Angiotensin-Converting Enzyme Inhibition Augments Coronary Release of Tissue Plasminogen Activator in Women But Not in Men

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Abstract—The renin-angiotensin system regulates the vascular fibrinolytic balance. In the human forearm vasculature, angiotensin-converting enzyme (ACE) inhibitors (ACE-I) increase the release of t-PA through endogenous bradykinin. We tested the hypothesis that ACE inhibition and sex modulate the endogenous coronary release of tissue plasminogen activator (t-PA) in hypertensive patients. Seventy-three patients underwent diagnostic coronary angiography and had normal coronary angiograms. Thirty-three patients (21 men and 12 women) were treated with imidapril (5 mg/day) for 4 weeks (ACE-I group), and 40 (23 men and 17 women) were not treated with ACE-I (non–ACE-I group). All of the women were postmenopausal. Coronary blood flow in the left anterior descending artery was evaluated by measuring Doppler flow velocity. Net coronary t-PA release was determined as (coronary sinus–aorta gradient of t-PA)×[(coronary blood flow)×[(100−hematocrit)/100]. Age, arterial pressure, heart rate, lipid levels, coronary flow, and the plasma level of t-PA at either aorta or coronary sinus were comparable among the 4 groups. In women, net t-PA release in the ACE-I group was significantly higher than that in the other groups (P<0.05; man non–ACE-I group: 1.4±2.6 ng/mL; woman non–ACE-I group: 1.4±3.1 ng/mL; man ACE-I group: −1.8±2.8 ng/mL; woman ACE-I group: 14.8±3.6 ng/mL). Correction for smoking status gave similar results. There was a significant negative correlation between serum ACE activity and coronary t-PA release in women (r=−0.38; P<0.05) but not in men. ACE inhibition increases coronary release of t-PA in women but not in men. (Hypertension. 2010;56:364-368.)

Key Words: angiotensin-converting enzyme inhibitor ■ bradykinin ■ sex ■ tissue plasminogen activator ■ coronary

Inhibition of angiotensin-converting enzyme (ACE) has been shown to improve endothelial function, which predicts future cardiovascular events. The renin-angiotensin system and the fibrinolytic system are linked through ACE at the level of the vascular endothelium. Inhibition of ACE favorably alters the fibrinolytic balance by increasing the release of bradykinin (BK)-induced tissue plasminogen activator (t-PA), decreasing the release of angiotensin II–mediated plasminogen activator inhibitor 1 (PAI-1), or both. t-PA is released from the endothelium both constitutively and in response to agonists such as BK and substance P. Exogenous BK stimulates t-PA release from the human forearm vasculature, and chronic ACE inhibition markedly potentiates this effect. Coronary release of t-PA from the endothelium is an important defense against coronary thrombosis. We have shown previously that intracoronary infusion of BK stimulates t-PA release in the human coronary vasculature without affecting plasma PAI-1 level and that ACE inhibition potentiates this effect. Endothelial fibrinolytic capacity, as measured by stimulated t-PA release, has been identified as a novel determinant of future cardiovascular risk. Recently, it has been shown that acute inhibition of ACE increases the constitutive release of t-PA through endogenous BK in the forearm circulation in women but not in men. However, to date, there have been no similar studies on the human coronary fibrinolytic system.

ACE inhibitors (ACE-I) have generally been shown to improve the fibrinolytic balance by reducing plasma PAI-1 level, and angiotensin receptor blockers (ARB) seem to have a neutral effect. The Blood Pressure Lowering Treatment Trialists’ Collaboration assessed the blood pressure–dependent and –independent effects of ACE-I and ARB on major cardiovascular events in patients with coronary risk factors. In this study, ACE-I but not ARB was suggested to have protective effects against coronary artery disease even in the absence of any reduction in blood pressure. Thus, we tested the hypothesis that ACE inhibition and sex modulate the coronary release of t-PA in hypertensive patients.

Methods

Study Patients
In the Shiga Plasminogen Activator in Coronary Circulation (SPAIC) Trial, we enrolled a total of 140 patients with suspected coronary artery disease and hypertension (systolic blood pressure...
Quantitative Coronary Angiography and Measurement of Coronary Blood Flow

For ≥3 days before the study, subjects received a low-sodium diet (NaCl 5 g/day). Patients in the ACE-I group received the last dose of imidapril or other drugs at 7:00 AM. Cardiac catheterization was performed between 9:00 AM and 11:00 AM in the fasting state to minimize variability attributed to circadian rhythms of t-PA and PAI-1 levels. With imidapril (5 mg/day) for 4 weeks (ACE-I group; n=70) and the other group was treated with antihypertensive agents other than ACE-I or ARB for 4 weeks (non–ACE-I group; n=70). Of the 140 patients who entered the study, 13 were later excluded: 8 withdrew from the study and 5 had poor compliance. Among the 127 patients who underwent diagnostic cardiac catheterization, 48 required immediate revascularization or had angiographically significant stenotic arteries of the left anterior descending coronary artery and were excluded. Of the remaining 79 patients, 6 were excluded from subsequent analysis because of failure of measurement of coronary flow velocity or cannulation of the coronary sinus (CS). Eventually, 33 patients (21 men and 12 women) in the ACE-I group and 40 patients (23 men and 17 women) in the non–ACE-I group completed the study protocol. Patients in the non–ACE-I group were treated with calcium channel blockers (n=35) or β-blockers (n=5). The ethical committee on human research of our institution approved the study protocols, and written informed consent was obtained from all of the patients. This study adheres to the principles of the Declaration of Helsinki and Truett 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001.

Blood Sampling and Biochemical Assays

Blood samples in the aorta (Ao) and CS were taken simultaneously for the measurement of t-PA and PAI-1 antigen, as described previously.5 12 Blood samples were collected on ice and centrifuged immediately, and plasma was stored at −70°C until the time of assay. Blood for the measurement of t-PA and PAI-1 was collected in tubes containing acidified buffered citrate. Plasma levels of t-PA antigen and PAI-1 antigen were determined by ELISAs (TintElize tPA, Biopool International, and TintElize PAI-1, Biopool International).

Statistics

All of the data are expressed as mean±SEM or n (percentage) of subjects. AP indicates arterial pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NS, not significant.

Arteriovenous concentration gradients were calculated by subtracting the plasma level measured in simultaneously collected arterial and CS venous blood. Thus, net release and uptake rates were calculated as net release = ([concentration_{CS}−concentration_{Ao}]/[(CBF×(100−hematocrit)/100])×CBF).

Results

Baseline Characteristics

Coronary t-PA release did not differ between the ACE-I group (4.26±3.13 ng/min) and the non–ACE-I group (1.43±1.33 ng/min). To determine whether sex or serum ACE activity affected coronary t-PA release, we compared the data among 4 groups. There were no significant differences in the baseline characteristics except for smoking status among the 4 groups (Table 1). Men showed a significantly higher prevalence of smokers than that in women. Serum levels of ACE in the man and woman ACE-I groups were lower than those in the man and woman non–ACE-I groups (Table 2). Serum levels of ACE were similar in men and women in the ACE-I group and the non–ACE-I group. There was no significant difference among men and women in the ACE-I and non–ACE-I groups with regard to office blood

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Data are expressed as mean±SEM or n (percentage) of subjects. AP indicates arterial pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NS, not significant.
pressure at the time of recruitment into the study (man non–ACE-I group: 155±3/97±2 mm Hg; woman non–ACE-I group: 152±3/92±3 mm Hg; man ACE-I group: 157±3/97±2 mm Hg; woman ACE-I group: 157±4/98±3 mm Hg).

Fibrinolytic Parameters

The plasma level of t-PA at either the Ao or CS did not differ among the 4 groups (Table 2). CBF in the left anterior descending arteries was comparable among the 4 groups. The CS-Ao gradient in the woman ACE-I group was significantly higher than that in the man ACE-I group (man non–ACE-I group: 0.09±0.20 ng/mL; woman non–ACE-I group: 0.08±0.19 ng/mL; man ACE-I group: −0.09±0.17 ng/mL; woman ACE-I group: 0.78±0.29 ng/mL; man ACE-I group versus woman ACE-I group: P<0.05).

Coronary t-PA release in the woman ACE-I group was significantly higher than that in the other groups (Figure 1). In male subjects in the ACE-I group, coronary t-PA release in nonsmokers (−2.71±4.24 ng/min) did not differ from that in smokers (−0.91±3.37 ng/min). In male subjects in the non–ACE-I group, coronary t-PA release in nonsmokers (−0.71±4.04 ng/min) did not differ from that in smokers (3.38±3.23 ng/min). Among nonsmokers, coronary t-PA release in the woman ACE-I group was significantly higher than that in the other groups (Figure 2).

There was a significant negative correlation between serum ACE activity and coronary t-PA release in women (r=−0.38; P<0.05) but not in men (Figure 3). In simple linear regression analyses, coronary t-PA release was not correlated with age, body mass index, arterial pressure, and plasma levels of total, low-density lipoprotein, or high-density lipoprotein cholesterol or triglycerides in men, women, and all patients (P value not significant).

The plasma level of PAI-1 at either the Ao or CS did not differ among the 4 groups (Table 2). The plasma level of PAI-1 was comparable between the Ao and CS in each group (Table 2).

Discussion

The SPAIC trial demonstrated that chronic inhibition of ACE increases the endogenous coronary release of t-PA without affecting PAI-1 level in the coronary circulation in hypertensive women. Coronary t-PA release was significantly correlated with ACE activity in women but not in men.

Pretorius et al6-7 reported that acute ACE inhibition increases basal t-PA release through a BK-dependent mechanism in the forearm circulation in women but not in men. We reported previously that intracoronary infusion of BK stimulates the release of t-PA from the coronary vasculature in patients with hypertension, and this effect is potentiated by chronic ACE inhibition.4-12 However, we did not address the effects of ACE inhibition and sex differences on basal t-PA release, because we previously studied a predominantly male population. Pretorius et al6 reported differences between the forearm and coronary vasculature with regard to the effect of ACE inhibition on constitutive t-PA release. The present data regarding the coronary circulation are consistent with those of Pretorius et al6 in the forearm circulation. There are differences between ACE-I and non–ACE-I with respect to endogenous forearm and coronary t-PA release, although blood pressure reduction itself could improve the capacity for pharmacologically stimulated t-PA release.14
There was a significant negative correlation between serum ACE activity and endogenous coronary t-PA release in women but not in men. Serum level of ACE was similar in men and women in each of the ACE-I and non–ACE-I groups. We reported previously that serum level of ACE activity showed a significant negative correlation with net coronary t-PA release in response to intracoronary infusion of BK. We and others have shown previously that ACE inhibition enhanced vascular t-PA release to a greater extent than did the vasodilator effect in response to BK. The present study suggests that ACE inhibition has a more favorable effect on t-PA production beyond blood pressure–lowering effects. Previous studies have indicated that ACE-Is increase BK type 2 receptor functions as allosteric enhancers by inducing a conformational change in ACE. Therefore, the mechanisms by which ACE inhibition enhances coronary t-PA release may include not only reduced degradation of endogenous BK but also enhanced sensitivity of the BK type 2 receptor. The alterations in BK degradation or BK receptor sensitivity by ACE inhibition may differ between men and women.

The clinical characteristics of the ACE-I and non–ACE-I groups, including coronary risk factors, were comparable, except for the frequency of smokers. The capacity of the vasculature to release t-PA is diminished in association with aging, hypertension, smoking status, obesity, and diabetes mellitus. Newby et al reported that the capacity for coronary t-PA release in response to substance P varies inversely with the plaque burden of the left anterior descending coronary artery. Even when we limited our analysis to nonsmokers, coronary t-PA release in ACE-I–treated women was greater than that in the other groups. We and other investigators reported that chronic cigarette smoking causes a reduction in coronary t-PA release in response to BK or substance P. Chronic nicotine administration causes a reduction in acute release of t-PA, whereas acute nicotine administration may enhance acute t-PA release. In this study, smokers refrained from smoking for ≥3 days before the study to eliminate the direct effects of nicotine and oxidants contained in cigarette smoke. Measurement of coronary t-PA release is suitable for the estimation of coronary fibrinolytic function but can only be carried out in selected subjects undergoing coronary angiography. Therefore, additional studies are needed to identify the contributions of genetic and cardiovascular risk factors to local vascular t-PA release in a larger population.

In the present study, we demonstrated that basal coronary t-PA release was augmented during ACE inhibition in postmenopausal women. In the forearm circulation, ACE inhibition increased basal t-PA release in both premenopausal and postmenopausal women, whereas ACE inhibition potentiated BK-stimulated t-PA release to a greater extent in premenopausal women than in either postmenopausal women or men. It remains unclear whether ACE inhibition augments coronary t-PA release to a greater extent in premenopausal women than in postmenopausal women, as was seen with forearm t-PA release. Stauffer et al reported that, in healthy middle-aged subjects, the forearm release of t-PA antigen in response to BK was significantly greater in women than in men. Hoetzer et al reported that acute and chronic treatment with 17β-estradiol augmented net t-PA antigen release in the forearm response to BK in postmenopausal women. Others have reported that 17β-estradiol augmented basal forearm vascular release of active t-PA in postmenopausal women. Hormonal status may, at least in part, contribute to basal coronary t-PA release during ACE inhibition in women. Further studies are needed to examine the differences between premenopausal and postmenopausal women with regard to coronary t-PA release during ACE inhibition.

In the present study, baseline t-PA and PAI-1 antigens in both the Ao and CS were similar among the 4 groups. Several studies have investigated the relationship between basal venous t-PA antigen concentrations and subsequent coronary heart disease. Basal venous t-PA antigen concentration is determined in part by increasing PAI-1 level and does not reflect the local vascular fibrinolytic capacity, which is estimated by the stimulated acute release of t-PA. We did not measure levels of t-PA and PAI-1 activity. The plasma t-PA antigen concentration reflects both active t-PA and inactive t-PA complexed with PAI-1. Free and unbound t-PA is physiologically active and leads to endogenous fibrinolysis. Therefore, the lack of measurement of t-PA and PAI-1 activity is a significant limitation. ACE-Is have generally been shown to improve the fibrinolytic balance by reducing plasma PAI-1 level, and ARBs seem to have a neutral effect. Because ARBs increase angiotensin II concentration, it has been suggested that PAI-1 may increase through stimulation of the angiotensin II type 4 receptor. In Japan,
nese patients with myocardial infarction, administration of imidapril (5 mg daily) for 1 month did not change the level of tPA antigen but decreased the level of PAI-1.28

In summary, the present study demonstrated that ACE inhibition increases constitutive coronary t-PA release without affecting PAI-1 level in women but not in men. The cardiovascular protective effect of ACE-I may be in part related to coronary t-PA release through the augmentation of endogenous BK.

Perspectives

Analyses by the Blood Pressure Lowering Treatment Trialists’ Collaboration have shown that ACE-I, but not ARB, may have blood pressure-independent effects on the risk of major coronary disease events.10,11 Data from the Blood Pressure Lowering Treatment Trialists’ Collaboration suggested that, for coronary heart disease, women tend to derive greater protection from ACE-I than from ARB compared with men. The positive effects of ACE-I on the coronary fibrinolytic balance may contribute to the reduction in myocardial infarction rate achieved in clinical trials.

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Disclosures

None.

References

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