Differential effects of enalapril and nitrendipine on the fibrinolytic system in essential hypertension

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Background Impaired fibrinolysis is associated with thromboembolic complications in hypertensive patients. It has been reported that cardiovascular morbidity and mortality rates are high even after lowering the elevated blood pressure with antihypertensive drugs. The aim of this study was to assess the effect of clinically used dosages of enalapril and nitrendipine on the fibrinolytic system.

Methods Tissue plasminogen activator antigen (tPA) and tissue plasminogen activator inhibitor-1 (PAI-1) activity were measured in 20 normotensive male subjects and 46 male patients with mild essential hypertension divided into 2 groups (22 patients treated with 5 to 10 mg enalapril once a day and 24 treated with 5 to 10 mg nitrendipine once a day) before and 3 months after drug administration. Plasma renin activity and norepinephrine concentration were also measured.

Results There were no significant differences in basal characteristics between the 2 hypertensive groups. In both hypertensive groups, blood pressure was significantly reduced to a similar level after drug treatment. In the 2 hypertensive groups, plasma renin activity significantly increased after drug treatment; however, there were no significant changes in norepinephrine concentration. Before drug treatment, the 2 hypertensive groups had significantly higher tPA and higher PAI-1 activity than the normotensive subjects. In the enalapril group, there was no significant change in tPA although PAI-1 activity significantly decreased after drug treatment. In the nitrendipine group, there was no significant change in tPA although PAI-1 activity significantly increased after drug treatment.

Conclusion Thus enalapril improved impaired fibrinolysis but nitrendipine further aggravated fibrinolysis in essential hypertension. Considering the effect of antihypertensive drugs on the fibrinolytic system, more effective and beneficial treatment of hypertensives, especially at a high risk for thrombus formation might be selected. (Am Heart J 1999;137:1094-9.)

Hypertension is a major risk factor for coronary artery disease. However, lowering elevated blood pressure has been shown to have little effect on reducing the risk of coronary artery disease in large-scale clinical trials,[1,2] although a profound reduction of the risk of stroke has been shown. There have been some reports that the incidences of cardiovascular disease increased in treated hypertensive patients with coronary artery disease.[3-6] It has been shown that hypertensive patients have impaired fibrinolysis and platelet hyperaggregability,[7-9] which are associated with development of atherosclerosis and thrombus formation. In particular, impaired fibrinolysis is important to develop thrombus formation, which plays a key role in acute ischemic syndromes.[10,11] Reports on the high incidence of acute myocardial infarction, even after lowering elevated blood pressure with antihypertensive drugs,[3-6] indicate the importance of understanding the effects of antihypertensive drugs on fibrinolysis.

At present, angiotensin-converting enzyme inhibitors (ACEI) and long-acting calcium channel blockers, among antihypertensive drugs, are widely used to treat hypertension, and their clinical use extends to cardiovascular diseases other than hypertension.[2,12-17] Although ACEIs have been shown to reduce the incidence of reinfarction,[15] short-acting calcium channel blockers have been associated with increased risk of acute myocardial infarction and death,[5,6] which throws doubt on the usefulness of long-acting calcium channel blockers in cardiovascular diseases. However, one recent clinical trial on hypertension[2] indicated that nitrendipine could reduce all cardiac events in older hypertensive patients.

In this study we compared the effects of enalapril, an ACEI, to those of nitrendipine, a long-acting calcium channel blocker, on fibrinolytic parameters in essential hypertension. These 2 drugs have been clinically demon-

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Table I. Distribution of clinical variables

Study group	Normotensive subjects	Hypertension treated with enalapril	Hypertension treated with nitrendipine
n	20	22	24
Age (y)	59 ± 10	60 ± 8	60 ± 9
Smoking	6	5	6
Hypercholesteremia	4	6	5
Family history of heart disease	8	8	6
Hyperuricemia	4	4	3
Body mass index (kg/m^2)	23 ± 2	24 ± 3	24 ± 2
Triglyceride (mg/dL)	104 ± 56	98 ± 31	107 ± 60

Values are expressed as number and mean ± SD.

strated to lower blood pressure to a similar level[18] and to be effective in the treatment of hypertension.[2,13]

Methods

Patients

We selected 46 male patients with mild essential hypertension older than 40 years (range 40 to 69 years) who were referred for cardiac catheterization because of chest pain or electrocardiographic abnormalities that revealed normal coronary arteries without spasm and normal cardiac function. They were randomly assigned to 2 groups: 22 men to receive oral enalapril 5 to 10 mg/day (59 ± 10 years) and 24 men to receive oral nitrendipine 5 to 10 mg/day (60 ± 8 years). Four patients (3 in the enalapril group and 1 in the nitrendipine group) were excluded from this study because 2 patients in the enalapril group could not continue to take enalapril because of severe dry cough and 2 patients were lost during this study. We also selected 20 normotensive male subjects (60 ± 9 years) with normal coronary arteries and left ventricular function as a control group. No study patients had diabetes mellitus. All hypertensive patients were recently diagnosed and had not undergone any antihypertensive therapy, except for diet therapy, before inclusion into this study. Before and 3 months after drug treatment, blood samples were collected from all study patients. Informed consent was obtained from each patient. This study protocol was approved by the hospital's ethics committee.

Coronary angiography

Coronary angiography with the acetylcholine provocation test was performed by the standard Judkins technique in all patients.[19]

Measurements of blood samples

After at least 12 hours of fasting, blood samples were collected after the patients had been lying undisturbed in a supine position for at least 10 minutes. Blood was drawn by venipuncture. After collection, the first few milliliters of blood were always discarded. The blood was immediately drawn into 3 separate polypropylene syringes for measurements of fibrinolytic components, lipids, and renin activity. For measurements of fibrinolytic components, 9 parts of blood were mixed with 1 part of 3.13% sodium citrate solution. Plasma was separated by centrifugation at 3300 rpm for 15 minutes and was immediately frozen and stored at −70° C until assayed for fibrinolytic components.

The enzyme-linked immunosorbent assay with reagents supplied by American Diagnostics (Greenwich, Conn) was used to determine the concentration of tissue plasminogen activator antigen (tPA) in the plasma.[20] The results are expressed in nanograms per milliliter. The intraassay and interassay coefficient of variation were 3.6% and 4.5%, respectively. Plasminogen activator inhibitor-1 (PAI-1) activity was determined by a chromogenic substrate assay with the reagent Spectrolys/pL kit (Biopool, Umea, Sweden).[21] The results are expressed in IU/mL. The intraassay and interassay coefficient of variation were 8.9% and 12.2%, respectively.

The serum level of triglycerides was determined by enzymatic methods (Determiner TG diagnostic kits from Kyowa Medex, Tokyo). Plasma norepinephrine concentration was determined by high-performance liquid chromatography. Plasma renin activity was also determined with a GammaCoat 125-I plasma renin activity radioimmunoassay kit (INCSTAR, Stillwater, Minn).[22] The results are expressed in nanograms per deciliter. The intraassay and interassay coefficient of variation were 2.7% and 4.5%, respectively.

Statistical analysis

Data are expressed as the mean ± SD. Comparisons among the 3 groups (normotensive subjects, patients receiving enalapril, and patients receiving nitrendipine) were performed by analysis of variance followed by the Bonferroni multiple comparison test. Statistical evaluation was also performed by analysis of variance with repeated measurements, which included the effects of enalapril and nitrendipine and comparisons between groups and, if any changes were found to be significant by analysis of variance, a paired *t* test was performed on the relevant data pair. Chi-square test or Fisher's exact test was used to determine the significance of differences in the observed occurrence rates. Probability values of $<.05$ were considered significant.

Results

Baseline characteristics

Table I shows baseline clinical characteristics of hypertensive patients and normotensive subjects. There were no significant differences in age, body mass index, triglyceride level, or coronary risk factors among the 3 groups, or in blood pressure levels between the 2 hypertensive groups.

Table II. Changes in clinical variables

	Enalapril	Nitrendipine
Systolic BP (mm Hg)		
Before	164 ± 10	174 ± 20
After	140 ± 11*	140 ± 15*
Diastolic BP (mm Hg)		
Before	97 ± 4	97 ± 10
After	80 ± 6*	77 ± 8*
HR (beats/min)		
Before	72 ± 4	70 ± 5
After	70 ± 6	73 ± 2
Norepinephrine(ng/L)		
Before	299 ± 134	276 ± 120
After	244 ± 108	269 ± 993
Triglyceride (mg/dL)		
Before	98 ± 31	107 ± 60
After	102 ± 44	100 ± 26
Renin (ng/dL)		
Before	1.5 ± 1.7	1.1 ± 0.7
After	2.3 ± 2.3†	1.3 ± 0.7†

Values are expressed as mean ± SD.
BP, Blood pressure, *HR,* heart rate.
*$P < .001$, †$P < .02$ compared with the value before drug treatment. There were no significant differences in any hemodynamic variable between the 2 groups.

Changes in hemodynamics and hormones

Table II shows the changes in blood pressure and heart rate, plasma triglyceride concentration, plasma norepinephrine concentration, and plasma renin activity after drug treatment. In both hypertensive groups, both systolic and diastolic blood pressures were significantly reduced after drug treatment, although heart rate did not significantly change. Plasma norepinephrine concentration was similar before drug treatment and did not significantly change after drug treatment in the 2 groups. However, plasma renin activity significantly increased after drug treatment in the 2 groups.

Changes in fibrinolytic parameters after drug treatment

Before drug treatment, the 2 hypertensive groups had significantly higher tPA (7.3 ± 2.6 ng/mL in normal subjects vs 11.2 ± 3.5 ng/mL in the enalapril group, $P < .0004$, and vs 9.8 ± 3.7 ng/mL in the nitrendipine group, $P < .004$) and higher PAI-1 activity (3.4 ± 2.2 U/mL in normal subjects vs 9.4 ± 5.1 U/mL in the enalapril group, $P < .0001$, and vs 6.9 ± 4.6 U/mL in the nitrendipine group, $P < .01$) than the normotensive subjects (Figure 1). Figure 2 shows fibrinolytic variables before and 3 months after drug treatment between the 2 hypertensive groups. In the enalapril group, there was no significant change in tPA (11.2 ± 3.5 ng/mL vs 10.2 ± 3.5 ng/mL, P = not significant [NS]) although PAI-1 activity significantly decreased after drug treatment (9.4 ± 5.1 U/mL vs 6.5 ± 4.7 U/mL, $P < .003$). In the nitrendipine group, there was no significant change in tPA (9.8 ± 3.7 ng/mL vs 10.7 ± 3.5 ng/mL, P = NS) although PAI-1 activity was significantly increased after drug treatment (6.9 ± 4.6 U/mL vs 9.0 ± 5.6 U/mL, $P < .02$).

In normotensive subjects, there were no significant changes in either tPA or PAI-1 activity before and 3 months after drug treatment (7.3 ± 2.6 ng/mL vs 7.0 ± 2.5 ng/mL in plasma tPA concentration, P = NS, and 3.4 ± 2.2 U/mL vs 3.3 ± 2.3 U/mL in PAI-1 activity, P = NS).

In this study, we found a positive correlation between tPA and PAI-1 activity: $r = 0.64$, $P < .004$).

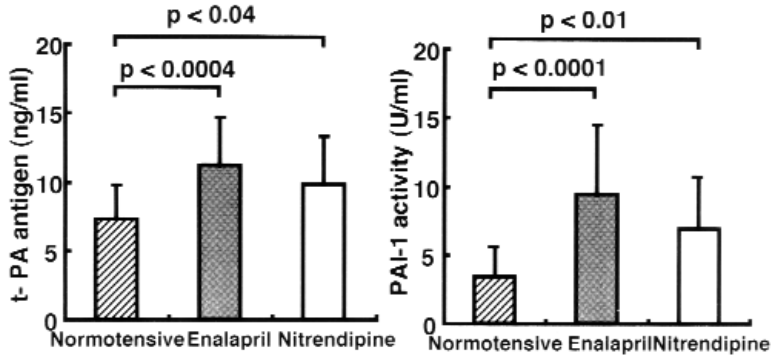
Discussion

In this study high PAI-1 activity in essential hypertension was improved with oral administration of enalapril compared with oral administration of nitrendipine, which further increased PAI-1 activity.

Essential hypertension and fibrinolytic system

Jansson et al[9] reported that patients with mild untreated hypertension had higher values for PAI-1 activity and lower values for tPA activity both before and after venous occlusion than did control subjects. Likewise, our study demonstrated that patients with hypertension had higher tPA and PAI-1 activity than normotensive subjects. It appears that elevated tPA in mild essential hypertension is associated with increased PAI-1 activity because of a positive correlation between tPA and PAI-1 activity seen in this study and reported by others.[23,24] In addition, several investigators[25] have suggested that tPA levels, to a large extent, reflect a circulating tPA/PAI-1 complex. Thus impaired fibrinolysis in essential hypertension is considered to result from high PAI-1 activity. Several mechanisms contributing to elevated PAI-1 activity in hypertension have been speculated. Hypertension is closely linked to several metabolic abnormalities,[26,27] as represented by syndrome X.[28] Hypertriglycedemia (high levels of very low density lipoprotein triglyceride) increases PAI-1 release.[29] Hyperinsulinemia also increases secretion and synthesis of PAI-1.[30] Likewise, PAI-1 release from activated platelets may increase in hypertension.[3] More importantly, recent attention has been focused on the association between renin-angiotensin system and fibrinolysis because angiotensin II is demonstrated to strongly enhance PAI-1 release both in vivo and in vitro.[31,32] Moreover, a recent study[33] has demonstrated that angiotensin IV, which is generated from angiotensin II by aminopeptidases localized to the endothelial surface, stimulates endothelial expression of PAI-1. In hypertension, the association is considered to be much stronger and more meaningful because the renin-angiotensin system plays a major role in hypertension.

Figure 1



Comparison of tPA and PAI-1 activity among 3 groups (normotensive, hypertensive patients treated with enalapril, and hypertensive patients treated with nitrendipine) before drug treatment. Values are expressed as the mean ± SD.

Effect of antihypertensive drugs on fibrinolytic parameters

In ischemic heart disease, several investigators[23,34] have already demonstrated that ACEIs could improve impaired fibrinolysis by reducing PAI-1 activity. However, it is possible that in coronary artery disease, improvement of fibrinolysis after drug treatment might result from improved hemodynamics or a reduction of ischemia. In our study, enalapril, an ACEI, could improve fibrinolysis by reducing PAI-1 activity in essential hypertension without ischemic heart disease. In contrast, nitrendipine, a calcium channel blocker, could impair fibrinolysis by increasing PAI-1 activity in essential hypertension. Thus changes in PAI-1 activity were not associated with those in hemodynamics.

Regarding the effect of calcium channel blocker on fibrinolytic system, Fujinishi et al[35] reported that nisoldipine did not affect fibrinolysis in coronary artery disease. In contrast, Gleerup et al[7] demonstrated that isradipine enhanced fibrinolytic activity. Thus it appears that the effect of each calcium channel blocker on the fibrinolytic system is different. In our study nitrendipine increased PAI-1 activity accompanying a significant increase in renin activity. Because nitrendipine has no direct effect on the renin-angiotensin system, an increase in the renin activity is probably caused by reduced renal perfusion pressure resulting from reduced systemic blood pressure. Increased renin activity results in enhanced production of angiotensin II, which increases PAI-1 release.[31,32] In contrast, as enalapril suppresses angiotensin II production by inhibiting ACE even if renin activity increases, PAI-1 production decreases. The renin-angiotensin system may play a more direct role in the control of endogenous fibrinolysis,[31] suggesting that enhanced fibrinolysis by enalapril is mainly caused by suppression of angiotensin II production. However, other mechanisms such as improvement of insulin resistance[36] and platelet hyperaggregability by ACEIs[37] may contribute to lowering PAI-1 activity.

Clinical implications

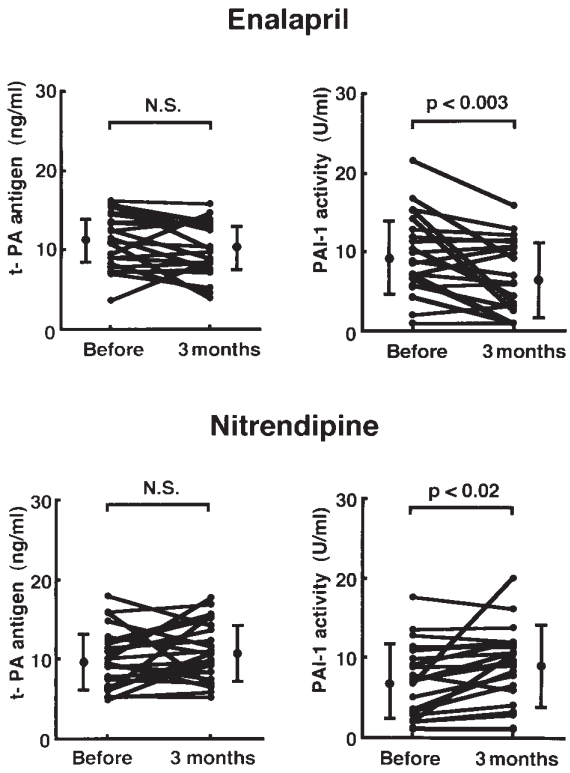
This study provided possible mechanisms for the facts that ACEIs reduce acute myocardial infarction[15] and that calcium channel blocker treatment increases the incidence of acute myocardial infarction and does not improve cardiovascular morbidity and mortality rates.[3-6,17] Therefore considerable attention must be paid when using calcium channel blockers for treatment of patients with hypertension and a high risk for thrombus formation. However, it is generally considered that long-acting calcium channel blockers do not aggravate cardiovascular mortality and morbidity rates.[38] In addition, a large number[2,17,18,35] of investigators have demonstrated that calcium antagonists have many beneficial effects on hemostatic parameters and the cardiovascular system. The Angina Prognosis Study in Stockholm showed that the effects of verapamil and metoprolol on fibrinolytic function did not influence cardiovascular prognosis[24]; therefore the adverse effect of nitrendipine on the fibrinolytic system also may not affect cardiovascular prognosis. In addition, impaired fibrinolysis by nitrendipine may be transient because another study did not find increased renin activity.[39]

At present, several large-scale clinical trials to examine the efficacy of long-acting calcium channel blockers in hypertension are ongoing. These results will help us judge the net effect of long-acting calcium channel blocker use on cardiovascular morbidity and mortality rates.

Conclusion

Our study showed that enalapril improved impaired fibrinolysis but nitrendipine further aggravated fibrinol-

Figure 2



Changes in tPA and PAI-1 activity before and 3 months after drug treatment. ***Upper and lower pannels*** show changes in these fibrinolytic parameters in the enalapril group and the nitrendipine group, respectively. Values are expressed as mean ± SD.

ysis in essential hypertension. Considering the differential effect of antihypertensive drugs on the fibrinolytic system, more effective and beneficial treatment of patients with hypertension and a high risk for thromboembolism might be selected.

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