from decreased formation of its hexapeptide metabolite Ang IV remains to be determined. Studies in bovine endothelial cells suggest that Ang II regulates PAI-1 expression through Ang IV and a unique non-AT\textsubscript{1}, non-AT\textsubscript{2} receptor. The effect of AT\textsubscript{1} receptor antagonists on PAI-1 remains to be defined in humans.

We have previously reported a molar ratio of PAI-1 to tPA of 3.9±0.2 measured in healthy human volunteers. In the present study, we observed that this ratio varied by up to 45% under low salt and by up to 51% under high salt conditions. In contrast, this index of vascular fibrinolytic balance was consistently at or below 4.1 during all 3 time periods during ACE inhibition and varied by <3%. Thus, although morning PAI-1 antigen was reduced by suppression of the RAS with high salt and interruption of the RAS with ACE inhibition, only ACE inhibition consistently preserved the normal molar ratio of PAI-1 to tPA. This improvement in fibrinolytic balance contrasts with the findings of Wright et al who reported a disproportional reduction in tPA compared with PAI-1 in infarct survivors treated with captopril but agrees with data from infarct survivors treated with ramipril. A lack of effect of ACE inhibition on tPA antigen in the present
study may simply reflect the effects of ACE inhibition on the kallikrein-kinin system as well as the RAS. ACE inhibitors not only decrease the production of Ang II but also decrease the degradation of bradykinin. Bradykinin has been shown to be a potent stimulus for tPA secretion in vitro and in vivo.

The present study may underrepresent the potential magnitude of the impact of activation of the RAS on plasma fibrinolytic balance because the majority of the subjects studied had low upright PRA during salt depletion. The reason for this is not clear because all but 1 of the subjects were white. Nevertheless, to the extent that low-renin subjects tend to be resistant to the effects of ACE inhibitors, the preponderance of low-renin subjects in the present study would be expected to attenuate the effect of activation of the RAS and of ACE inhibition on PAI-1. The small number of subjects studied did not allow us to compare the effects of salt and ACE inhibition on PAI-1 in low-renin versus high-renin subjects; however, there was an interaction between renin status and the effect of ACE inhibition on PAI-1 antigen and activity. The preponderance of low-renin subjects studied may also explain the lack of a blood pressure effect of ACE inhibition during salt depletion.

In summary, this study provides evidence for a direct functional link between the RAS and fibrinolytic system in humans. It suggests a mechanism through which ACE inhibitors, the preponderance of low-renin subjects in the present study may underrepresent the potential magnitude of the impact of activation of the RAS on plasma fibrinolytic balance because the majority of the subjects studied had low upright PRA during salt depletion. The reason for this is not clear because all but 1 of the subjects were white. Nevertheless, to the extent that low-renin subjects tend to be resistant to the effects of ACE inhibitors, the preponderance of low-renin subjects in the present study would be expected to attenuate the effect of activation of the RAS and of ACE inhibition on PAI-1. The small number of subjects studied did not allow us to compare the effects of salt and ACE inhibition on PAI-1 in low-renin versus high-renin subjects; however, there was an interaction between renin status and the effect of ACE inhibition on PAI-1 antigen and activity. The preponderance of low-renin subjects studied may also explain the lack of a blood pressure effect of ACE inhibition during salt depletion.

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References


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