Endogenous NO Regulates Plasminogen Activator Inhibitor-1 During Angiotensin-Converting Enzyme Inhibition

Nancy J. Brown, James A.S. Muldowney III, Douglas E. Vaughan

Abstract—To test the hypothesis that NO contributes to effects of angiotensin-converting enzyme inhibitors on fibrinolysis, fibrinolytic balance was assessed in 17 normal subjects during placebo and after randomized, double-blind 4-week treatment with the NO precursor L-arginine (3 g TID), ramipril (10 mg QD), or L-arginine+ramipril. Neither L-arginine nor ramipril alone affected basal plasminogen activator inhibitor-1 or tissue-type plasminogen activator (t-PA) antigen in these salt-replete subjects in whom plasma renin activity was suppressed (mean±SD 0.7±0.5 ng angiotensin I/mL per hour). In contrast, L-arginine+ramipril reduced morning plasminogen activator inhibitor-1 antigen (10.8±9.5 ng/mL) and the molar ratio of plasminogen activator inhibitor-1:t-PA (2.3±1.6) compared with placebo (13.5±10.8 ng/mL, P=0.006; ratio 2.9±2.1, P=0.015) or ramipril alone (15.2±13.2 ng/mL, P=0.009; ratio 3.7±3.3, P=0.005). L-arginine and ramipril synergistically increased t-dimers (23.1±31.5, 29.7±50.0, 35.1±50.0, and 57.1±144.8 ng/mL during placebo, L-arginine, ramipril, and L-arginine+ramipril, respectively; P<0.05 for L-arginine+ramipril versus any other group). During ramipril, the NO synthase inhibitor L-G-nitro-arginine-methyl-ester (2 mg/kg) significantly increased plasminogen activator inhibitor–antigen after 2 hours (from 9.4±8.6 ng/mL during vehicle to 13.5±11.0 ng/mL during L-G-nitro-arginine-methyl-ester; P=0.020), consistent with an effect on expression but rapidly increased t-PA activity (from 0.4±0.3 to 0.5±0.4 IU/mL; P=0.031), consistent with an effect on release. Both effects of L-G-nitro-arginine-methyl-ester were reversed by L-arginine. During angiotensin-converting enzyme inhibition, endogenous NO decreases plasminogen activator inhibitor-1 antigen and improves fibrinolytic balance in normotensive salt-replete subjects. (Hypertension. 2006;47:441-448.)

Key Words: nitric oxide ■ nitric oxide synthase ■ angiotensin ■ renin ■ plasminogen

Plasminogen activators play a critical role in the regulation of vascular fibrinolysis and the degradation of extracellular matrix. Plasminogen activator inhibitor-1 (PAI-1), a principal inhibitor of plasminogen activators, promotes thrombosis and fibrosis.1 PAI-1 expression is increased in atherosclerotic lesions and at sites of vascular injury.2,3 Circulating PAI-1 concentrations are increased in patients with risk factors for atherosclerosis, particularly in those with insulin resistance.4 Furthermore, increased PAI-1 concentrations are associated with increased risk of myocardial infarction.5 In addition to glucose and insulin, other growth factors, cytokines, and hormones regulate PAI-1 expression, including transforming growth factor-β, tumor necrosis factor-α, and angiotensin II (Ang II).1 Increasing evidence suggests that the deleterious vascular effects of activation of the renin-angiotensin-aldosterone system (RAAS) derive in part from Ang II and aldosterone-induced PAI-1 expression.6

On the other hand, studies in vitro and in animal models suggest that NO inhibits PAI-1 release and expression. For example, NO donors reduce PAI-1 release from platelets.7,8 Feener et al reported that NO diminishes Ang II or platelet-derived growth factor–stimulated PAI-1 expression in vascular smooth muscle cells via a cGMP-dependent pathway.9 In rodents, NO synthase (NOS) inhibition using L-G-nitro-arginine-methyl-ester (L-NAME) induces vascular PAI-1 expression.10,11 Co-administration of an angiotensin-converting enzyme (ACE) inhibitor abolishes L-NAME–induced PAI-1 expression and vascular injury, further suggesting that NO modulates Ang II–stimulated PAI-1 expression in vivo.10

The role of NO in the regulation of PAI-1 expression in humans has not been established. Korbut et al reported that intravenous infusion of the NO precursor L-arginine decreased circulating PAI-1 in 2 men with hypertension and hypercholesterolemia.12 More recently, Sakamoto et al reported that nicorandil, a combined KATP channel opener and NO donor that significantly reduced cardiovascular end points in patients with stable angina,13 decreases PAI-1 activity.14 ACE inhibition decreases circulating PAI-1 and enhances fibrinolytic balance,
particularly during activation of the RAAS.\textsuperscript{15–21} Although ACE inhibition likely improves fibrinolytic balance by attenuating Ang II–induced PAI-1 expression,\textsuperscript{22} ACE inhibition could also modulate PAI-1 expression by increasing kinin-mediated NO production and release.\textsuperscript{23}

This study tests the hypothesis that NO contributes to the effect of ACE inhibitors on fibrinolytic balance. Specifically, we tested the hypothesis that coadministration of the NO precursor L-arginine would enhance the effect of ACE inhibition on circulating PAI-1 concentrations, whereas NOS inhibition would abrogate the effects of ACE inhibition on fibrinolytic balance.

Methods

The study protocol (Figure 1) was approved by the Vanderbilt institutional review board. All subjects gave written informed consent. As reported previously, after screening, subjects were given placebo tablets for 2 weeks.\textsuperscript{24} On the mornings of the 12th and 14th days of placebo, subjects reported to the Vanderbilt General Clinical Research Center (GCRC) for infusion of L-NAME (Clinalfa AG) or vehicle (normal saline) in randomized order during normal sodium intake. At the end of the second infusion day, subjects were randomized to double-blind treatment with L-arginine–placebo, ramipril–placebo, or L-arginine–ramipril for 4 weeks. L-arginine (Professional Compounding Centers of America) was started at 750 mg TID and titrated to 3 g TID over 1 week. Ramipril (Monarch Pharmaceuticals) was given at 2.5 mg per day and titrated to 10 mg per day over 1 week. Medications and identical placebos were prepared by the Vanderbilt Investigational Pharmacy. On the 26th and 28th days of treatment, subjects again underwent infusion of L-NAME or vehicle. After the second infusion, subjects repeated 2 additional cycles of 2-week washout, 4-week treatment, and infusion studies until they had completed all active treatment arms.

On infusion days, subjects reported to the GCRC fasting and were studied in the supine position. At 8:00 AM, a catheter was placed in a vein of each arm for drawing blood and administering drugs. One half-hour later, oral study medication was given and 2 mg/kg L-NAME or vehicle was given intravenously in 250 mL over 30 minutes (66 \(\mu\)g/kg per minute) or until systolic blood pressure (SBP) increased 20 mm Hg from the 8:30 AM baseline. Blood pressure and heart rate were measured every 5 minutes for 4 hours after the start of the infusion using an automated oscillometric cuff (Critikon) and telemetry. L-NAME was stopped early because of an exaggerated hypertensive response in 2 of the 17 subjects (after 15 and after 20 minutes). After the first L-NAME infusion, the same dose was used for each L-NAME study day in the same subject. Blood was drawn for measurement of PAI-1 and tissue-type plasminogen activator (t-PA) antigen before the start of infusion and hourly thereafter for 4 hours. Blood was drawn for measurement of ACE activity before infusion and for plasma renin activity (PRA), Ang II, and aldosterone before and 1 and 4 hours after the start of infusion.

Laboratory Analysis

For laboratory analysis, please see the online supplement, available at http://www.hypertensionaha.org.

Statistical Analysis

Data are presented as means±SD in text and the Table and means±SEM in the figures. A sample size of 17 was calculated to have a power of 0.79 to detect a within-group difference in PAI-1 antigen between treatment arms of 3.2 ng/mL with \(\alpha=0.05\) and an SD of the difference of 4.5 ng/mL. The effect of treatment on hemodynamic, endocrine, and fibrinolytic variables was assessed using a general linear model repeated-measures ANOVA in which within-subject variables were treatment and time after normality of the data and equality of variances were confirmed. D-dimer and plasmin-\(\alpha_2\)-antiplasmin concentrations were log transformed before analysis. For fibrinolytic parameters, quartile of body mass index and renin status were included as between-subject variables because they affect PAI-1 concentrations.\textsuperscript{4,18} There was no effect of gender on fibrinolysis, and therefore this was not included in analyses. Unless otherwise noted, \(P\) values from the ANOVA are presented in the text and the Table. \(P\) values for paired comparisons are presented in the figures. A 2-tailed \(P\) value \(\leq 0.05\) was considered significant. Analyses were performed using SPSS for Windows (version 11.0; SPSS).

Results

Effect of ACE Inhibition and L-Arginine on Basal RAAS, NO Metabolites, and Hemodynamics

Seventeen moderately active subjects (11 males and 6 females; 15 whites and 2 blacks) completed the study. Mean age was 36.1±10.7 years. Mean body mass index was
26.8±1.9 kg/m². Five women were premenopausal, and 1 was taking hormone replacement therapy. Treatment with ramipril significantly reduced serum ACE activity, SBP, and aldosterone and increased PRA (Table). L-Arginine did not affect blood pressure or the RAAS or alter the effects of ramipril. L-Arginine supplementation significantly increased circulating L-arginine and L-citrulline concentrations whether given alone or in combination with ramipril. Neither ramipril nor L-arginine affected baseline NO metabolite concentrations.

Effect of ACE Inhibition and L-Arginine on Basal Fibrinolytic Balance

Figure 2 shows the effect of L-arginine and ramipril alone and in combination on basal morning (8:00 AM) PAI-1 antigen, PAI-1 activity, D-dimers, and plasmin-β2-antiplasmin complexes. In contrast to previous studies in individuals in whom the RAAS has been activated, there was no effect of ramipril alone on morning PAI-1 antigen, t-PA antigen, or the molar ratio of PAI-1 to t-PA. L-Arginine alone did not significantly affect morning PAI-1 antigen. However, in combination with ramipril, L-arginine reduced PAI-1 antigen compared with either placebo (P=0.006) or ramipril (P=0.009) alone. There was no effect of L-arginine alone or in combination on t-PA antigen (data not shown). Consequently, combined treatment with ramipril and L-arginine significantly reduced the molar ratio of PAI-1 to t-PA (2.3±1.6) compared with either placebo (2.9±2.1; P=0.015) or ramipril (3.7±3.3; P=0.005) alone but not compared with L-arginine alone (2.8±2.3). PAI-1 activity was also suppressed 25% by combination therapy (Figure 2B) and correlated with the molar ratio of PAI-1 to t-PA antigen (R²=0.652; P<0.001). Basal t-PA activity was unchanged by any treatment (data not shown). To determine

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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>L-Arginine</th>
<th>Ramipril</th>
<th>L-Arginine + Ramipril</th>
<th>L-Arginine</th>
<th>Ramipril</th>
<th>L-Arginine × Ramipril</th>
<th>Interaction</th>
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<tr>
<td>SBP (mm Hg)</td>
<td>113.3±10.1</td>
<td>113.0±12.4</td>
<td>109.6±10.3</td>
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<td>0.003</td>
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<td>DBP (mm Hg)</td>
<td>66.9±9.1</td>
<td>66.0±9.2</td>
<td>64.9±8.4</td>
<td>66.4±8.7</td>
<td>0.270</td>
<td>0.789</td>
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<td>Heart rate (bpm)</td>
<td>61.7±7.4</td>
<td>61.6±8.4</td>
<td>62.0±8.7</td>
<td>62.4±9.3</td>
<td>0.638</td>
<td>0.859</td>
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<tr>
<td>ACE activity (IU/mL)</td>
<td>30.0±11.4</td>
<td>28.7±12.0</td>
<td>7.0±3.66</td>
<td>9.5±4.55</td>
<td>0.386</td>
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<td>PRA (ng Ang I/mL/hr)</td>
<td>0.7±0.5</td>
<td>0.7±0.5</td>
<td>1.5±1.3</td>
<td>3.1±5.9</td>
<td>0.319</td>
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<td>Ang II (pg/mL)</td>
<td>38.4±10.2</td>
<td>40.0±11.6</td>
<td>38.2±14.2</td>
<td>41.7±16.3</td>
<td>0.177</td>
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<td>Aldosterone (ng/dL)</td>
<td>6.6±3.2</td>
<td>6.6±3.3</td>
<td>5.2±2.3</td>
<td>5.3±2.3</td>
<td>0.842</td>
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<tr>
<td>L-Arginine (µmol/L)</td>
<td>59.1±14.7</td>
<td>113.1±31.9</td>
<td>58.8±10.3</td>
<td>118.8±25.6</td>
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<td>L-Citrulline (µmol/L)</td>
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<td>31.4±7.2</td>
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<td>31.4±8.4</td>
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<td>NO metabolites (µmol/L)</td>
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<td>17.6±6.6</td>
<td>16.1±4.82</td>
<td>14.9±4.9</td>
<td>0.191</td>
<td>0.371</td>
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</table>

DBP indicates diastolic blood pressure.

To convert aldosterone to pmol/L, multiply by 27.74. For Ang II, pg/mL is equivalent to nmol/L. For paired comparisons, *P<0.01 vs placebo, †P<0.05 vs placebo, ‡P<0.05 vs L-arginine alone, §P<0.001 vs placebo, ||P<0.001 vs L-arginine alone, ¶P<0.001 vs ramipril alone.
whether decreased PAI-1 antigen and activity resulted in increased fibrinolysis, we measured D-dimers and plasmin-α2-antiplasmin complexes; l-arginine and ramipril synergistically increased circulating D-dimers (Figure 2C) and plasmin-α2-antiplasmin (Figure 2D).

**Effect of Acute l-NAME Infusion on the RAAS, NO Metabolites, and Hemodynamics**

During the placebo arm, l-NAME significantly increased blood pressure ($P < 0.001$), and this effect lasted for $\approx 210$ minutes after discontinuation of the infusion, consistent with the conversion of l-NAME to a long-acting active metabolite. However, there was no carryover effect on blood pressure between treatment days. l-NAME also increased blood pressure during the ramipril treatment arm ($P = 0.008$) and the l-arginine treatment arm ($P < 0.001$). However, pretreatment with ramipril ($P = 0.014$ for change in SBP in response to l-NAME during ramipril versus during placebo) or l-arginine ($P = 0.046$) significantly blunted the pressor response after l-NAME. Hence, the mean increase in SBP after l-NAME was 10.1±8.7 mm Hg during the placebo arm and 6.2±7.8 and 7.3±8.7 mm Hg during the ramipril and l-arginine treatment arms, respectively. During combined treatment with l-arginine + ramipril, l-NAME induced a transient increase in SBP but the change in SBP over the 4 hours after l-NAME was no longer significant compared with vehicle (4.6±9.1 mm Hg; $P = 0.06$).

As we have reported previously in a subset from this study, l-NAME increased circulating aldosterone concentrations compared with vehicle during placebo ($P = 0.013$ for the current study), l-arginine ($P = 0.031$), and ramipril ($P = 0.049$) but not during combined treatment with l-arginine + ramipril ($P = 0.236$). There was no effect of l-NAME on PRA, Ang II concentrations, or NO metabolites (data not shown).

**Effect of Acute l-NAME Infusion on Fibrinolytic Balance**

Figure 3 illustrates the effect of l-NAME and vehicle infusion on PAI-1 antigen concentrations from 8:00 AM to 12:00 PM. PAI-1 antigen concentrations decreased with time ($P = 0.023$) during vehicle infusion, consistent with the previously described diurnal variation in PAI-1. There was no effect of l-NAME infusion on PAI-1 antigen concentrations in subjects during either the placebo (Figure 3A) or l-arginine (Figure 3B) treatment arm. However, during ramipril treatment (Figure 3C), l-NAME significantly increased plasma PAI-1 antigen concentrations compared with vehicle ($P = 0.020$). This effect became evident 2 hours after the initiation of l-NAME, with a 44% increase in PAI-1 antigen from 9.4±8.6 to 13.5±11.0 ng/mL ($P = 0.020$). Simultaneous treatment with the NOS precursor l-arginine abolished this effect (Figure 3D). l-NAME increased t-PA antigen compared with vehicle during placebo treatment ($P = 0.017$; data not shown); however, there was no effect of l-NAME on t-PA antigen during l-arginine, ramipril, or combination. Because the majority of t-PA antigen circulates complexed to PAI-1 and the effect of l-NAME on t-PA antigen may reflect effects of NOS inhibition on PAI-1 expression, PAI-1 release or t-PA expression or release, we measured the effect of l-NAME on active t-PA. l-NAME significantly increased t-PA activity during either placebo treatment (Figure 4A; $P = 0.004$) or ramipril (Figure 4C; $P = 0.017$) alone; in either case, pretreatment with l-arginine abolished this effect (Figure 4B and 4D). In contrast to the effect of l-NAME on PAI-1 antigen,
the effect of L-NAME on t-PA activity was already present 1 hour after the initiation of infusion.

**Discussion**

Previous studies in vitro and in animal models suggest that NO regulates PAI-1 expression.9,10 Administration of an exogenous NO donor has been reported to decrease PAI-1 activity in patients with coronary artery disease.14 The present study indicates that during interruption of the RAAS by ACE inhibition, endogenous NO modulates PAI-1.

Unexpectedly and in contrast to data from several previous studies,15–21 ACE inhibition alone did not decrease PAI-1 antigen in the normotensive salt-replete subjects studied. Most previous studies of the effect of ACE inhibition on fibrinolytic balance have been conducted in subjects in whom the circulating RAAS was activated by dietary salt restriction,18 by concurrent diuretic use,20 or after myocardial infarction.15–17 However, in the current study, we studied normal subjects during free sodium intake such that both PRA and aldosterone concentrations were depressed compared with our previous studies.18,20 Under these conditions, ramipril did not decrease circulating Ang II concentrations, and this might have contributed to the lack of effect of ramipril on PAI-1 concentrations. Against this, ramipril significantly decreased ACE activity and aldosterone and increased PRA, indicating that adequate ACE inhibition was achieved and that there was loss of feedback inhibition of Ang II on renin synthesis.27 Thus, we hypothesize that in the sodium-replete state, factors other than Ang II and aldosterone, such as insulin, glucose, triglycerides, or NO, primarily regulate endogenous PAI-1 expression.1

ACE inhibition increases the bioavailability of endothelial NO in vivo in humans as measured, for example, by effects on endothelium-dependent vasodilation.28–30 In this study, treatment with an ACE inhibitor unmasked a role for NO in the regulation of PAI-1 expression in humans. Thus, during

**Figure 4.** Effect of L-NAME or vehicle on t-PA activity during treatment with placebo (A), L-arginine (B), ramipril (C), or L-arginine and ramipril (D). *P<0.05 vs vehicle; †P<0.01 vs vehicle.
ACE inhibition, the NO precursor l-arginine significantly decreased active PAI-1 and the molar ratio of PAI-1 to t-PA antigen, whereas acute administration of the NOS inhibitor l-NAME attenuated the diurnal decrease in PAI-1, and this effect was reversed by pretreatment with l-arginine. No effect of l-arginine or l-NAME on PAI-1 concentrations was observed in the absence of ACE inhibition, suggesting that interruption of the RAAS enhances the effect of NO to modulate PAI-1 expression.

An alternative explanation for the effect of l-NAME on PAI-1 antigen concentrations during ramipril is that ACE inhibition enhances an effect of endogenous NO not on the expression of PAI-1 but rather on the release of PAI-1 from platelets. Platelets contain PAI-1 in their α-granules. ACE inhibitors are known to decrease platelet activation, and NO donors reduce PAI-1 release from platelets. Although we cannot exclude this possibility, the time course of the effect of l-NAME on circulating PAI-1 concentrations would mediate against an immediate effect on PAI-1 release and is consistent with the time course of effects of Ang II on PAI-1 expression. Similarly, it is possible that l-NAME increased PAI-1 antigen concentrations not through a direct effect of NOS inhibition but rather through an indirect effect of increased aldosterone. Aldosterone stimulates PAI-1 expression in vascular cells and monocytes. However, if the effect of l-NAME on PAI-1 antigen were mediated via aldosterone, l-NAME would be expected to increase PAI-1 antigen during all of the experimental conditions (placebo, l-arginine alone, and ramipril alone), during which l-NAME also increased circulating aldosterone concentrations relative to vehicle.

Neither ACE inhibition nor l-arginine significantly affected basal t-PA antigen or activity; however, acute inhibition of NOS with l-NAME significantly increased active t-PA. The rapid onset of this effect is consistent with an effect on t-PA release. t-PA is stored in endothelial cells in either small dense granules or Weible-Palade bodies and released via G-protein–coupled receptor-mediated, calcium-dependent pathways. ACE inhibition enhances endothelial t-PA release through a bradykinin B2 receptor-dependent pathway. Tranquille and Emeis reported that both the NO donor sodium nitroprusside and atrial natriuretic factor inhibit bradykinin-stimulated t-PA release; although this would seem to suggest a cGMP-dependent mechanism, the cGMP analogue 8-bromo-cGMP does not reproduce the inhibitory effect. More recently, Matsushita et al reported that NO inhibits exocytosis of Weible-Palade bodies by nitrosylating cysteine residues of N-ethylmaleimide-sensitive factor (NSF), thereby inhibiting NSF disassembly of soluble NSF attachment protein receptor. Interestingly, circulating t-PA activity, but not tissue t-PA expression, is increased in endothelial NO−deficient mice, again consistent with a moderating effect of NO on t-PA release. In the human forearm, although low doses of the NOS inhibitor l-N(G)-mono-methyl-arginine (l-NMMA) do not affect bradykinin-stimulated t-PA release, Smith et al reported that high-dose l-NMMA enhances bradykinin-stimulated t-PA release. Together with the data from the present study, these data suggest that NO inhibits t-PA release in humans.

A few study limitations require comment. First, because of safety considerations and the prolonged effect of l-NAME on blood pressure, we chose to study normotensive subjects. Additional studies will be needed to confirm these findings in individuals with endothelial dysfunction. Second, neither chronic administration of l-arginine nor acute administration of l-NAME altered circulating concentrations of NO metabolites. Although this could suggest that l-arginine and l-NAME did not affect endogenous NO bioavailability, these findings are compatible with data from several other studies indicating that circulating NO metabolite concentrations do not adequately reflect the effect of l-arginine or l-NAME on endothelial NOS function. Moreover, the observations that l-NAME significantly increased blood pressure as well as PAI-1 antigen and t-PA activity, whereas l-arginine pretreatment counteracted the effect of l-NAME administration on blood pressure, PAI-1 antigen, and t-PA activity, provide functional evidence that the effects of l-NAME were mediated via NOS inhibition.

In summary, the findings of this study suggest that during ACE inhibition, endogenous NO decreases PAI-1 expression but also attenuates endothelial t-PA release in normotensive salt-replete subjects in whom the RAAS is suppressed. Hence, combined administration of an ACE inhibitor and the NO precursor l-arginine produces a significant decrease in plasma PAI-1 antigen and activity and the molar ratio of PAI-1 to t-PA without a significant change in t-PA activity, resulting in an increase in fibrinolytic activity as measured by D-dimers and plasmin-α2-antiplasmin complexes.

Perspectives
Recent clinical trials suggest that NO donors decrease PAI-1 activity and improve mortality in congestive heart failure patients treated concurrently with ACE inhibitors or angiotensin receptor blockers. The finding that endogenous NO regulates PAI-1 activity during ACE inhibition in normal controls raises the possibility that an NO donor could also enhance the effect of ACE inhibition on fibrinolytic balance in individuals with endothelial dysfunction. Moreover, because NO decreases PAI-1 expression in vitro through a cGMP-dependent mechanism but may attenuate t-PA release through a cGMP-independent mechanism, additional studies are needed to define the effects of pharmacological strategies to increase cGMP on fibrinolytic balance during ACE inhibition.

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