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THE ACE-INHIBITOR LISINOPRIL AFFECTS PLASMA INSULIN LEVELS BUT NOT FIBRINOLYTIC PARAMETERS

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Abstract There is evidence that ACE-inhibitors exert beneficial effects on endogenous fibrinolysis in patients with previous myocardial infarction. It is still unknown if this effect is restricted to this patient group only and by which mechanisms ACE-inhibitors exhibit the profibrinolytic effects. One possible explanation might be the positive influence of ACE-inhibitors on insulin metabolism by decreasing plasma insulin which in turn could decrease PAI-1, a major regulator of the fibrinolytic system. Therefore the present study examines the relationship between insulin and PAI-1 plasma levels during intravenous glucose tolerance tests before and after administration with the ACE-inhibitor lisinopril in 12 male obese patients with angiographically proven coronary artery disease and borderline hypertension. After a 4-weeks wash-out period glucose tolerance tests were performed before and after lisinopril-treatment (10mg/d) for 12 weeks. After the treatment period, fasting plasma insulin level decreased from 15.6 ± 2.1 to 11 ± 1.8 uU/ml, $p \leq 0.01$. Stimulated levels of insulin during glucose tolerance test also significantly decreased by lisinopril (peak insulin from 57 ± 10 to 41.2 ± 7.3 uU/ml, $p \leq 0.02$). Basal plasma tissue plasminogen activator antigen, PAI-1 total antigen and PAI-1 "active" antigen were unaffected by therapy (8.4 ± 0.5 vs 8.6 ± 0.5 ng/ml, 118 ± 20 vs 124 ± 16 ng/ml and 21 ± 7 vs 30 ± 7 ng/ml, respectively). Our data confirm a beneficial effect of lisinopril on plasma levels of insulin but failed to demonstrate any profibrinolytic effect in this study population, thus questioning the postulated mechanism of influencing endogenous fibrinolysis by changes of plasma insulin.

Key words: glucose tolerance test, insulin, lisinopril, plasminogen activator inhibitor-1, tissue plasminogen activator.

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There is evidence that an impaired endogenous fibrinolysis, mainly determined by plasminogen activator inhibitor type 1 (PAI-1) and tissue plasminogen activator (t-PA), constitutes a risk factor for coronary artery thrombosis (1-5). Recent data suggest that in patients with previous myocardial infarction, treatment with angiotensin converting enzyme (ACE) inhibitors exert beneficial effects on endogenous fibrinolysis (6,7). This might explain the reduced incidence of acute coronary syndromes associated with the use of ACE-inhibitors in patients with acute myocardial infarction as shown in several large cohort studies (8,9).

So far, there is no information how ACE-inhibitors exert their proposed beneficial effect on the fibrinolytic system and whether this effect is restricted to patients with recent myocardial infarction only. Clinical studies have demonstrated a positive correlation between levels of fasting insulin and PAI-1 (10,11), a decrease of plasma PAI-1 during glucose tolerance test (GTT) (12,13) as well as a concomitant decrease of fasting insulin and PAI-1 in intervention studies (10,14,15,16), indicating that insulin might play a role in the regulation of PAI-1. Several recent reports have shown beneficial effects of ACE-inhibitors on insulin metabolism suggesting that the fibrinolytic system might be influenced via this pathway (17,18,19).

We therefore investigated the effect of the ACE-inhibitor lisinopril at baseline and during an intravenous glucose tolerance test in a population with proven stable coronary artery disease, borderline hypertension and central obesity.

SUBJECTS AND METHODS

Patients.

Twelve moderately obese, male patients of our out-patient ward with angiographically proven coronary artery disease (Canadian Cardiovascular Society Class I-II), mild hypertension or borderline isolated systolic hypertension (diastolic blood pressure 90-104 mmHg or systolic blood pressure 140-160 mmHg, respectively) were included into the study and gave their informed consent according to Helsinki's declaration. Patients were free of other diseases as determined by case history and thorough physical examination. There was no laboratory or clinical evidence of renal, hepatic or thyroid malfunction. All patients were non-smokers. Patients were given instructions about maintaining similar dietary habits, weight and physical exercise throughout the study. Waist circumference was measured with a soft tape midway between the iliac crest and the lowest rib margin in standing position. The hip circumference was measured over the widest part of the gluteal region and the waist/hip ratio was calculated. Body mass index (BMI) was calculated as weight (in kg) divided by height squared (in meters). Clinical characteristics of patients are given in Table 1.

Study design.

The protocol consisted of an initial four weeks wash-out period. During this period the patients were given only aspirin (100mgs/d) and sublingual nitrates in case of anginal pain. None of the patients used nitrates within 72 hours before blood sampling. Thereafter, patients received lisinopril at a dosage of 10mgs/d for 12 weeks. Laboratory, clinical and glucose tolerance tests were performed after wash-out and treatment period. All tests were carried out in the morning after a 14 hours overnight fast around 8.00 a.m. without prior intake of lisinopril that day. Blood

pressure was measured three times in recumbent position after a rest of 10 minutes. Following this fasting blood samples were drawn with a minimum of stasis. Then intravenous glucose tolerance test was performed consisting of injection of 300 mg glucose/kg (33% glucose solution) within 1.5 minutes. Additional blood samples for chemical determination were drawn at 5, 10, 30, 60, 90, 120 minutes, with the patient in remaining position. Glucose, insulin, and triglycerides were analyzed by standard techniques. Fibrinolytic parameters t-PA antigen and PAI-1 total and "active" antigen were determined by use of assay systems (Technoclone[®], Vienna, Austria) (20,21).

Statistical analysis.

Two way intra-intra subjects analysis of variance was used to test changes after lisinopril treatment and during ivGTT. Correlations were calculated by use of the Spearman correlation coefficient. Data are presented as mean+SE. $P < 0.05$ was considered to be significant.

RESULTS

The demographic characteristics of the patient groups are shown in Table 1. Body weight remained constant throughout the study. Systolic and diastolic blood pressure significantly decreased during lisinopril administration from 148 ± 5 and 92 ± 2 mmHg to 134 ± 6 and 79 ± 4 mmHg, $p < 0.05$ respectively.

Basal as well as stimulated plasma levels of glucose during ivGTT were unaffected by lisinopril (Fig. 1). During treatment with lisinopril fasting plasma insulin level decreased from 15.6 ± 2.1 to 11 ± 1.8 uU/ml ($p < 0.01$). Stimulated levels of insulin during ivGTT also significantly decreased by lisinopril (Fig.1) (peak insulin from 57 ± 10 to 41.2 ± 7.3 uU/ml; $p < 0.02$). The area under the insulin concentration time curve decreased significantly during lisinopril therapy by 28.7% (from 4385 ± 605 to 3115 ± 479 ; $p < 0.008$).

Triglycerides, basal plasma tissue plasminogen activator antigen, PAI-1 total antigen and PAI-1 "active" antigen were unaffected by therapy (245 ± 21 vs 238 ± 18 mg%, 8.4 ± 0.5 vs 8.6 ± 0.5 ng/ml, 115 ± 20 vs 124 ± 16 ng/ml and 21 ± 7 vs 30 ± 7 ng/ml, respectively) Figures 2 demonstrates a significant decrease of PAI-1 "active" antigen and PAI-1 total antigen during ivGTT after 60-90 minutes as compared to baseline.

Fasting insulin levels correlated significantly with fasting PAI-1 total antigen and PAI-1 "active" antigen ($r = 0.66$, $p \leq 0.05$ and $r = 0.68$, $p < 0.05$, respectively). During ivGTT this correlation no longer could be demonstrated. Triglycerides positively correlated with PAI-1 total and active antigen ($r = 0.35$, n.s. and $r = 0.62$, $p < 0.02$, respectively). Basal and stimulated plasma levels of t-PA antigen, PAI-1 total antigen and PAI-1 "active" antigen were unaffected by therapy (Fig. 2).

TABLE 1

Clinical Characteristics of Patients

number	12
age (years)	57.4±2.8
BP systolic (mmHg)	148±5
BP diastolic (mmHg)	92±2
height (cm)	175±3
weight (kg)	91.4±2.5
waist/hip ratio	0.96±0.02
BMI	29.1±0.9

Values are mean±SEM. BP, blood pressure; BMI, body mass index

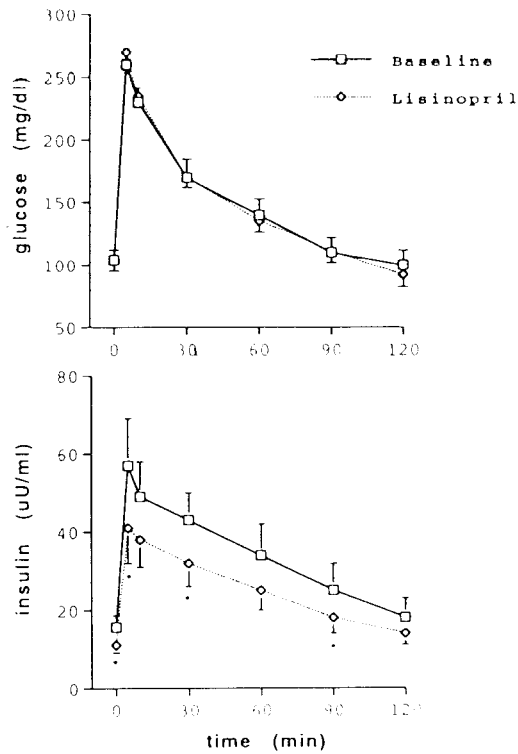


FIG. 1.

Effect of lisinopril on plasma levels of glucose and insulin during intravenous glucose tolerance tests.

* = $p < 0.05$ as compared to baseline.

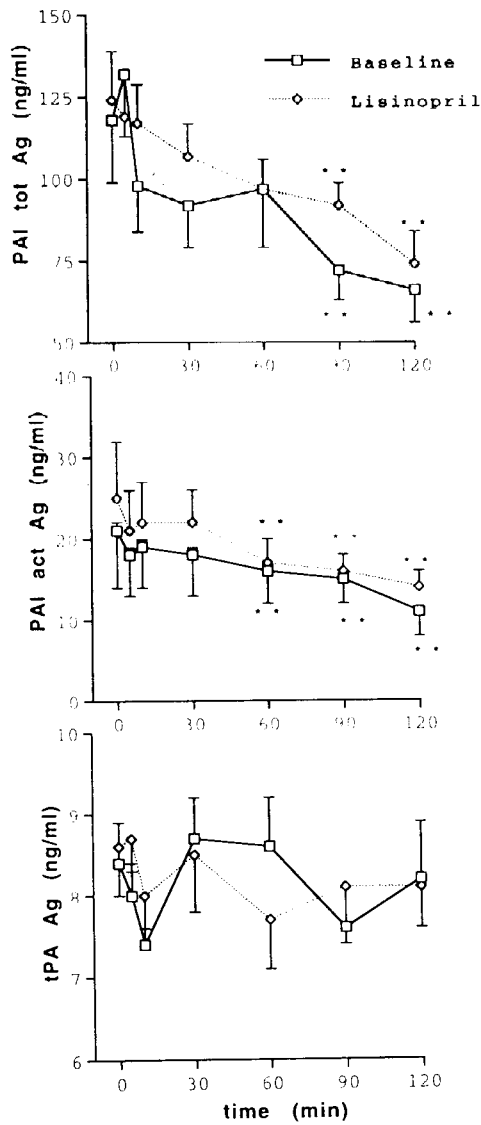


FIG. 2.

Effect of lisinopril on plasma levels of PAI-1 total and active antigen as well as t-PA antigen during intravenous glucose tolerance tests. ** = $p < 0.05$ as compared to fasting values.

DISCUSSION

Several large-scale trials have demonstrated that administration of ACE-inhibitors in patients after myocardial infarction resulted in a decreased incidence of adverse coronary events (8,9). There is evidence that in these patients treatment with ACE inhibitors results in beneficial effects on endogenous fibrinolysis which might explain the reduction of thrombotic risk (6,7).

However, little is known on the mechanism of ACE-inhibition on fibrinolysis and whether this effect also could be demonstrated in other populations. Therefore in the prevailing report, a different patient group, consisting of patients with hypertension, central obesity and proven stable coronary artery disease was studied. This patient group was chosen as due to the cluster of cardiovascular risk factors an improvement of the metabolic profile and an increase of the fibrinolytic potential is thought to favourably influence long term morbidity and mortality from cardiovascular disease (1-3). On the other hand these patients are prone to insulin resistance with concomitant hyperinsulinemia (22) and thus it might be expected that improvement of insulin metabolism by ACE-inhibition and hence improvement of the fibrinolytic profile should be more pronounced. In addition, to gain further insight into the pathway of ACE-inhibition on fibrinolysis, insulin as well as fibrinolytic parameters were determined during ivGTT.

Lisinopril administration resulted in a significant decrease of fasting insulin levels. Furthermore, after ivGTT early insulin peak as well as late insulin response were attenuated, resulting in a significant decrease of the insulin concentration time curve. These findings are in accordance to previous studies on the effects of ACE-inhibitors on insulin metabolism. In contrast to the beneficial effect of lisinopril on plasma insulin, no effects on PAI-1 nor t-PA plasma levels could be observed. Similar to other reports (10,11) we were able to demonstrate a positive correlation between fasting levels of PAI-1 and insulin in our study. However, despite a marked decrease of both fasting and stimulated insulin, lisinopril treatment did not result in a concomitant change of any fibrinolytic parameter measured. Influence of other accompanying medication on PAI-1 plasma levels is unlikely: Nitrates were only allowed to be used in case of anginal pain and were not used within 72 hours before blood sampling in any patient. Aspirin was taken throughout the study period. Divergent data exist on the effect of aspirin on fibrinolytic parameters (23,24). However, all patients have already taken aspirin before entering the study. Thus it seems unlikely that aspirin therapy might have affected results during the study.

The effect of decreasing PAI-1 levels by a decrease in plasma insulin has been demonstrated in several studies by use of the antidiabetic biguanide metformin (14,15), suggesting that insulin might play a role in the regulation of PAI-1. Recently, Wright et al (6) were able to demonstrate a beneficial effect of captopril on endogenous fibrinolysis in patients with recent uncomplicated myocardial infarction by significantly decreasing PAI-1 activity and t-PA antigen plasma levels. These beneficial effects of ACE-inhibitors on endogenous fibrinolysis might be responsible for the positive effects of this substance class in patients after myocardial infarction as also demonstrated by Jansson et al who found significantly lower t-PA antigen plasma levels in patients after myocardial infarction treated with enalapril (7). While the latter study did not measure plasma levels of insulin at all, Wright et al observed this profibrinolytic effect without any change on plasma insulin. Alternatively it may be

suggested that plasma insulin either directly or by indirect mechanisms via a decrease in triglyceride levels might regulate plasma levels of PAI-1 (4,11,14,25) but in the cited study, also triglyceride levels were unaffected by ACE-inhibitor treatment, indicating that other factors than insulin or triglycerides could be important in the regulation of PAI-1. There is evidence, that angiotensin II induces expression of PAI-1 in vascular endothelial cells, as well as an increase of PAI-1 antigen by infusion of angiotensin II in patients with hypertension, suggesting an alternative pathway of ACE-inhibition on endogenous fibrinolysis (26,27). From these data and our own results it can be suggested that alterations of insulin plasma levels due to an ACE-inhibitor do not necessarily result in parallel changes of PAI-1 levels, which might be directly influenced by ACE-inhibition based on reduced angiotensin II activity. The fact that we were not able to demonstrate a reduction of PAI-1 due to the action of the ACE-inhibitor lisinopril might be explained by dosage related reasons and by the different study population. In addition, other parameters known to be closely related to PAI-1 levels, e.g. body mass index and glucose plasma levels (28,29) remained unchanged during lisinopril treatment which also could explain the absence of change of PAI-1 levels.

As the aim of this study also was to further elucidate the relationship of plasma insulin and PAI-1, these parameters were not only determined in the fasting state but also throughout the ivGTTs. Several clinical studies have failed to demonstrate acute effects of insulin on fibrinolytic parameters (30-32) by using either glucose clamp technique or oral glucose tolerance test. Up to now, no data have been published on insulin, PAI-1 and t-PA plasma levels during ivGTT. As compared to oral glucose tolerance test and glucose clamp technique, this model might have the advantage of more dynamic changes and higher peak values of plasma insulin which in turn might give rise to a more pronounced effect on the fibrinolytic system. However, we also could not observe acute changes of PAI-1 plasma levels during ivGTT whereby the correlation between insulin and PAI-1 no longer could be demonstrated. These data suggest that PAI-1 plasma concentration is not directly related to insulin levels at least under acute conditions, indicating the effect of other hormonal mediators. Similar to other authors using oral glucose tolerance test (13,33) we were able to demonstrate a decrease in PAI-1 levels during ivGTT which reached significance after 60-90 minutes. This decrease was more pronounced as might be expected from the physiologic diurnal fluctuation (34,35) and might be due to direct effects of insulin or due to indirect effects of the insulin-antagonistic hormones cortisol, catecholamines or growth hormone (36,37).

Conclusion.

Our data confirm a beneficial effect of the ACE-inhibitor lisinopril on plasma levels of insulin. However, although other ACE-inhibitors in different study populations have been shown to affect the fibrinolytic system, in our study lisinopril failed to demonstrate a concomitant improvement of endogenous fibrinolysis thus questioning on one hand the effect of ACE inhibition on fibrinolysis and on the other hand the postulated mechanism of influencing endogenous fibrinolysis by changes of plasma insulin. In addition, no acute regulatory action of insulin on PAI-1 levels could be demonstrated in this study and further research is therefore needed to elucidate these mechanisms.

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