

# Comparative cross-over study of the effects of lisinopril and doxazosin on insulin, glucose and lipoprotein metabolism and the endogenous fibrinolytic system

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**Summary** *Objective:* The present study was performed to compare the effects of the alpha-1-blocker doxazosin (4 mg/d) with the ACE-inhibitor lisinopril (10 mg/d) in a cross-over study on plasma levels of metabolic and fibrinolytic parameters.

*Patients, methods:* In 10 male patients with upper body obesity, proven stable coronary artery disease and hypertension, measurements included baseline determination of lipoproteins and fibrinolytic parameters and determinations of glucose and insulin during intravenous glucose tolerance tests after two 12-week treatment periods.

*Results:* Basal insulin levels were significantly decreased by both doxazosin and lisinopril (from  $15.5 \pm 3.5 \mu\text{U/ml}$  to  $11.6 \pm 2 \mu\text{U/ml}$ ,  $P \leq 0.05$  and from  $16.5 \pm 2.8 \mu\text{U/ml}$  to  $11.2 \pm 2.4 \mu\text{U/ml}$ ,  $P \leq 0.001$ ; respectively). Lisinopril decreased the area under the insulin-concentration time curve by 31.9% ( $P \leq 0.007$ ) as compared to 23.6% (n.s.) after doxazosin treatment. HDL-cholesterol was increased by lisinopril from  $38 \pm 3.5$  to  $43.5 \pm 4.4 \text{ mg/dl}$  ( $P \leq 0.05$ ), t-PA antigen was increased by doxazosin from  $8.3 \pm 0.7$  to  $11.4 \pm 1.6 \text{ ng/ml}$  ( $P \leq 0.05$ ) and PAI-1 was not affected by either therapy.

*Conclusion:* These potentially favorable effects on insulin and lipid metabolism and the endogenous fibrinolytic system might contribute to a higher efficacy of antihypertensive treatment in patients with coronary artery disease and accompanying metabolic cardiovascular risk factors.

## INTRODUCTION

Hypertension in association with other cardiovascular risk factors, e.g. abnormalities in plasma glucose, insulin and lipoprotein metabolism and obesity favors the development of coronary artery disease (CAD) and increases cardiovascular morbidity and mortality.<sup>1</sup> There is evidence that insulin resistance and concomitant hyperinsulinemia is the link between all of these risk factors.<sup>2-6</sup>

Antihypertensive treatment has been shown to significantly reduce morbidity and mortality from stroke, congestive heart failure and renal hypertensive disease, whereas the effects on the incidence of cardiovascular

events are less than expected.<sup>7</sup> This may be explained by adverse metabolic effects of the antihypertensive drugs used in these studies, namely  $\beta$ -blockers or thiazide diuretics, thus possibly counteracting the beneficial effect of blood pressure reduction. Therefore, antihypertensive strategies should include both reduction of elevated blood pressure and improvement of the metabolic profile. Over the past years, two classes of antihypertensive agents, alpha-1-blockers and angiotensin converting enzyme (ACE)-inhibitors, have been shown to reduce metabolic risk by positive alterations of the lipid profile, as well as by increasing insulin sensitivity in hypertensive and hyperinsulinemic patients.<sup>8,9</sup> Furthermore, there is evidence that alpha-1-blockers as well as ACE-inhibitors may increase the endogenous fibrinolytic potential.<sup>10,11</sup> However, these results have not been confirmed, and no data exist so far comparing the

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effects of these drugs on plasma levels of insulin, glucose, lipoprotein, or on fibrinolytic parameters in a cross-over study. Accordingly, it was the aim of this study to evaluate and compare the effects of the alpha-1-blocker doxazosin and the ACE-inhibitor lisinopril on metabolic and fibrinolytic parameters in a group of obese, male patients with hypertension and proven stable CAD.

## PATIENTS AND METHODS

### Patients

Ten consecutive male patients with upper body obesity, angiographically-proven CAD, mild hypertension (diastolic blood pressure 90–104 mmHg) or borderline isolated systolic hypertension (systolic blood pressure 140–160 mmHg),<sup>12</sup> and stable angina pectoris CCS class I and II<sup>13</sup> who attended our out-patients ward for control purposes were included in the study. All patients had no medication with the exception of aspirin. The nature of the trial was fully explained to all patients before receiving their consent to participate. Patients were free to withdraw from the study at any time. Demographic clinical data of the study group at the end of the initial wash-out period are shown in Table 1. Five patients had a history of myocardial infarction and four had a history of aorto-coronary bypass surgery. All patients were free of other diseases as determined by case history, thorough physical examination and laboratory tests for renal, hepatic or thyroid function. All patients were non-smokers and non-diabetics. Patients were given instructions about maintaining comparable dietary and physical exercise habits.<sup>9</sup> 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. Only patients with upper body obesity, defined as a waist-hip ratio >0.85 and a body mass index (weight (in kilograms) divided by height (in meters) squared) >27 were recruited for this study.<sup>1</sup>

**Table 1** Clinical characteristics of patients

Number	10
Age (years)	58.2 ± 1.5
BP systolic (mmHg)	141 ± 5
BP diastolic (mmHg)	84 ± 2
Height (cm)	176 ± 2
Weight (kg)	90.5 ± 2
Waist/hip ratio	0.93 ± 0.01
BMI	30.4 ± 1.7

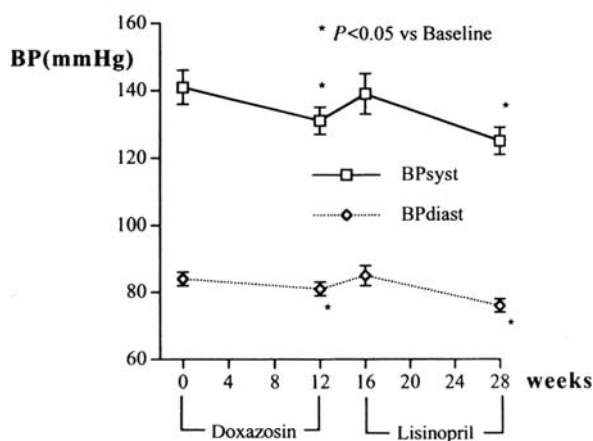
Values are mean ± SEM. BP, blood pressure; BMI, body mass index.

### Study design

During an initial 4-week period, patients were given only aspirin (100 mg/d) and allowed to use nitroglycerin in case of anginal pain. Thereafter, patients received doxazosin (4 mg/d, single dose) for 12 weeks. After completion of this treatment period, patients were discontinued from doxazosin and another wash-out period for 4 weeks followed. Finally, patients were crossed over to lisinopril (10 mg/d, single dose) for 12 weeks.

### Laboratory determinations

Blood pressure determinations and blood collections at basal conditions and during intravenous glucose tolerance test (ivGTT) were performed after each phase of the study (Fig. 1) in the morning (08.00 h) after a 14 h overnight fast without prior intake of doxazosin or lisinopril. Blood pressure was measured three times in recumbent position after a 10-min rest. The diastolic blood pressure was recorded at the disappearance of Korotkoff sounds (phase 5). The mean of three measurements was used. Blood was drawn with a minimum of stasis directly into plastic tubes containing EDTA (final concentration 50 mM) for the determination of fibrinolytic parameters and into citrated plastic tubes (0.11 M final concentration) for all other measurements. IvGTTs were performed by injection of 300 mg glucose/kg (33% glucose solution) within 1.5 min,<sup>9</sup> followed by blood collections at 5, 10, 30, 60, 90 and 120 min. Routine-parameters, i.e. blood glucose,<sup>14</sup> insulin,<sup>15</sup> triglyceride,<sup>16</sup> cholesterol,<sup>17</sup> HDL and LDL cholesterol,<sup>18</sup> fibrinogen<sup>19</sup> and HbA1c<sup>20</sup> and Lp(a)<sup>21</sup> were analyzed as indicated. The fibrinolytic parameters tissue-type plasminogen activator (t-PA) antigen and plasminogen activator inhibitor type-1 (PAI-1) total antigen were determined by means of commer-



**Fig. 1** Effect of doxazosin and lisinopril on systolic and diastolic blood pressure.

**Table 2** Effect of antihypertensive therapy on metabolic and fibrinolytic parameters

Parameter	Baseline (A)	Doxazosin (B)	Baseline (C)	Lisinopril (D)
Chol. (mg%)	230 ± 8	243 ± 10	228 ± 14	235 ± 8
HDL (mg%)	40.8 ± 3.1	41.8 ± 4.4	38 ± 3.5	43.5 ± 4.4*
Chol/HDL	5.8 ± 0.4	6.1 ± 0.4	6.3 ± 0.5	6.4 ± 0.6
LDL (mg%)	152 ± 5	158 ± 12	155 ± 10	163 ± 12
Triglycerides (mg%)	188 ± 30	212 ± 30	229 ± 28	212 ± 35
HbA1c (rel. %)	6.5 ± 0.4	6.6 ± 0.4	5.9 ± 0.4	6.2 ± 0.4
Lipoprotein (a) (mg/dl)	286 ± 86	308 ± 94	255 ± 101	268 ± 89
PAI-1 antigen (ng/ml)	142 ± 29	134 ± 26	118 ± 20	124 ± 16
t-PA antigen (ng/ml)	8.3 ± 0.7	11.4 ± 1.6*	8.4 ± 0.5	8.6 ± 0.5

Values are mean ± SEM. Chol, total cholesterol; HDL, HDL-cholesterol; LDL, LDL-cholesterol; PAI-1 antigen, type-1 plasminogen activator inhibitor total antigen; t-PA antigen, tissue-type plasminogen activator antigen. \*  $P < 0.05$  as compared to the respective baseline.

cially-available, recently-developed assay systems (Technoclone, Vienna, Austria).<sup>22,23</sup>

### Statistics

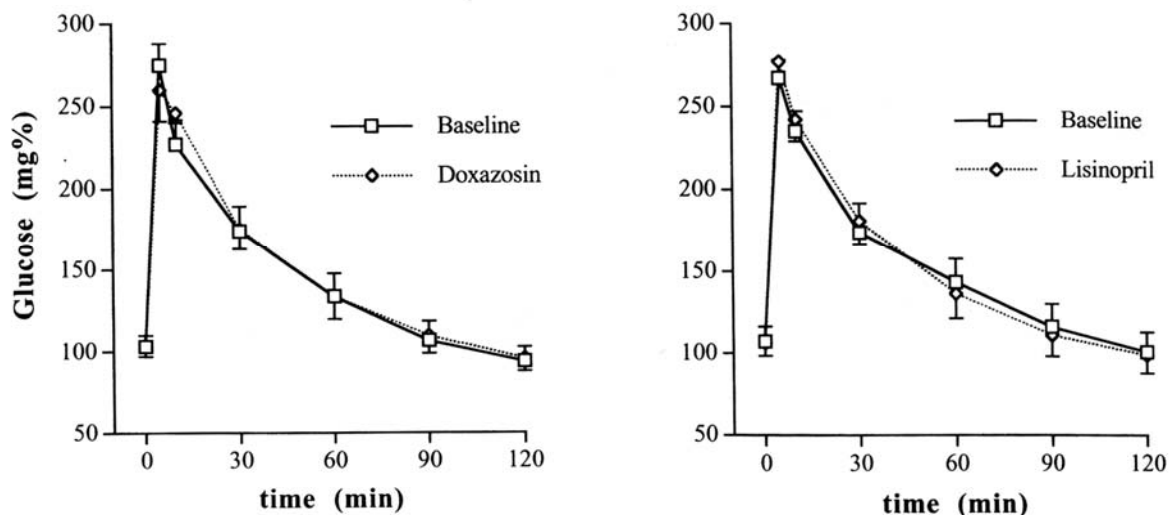
All results are expressed as mean ± SEM. Student's paired *t*-test or Wilcoxon signed ranked test, as appropriate, were used to compare the differences after treatment with the respective baseline values. Two-tailed tests were performed and a  $P \leq 0.05$  was considered to be significant. All analyses were performed using a computer program (StatView 4.0, Apple-McIntosh version 7.01).

### RESULTS

Systolic and diastolic blood pressure decreased significantly and to a similar extent with both doxazosin and lisinopril (Fig. 1). In Table 2, baseline values of blood

lipids, HbA1c, fibrinogen and fibrinolytic parameters are presented. Significant alterations could be observed only for HDL-cholesterol, which was significantly increased by lisinopril, and for t-PA antigen, which was significantly increased by doxazosin.

Basal plasma levels and glucose levels during ivGTT were unaffected by both doxazosin and lisinopril (Fig. 2). During treatment with doxazosin (Fig. 3, left panel) and lisinopril (Fig. 3, right panel), fasting plasma insulin levels decreased from  $15.5 \pm 3.5$  to  $11.6 \pm 2 \mu\text{U/ml}$  ( $P \leq 0.05$ ) and  $16.5 \pm 2.8$  to  $11.2 \pm 2.4 \mu\text{U/ml}$  ( $P \leq 0.001$ ), respectively. However, glucose-stimulated insulin levels during ivGTT were significantly decreased only by lisinopril. The area under the insulin-concentration time curve decreased significantly during lisinopril therapy by 31.9% (from  $4717 \pm 824$  to  $3211 \pm 546$ ;  $P \leq 0.007$ ) compared to 23.6% (from  $4995 \pm 1523$  to  $3816 \pm 638$ ; n.s.) during doxazosin therapy (doxazosin vs. lisinopril:  $P \leq 0.06$ ).



**Fig. 2** Effect of doxazosin and lisinopril on plasma levels of glucose.

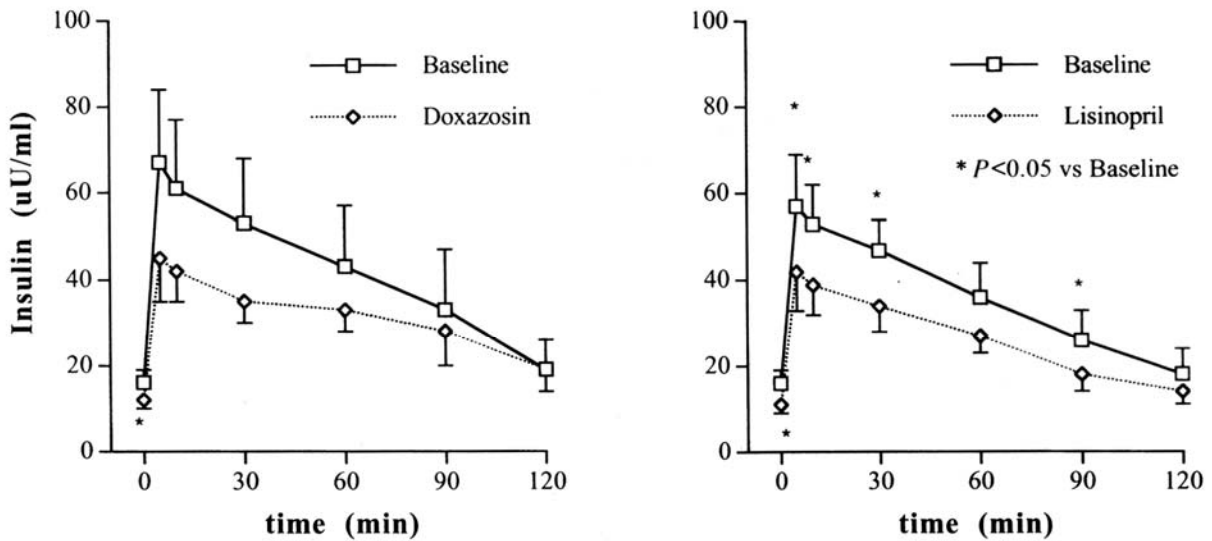


Fig. 3 Effect of doxazosin and lisinopril on plasma levels of insulin. Statistically significant changes for each time-point before and after treatment are indicated by asterisks.

## DISCUSSION

Insulin resistance and its main indicator, hyperinsulinemia, play an important role in the development of cardiovascular disease.<sup>2-6</sup> Recently, several reports have shown that a decreased insulin sensitivity with concomitant hyperinsulinemia is the link between upper body obesity, hypertension and glucose intolerance. All of these metabolic abnormalities have been identified as independent risk factors for cardiovascular disease.<sup>3,5</sup> Cardiovascular risk is greatly enhanced in case of the coexistence of all four mentioned metabolic abnormalities, which has also been referred to as 'syndrome X' or the 'deadly quartet'.<sup>1</sup>

In the present study, treatment with doxazosin as well as with lisinopril was associated with significant blood pressure reductions of comparable extent. Furthermore, glycemic control in response to ivGTTs did not change due to either treatment. This is compatible with other reports.<sup>24-26</sup> HbA1c levels, as indicator of blood glucose control, were also not significantly different between baseline and post-treatment values.

Little effects on blood lipids were found. Lisinopril therapy resulted in an increase of HDL-cholesterol. However, divergent reports exist regarding the effect of alpha-1-blockers and ACE-inhibitors on alteration of the lipoprotein profile. A number of studies have addressed this issue and showed either improvement or neutral effects on the lipid profile of both drugs.<sup>27-30</sup> In patients with proteinuria, the ACE-inhibitor fosinopril resulted in a sustained reduction of plasma lipoprotein(a).<sup>31</sup> However, in our study, lisinopril administration failed to demonstrate such an effect.

The treatment with both drugs resulted in a significant decrease in fasting insulin levels. In addition, the glucose-stimulated insulin response was reduced, as was the area under the insulin-concentration time curve; an effect more pronounced after administration of lisinopril.

There is no uniform explanation for the action of alpha-1-blockers and ACE-inhibitors on insulin metabolism. It is suggested that relaxation of systemic arterioles increases blood flow to the muscle tissues, thus augmenting access of insulin and glucose to the main site of the insulin-mediated removal of glucose, resulting in improved tissue response.<sup>32</sup> In addition, ACE-inhibitors inhibit sympathetic nervous system activity and enhance bradykinin-mediated actions, which also improve insulin sensitivity, possibly via an increase in local prostaglandin production.<sup>30</sup>

A positive relation between PAI-1 and insulin plasma levels has been described in obese patients and in patients with type 2 diabetes mellitus.<sup>33-36</sup> While Vague et al could demonstrate that the antidiabetic drug metformin was capable of lowering plasma insulin levels and, in parallel, PAI-1 activity levels,<sup>37</sup> another group demonstrated a decrease of PAI-1 antigen levels in type 2 diabetic patients by metformin without affecting plasma insulin.<sup>38</sup>

Furthermore, it could be shown that the alpha blocker doxazosin increased post-venous occlusion t-PA activity after 6 months of treatment using a mean daily dosage of 2.75 mg, while no significant alterations of basal t-PA antigen and activity levels, basal PAI-1 activity levels or post-venous occlusion t-PA antigen levels could be demonstrated.<sup>10</sup> The authors suggested that these effects

might be due to a direct effect or secondary to the reduction of pre-existing risk factors like elevated blood pressure or hypertriglyceridemia during the study. In the present study, both doxazosin and lisinopril induced a significant reduction of plasma insulin levels at basal conditions but PAI-1 antigen levels were not affected. These results confirm recent studies which also could not demonstrate parallel alterations of PAI-1 and insulin plasma levels and, therefore, do not support the idea of a crucial role of insulin in the regulation of plasma PAI-1.<sup>10,38,39</sup>

In addition, there is evidence that ACE-inhibitors might have a positive influence on the fibrinolytic system by reducing t-PA antigen and PAI-1 activity in patients with coronary artery disease after uncomplicated myocardial infarction.<sup>11</sup> This contrast to our findings might be explained by the different ACE-inhibitor used and/or by the different study population.

While Jansson et al demonstrated a significant decrease on basal t-PA antigen levels,<sup>10</sup> we found a significant increase. These discrepancies might be explained by the different study population and dosages used. This significant drug-induced increase of t-PA plasma levels was not accompanied by significant alterations of plasma PAI-1 levels and, therefore, might increase fibrinolytic capacity.<sup>39</sup> However, elevation of plasma t-PA does not always represent a sign of clinical benefit. In patients with coronary artery disease, elevated t-PA antigen levels have been shown to be associated with high risk of acute ischemic events including unstable angina, acute myocardial infarction and cardiac death.<sup>41-44</sup> In these studies, in contrast to the present one, elevated t-PA levels in patients with coronary artery disease are paralleled by elevations of PAI-1 levels and seem to be rather indicative of a reactively-increased t-PA release due to the high prothrombotic state in those patients.

In conclusion, these data suggest that treatment with the alpha-1-blocker doxazosin or the ACE-inhibitor lisinopril result in a combination of beneficial effects on blood pressure, insulin, lipid parameters and on endogenous fibrinolysis. Thereby, lisinopril seems to be more potent in respect of lowering plasma insulin and increasing HDL-cholesterol, whereas doxazosin has the capability of increasing the fibrinolytic potential. As the objective of treating hypertension is not simply to lower blood pressure, but also to reduce the excess risk of cardiovascular disease, alpha-1-blockers and ACE-inhibitors should be taken into consideration as first-line therapy when additional metabolic risk factors, e.g. hyperinsulinemia, glucose intolerance and dyslipidemia are present. However, it must be emphasized that the improvement in insulin and lipid metabolism, as well as an increase of the fibrinolytic potential due to alpha-1-blockers as well as ACE-inhibitors, has been studied only

in small study groups and that a clinical relevance of these beneficial effects with respect to a reduction of morbidity and mortality from coronary artery disease has still to be proven.

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