

Paper

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Effect of angiotensin-converting enzyme inhibition on endothelial function and insulin sensitivity in hypertensive patients

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Abstract Introduction

Evidence suggests an association between insulin resistance, hypertension and impaired endothelial function. Studies have shown that insulin resistance precedes the development of hypertension. By improving insulin sensitivity, it may be possible to improve hypertension and the subsequent damage to vessel walls. Some data indicates beneficial effects of angiotensin-converting enzyme (ACE) inhibitors on insulin sensitivity and endothelial function. We aimed to investigate these effects of ACE inhibition in the same group of patients with essential hypertension.

Materials and methods

Nine non-smoking, untreated hypertensive patients (38.3±9 years, 4/5 male/female) and 12 age-matched healthy subjects (35.2±6.7 years, 5/7 male/female) were included in the study. Hypertensive patients were given enalapril maleate (5–40 mg/day) for six months. The following parameters were studied at baseline and at the end of treatment period. Whole body insulin sensitivity was measured by a formula derived from an oral glucose tolerance test and named as the insulin sensitivity index (ISI). Insulin was measured by chemiluminescence and glucose by a glucose oxidase method. Endothelial function was evaluated as flow-mediated dilatation (FMD) of the brachial artery by ultrasonography and expressed as a percentage change relative to baseline diameter. Endothelial-independent vasodilatation was measured after sublingual nitroglycerine.

Results

FMD was impaired in the hypertensive group compared with healthy subjects (7.3±3.1% vs. 15.3±4.8%, $p<0.0005$), and ISI values were 1.18±0.6 vs. 4.4±0.9 ($p<0.0001$) respectively. Both insulin sensitivity and FMD improved after the treatment period compared with baseline values, FMD increased from 7.3±3.1% to 16.0±2.9% ($p<0.0005$) and ISI from 1.18±0.6 to 4.2±1.0 ($p<0.0001$). FMD and ISI showed a significant positive correlation ($r=0.67$, $p<0.001$) in the hypertensive group.

Conclusions

Patients with essential hypertension have impaired endothelial function and decreased whole body insulin

sensitivity compared with healthy subjects. Treatment for six months with enalapril maleate seems to improve both FMD and ISI. This study confirms the beneficial effects of ACE inhibition on both endothelial function and insulin sensitivity tested in the same group of essential hypertensive patients. The mechanism of these favourable effects of ACE inhibition needs to be clarified.

Introduction

Studies have shown an independent association of hypertension with insulin resistance. Strong data indicate that insulin resistance precedes the development of hypertension and essential hypertension may itself be an insulin-resistant state.^{1,2} Approximately half of patients with hypertension are insulin resistant and hyperinsulinaemic. Both insulin resistance and hypertension have been associated with impaired endothelial function.

Endothelial dysfunction is no longer seen by some as a consequence, but as a cause of insulin resistance.³ A Losartan Interaction for Endpoint reduction in hypertension (LIFE) substudy indicates the link between endothelial dysfunction and insulin resistance in hypertension.⁴ Reduced insulin-mediated vasodilation due to impaired nitric oxide (NO) synthesis may limit insulin and glucose access to target tissues, thereby causing insulin resistance in essential hypertension.⁵

Angiotensin II (Ang II) is a potent vasoconstrictor and stimulator of superoxide production. Ang II can affect the structure, function, and development of atherosclerosis of a blood vessel through a variety of different mechanisms and may promote endothelial dysfunction.⁶ Angiotensin-converting enzyme (ACE) not only generates Ang II, but also inactivates kinins. ACE inhibition prevents the production of Ang II and also acts to prevent the ACE-mediated breakdown of bradykinin. Inhibition of kinin breakdown enhances the synthesis and release of NO, resulting in improved endothelial function.⁷ The beneficial effects of ACE inhibitors (ACE-Is) on endothelial function have been documented in a number of studies.^{8–13} Insulin-mediated vasodilation is also impaired in hypertension and ACE-Is have been shown to enhance insulin sensitivity in hypertensive patients and to exert beneficial effects on

vascular function.¹⁴⁻¹⁶ The present study was designed to investigate the effect of enalapril maleate on endothelial function and insulin sensitivity in the same group of hypertensive patients.

Material and methods

Subjects

Twelve untreated patients with essential hypertension (mild to moderate, according to JNC VI) were included in the study after exclusion of secondary hypertension. All of the participants underwent initial evaluation by means of medical history, physical examination, haematological and biochemical profile, including measurement of blood glucose, serum electrolytes (sodium, potassium), urea, creatinine, lipids, thyroid function tests and urine analysis. Diabetes was excluded according to the American Diabetes Association criteria. Renal ultrasound and Doppler examinations were normal in all hypertensive patients. Twelve healthy volunteers were taken as a control group. No patient in either group was taking lipid-lowering agents, hormone replacement therapy, antioxidant therapy, antiaggregants, steroids or other drugs which might affect blood pressure (BP). Baseline characteristics of the treatment and control groups are shown in Table 1.

Exclusion criteria included a history of malignant hypertension, myocardial infarction, cerebrovascular disease, heart failure, serum creatinine > 200 µmol/L, connective tissue disorders, other systemic diseases and smoking.

The local ethics committee approved the study protocol and patients gave written informed consent.

All of the patients were hypertensive on at least three measurements, according to outpatient clinics or family doctor reports, and they had not taken antihypertensive treatment for six months prior to the study.

Patients were given enalapril maleate (dosage range; 5–40 mg/day). After a six-week titration period to reach adequate BP control (BP < 140/90 mmHg), patients were followed by the same physician with monthly clinic BP measurements for six months. Clinic BP was measured at each visit between 0700 to 1000 hours, 24 hours after the last dose, using a standard sphygmomanometer and an appropriately sized cuff, and taking Korotkoff phases I and V as the systolic and diastolic values respectively. All readings were performed in triplicate, with the subject in a sitting position after 10 minutes rest. Compliance and tolerability to study treatment was assessed by monitoring of spontaneous reports of adverse events and by taking a pill count at each visit. Before and after six months of antihypertensive treatment, the following parameters were evaluated:

Insulin sensitivity was determined by an oral glucose tolerance test (OGTT) based on the formula described by Matsuda and DeFronzo and named as the insulin sensitivity index composite (ISI Composite).¹⁷ Whole-body insulin sensitivity during the OGTT was calculated by the following formula:

Table 1 Characteristics of the study population

| | Patients (n=9) | Controls (n=12) |
|--------------------------|----------------|-----------------|
| Age (years) | 38.3±9 | 35.2±6.7 |
| Male/female | 4/5 | 5/7 |
| BMI (kg/m ²) | 25.2±4.0 | 23.8±4.5 |
| Duration of HT (years) | 2.3±2.2 | - |
| Retinopathy | 3/9 | - |

Data presented are mean value±SD; HT = hypertension; BMI = body mass index.

$$10000 / \sqrt{(FPG \times FPI) \times (\text{mean OGTTG} \times \text{mean OGTTI})}$$

Where FPG = fasting plasma glucose
FPI = fasting plasma insulin
OGTTG = OGTT plasma glucose
OGTTI = OGTT plasma insulin

After an overnight fast an OGTT (75 g glucose) was performed between 0800 and 0900 hours. Blood samples were taken just before (0 minutes) and 30, 60, 90 and 120 minutes after the administration of glucose for the measurement of serum glucose and insulin concentrations.

Endothelial function was determined by a non-invasive method described by Celermajer *et al.*¹⁸ This noninvasive method evaluates endothelial function by using post-ischæmic (forearm) vasodilatation, which causes enhanced flow in the proximal brachial artery and consequently a shear stress-induced vasodilatation which is regarded as endothelium dependent.

Endothelium-dependent vasodilatation was measured using a high resolution ultrasound (GE Logic 700) with a 8.5 MHz linear-array transducer. Subjects had to rest for at least 10 minutes before the first scan was recorded. Increased flow was induced by deflating a pneumatic tourniquet after a five-minute suprasystolic arterial forearm compression. The post-ischæmic scan was performed 45 to 60 seconds after cuff deflation. To test endothelium-independent dilatation, further scans were performed at rest and four minutes after sublingual administration of 0.4 mg nitroglycerine as a direct NO donor. The time interval between the first and second measurements was 20 minutes, to allow for vessel recovery.

The ECG was monitored continuously. Vessel diameters were analysed on frozen images over the length of an artery of > 1 cm (brachial artery) according to operator judgement. Three measurements were taken for three cardiac cycles at the end of diastole (R wave on the ECG) and the mean was calculated. The difference in lumen diameter between rest and reactive hyperaemia, expressed as percent change, was regarded as endothelium-dependent vasodilatation (FMD%). Ultrasonography was performed in a blinded fashion by the

Table 2 Blood pressure measurements, flow-mediated vasodilatation and insulin sensitivity index values of the study population

| | Patients (n=9) | | Controls (n=12) |
|------------|------------------|-----------------|-----------------|
| | Before treatment | After treatment | |
| SBP (mmHg) | 147.4±10.1 | 126±9.4* | 119.1±13.1* |
| DBP (mmHg) | 97.6±7.0 | 78.6±9.8** | 76.6±6.9** |
| ISI | 1.18±0.6 | 4.2±1.0** | 4.4±0.9** |
| FMD (%) | 7.3±3.1 | 16.0±2.9*** | 15.3±4.8*** |

Data presented are mean value±SD; SBP = systolic blood pressure, DBP = diastolic blood pressure; ISI = insulin sensitivity index; FMD = flow mediated vasodilatation; *p<0.005; **p<0.0001; ***p<0.0005 vs. before treatment.

same investigator. Intra-observer variability in image acquisition and analysis was below 2%.

Assays

Insulin levels were measured by an Immulite analyser using an immunometric method (DPC, Los Angeles, CA). The intra-assay precision was 4.8–5.4% and total precision was 4.8–7.6% for a mean range of 10 ± 0.51 to 439 ± 16.5 $\mu\text{u/ml}$. Plasma glucose levels were determined by the glucose oxidase method.

Statistical analysis

Statistical analysis was performed with Instat III software package. Comparisons were done with paired and unpaired *t*-test where appropriate. Correlation analyses were determined by calculating the Pearson coefficient. Levels of statistical significance were set at $p < 0.05$. The results are expressed as mean \pm standard deviation (SD).

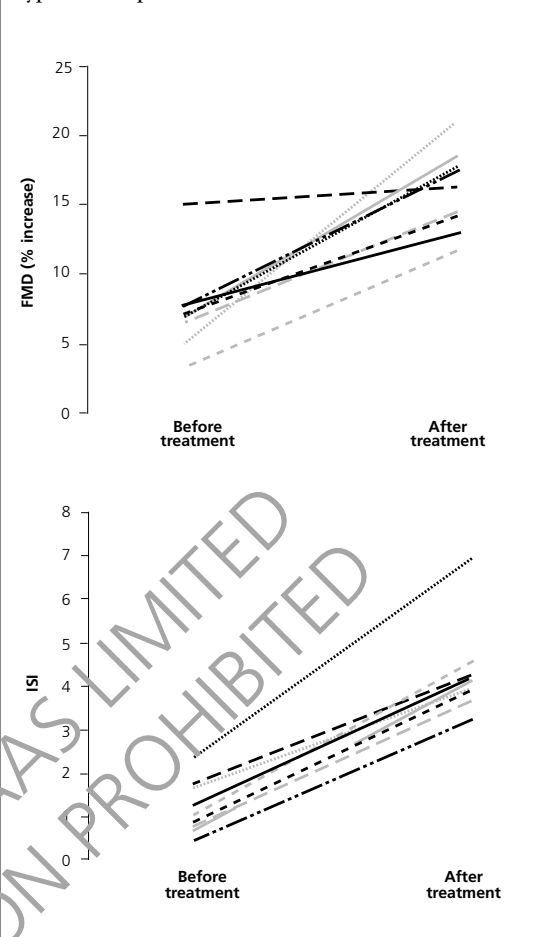
Results

The study population consisted of 12 patients and healthy controls. Baseline demographic parameters were well-matched between groups. Three patients withdrew before completion of the study; two for adverse effects (cough) in the titration period and one for uncontrolled hypertension at the end of eight weeks. Characteristics of the study population are summarised in Table 1.

Baseline systolic BP (SBP) ($p < 0.005$) and diastolic BP (DBP) ($p < 0.0001$), in the hypertensive group were significantly higher than in the control group and decreased significantly at the end of treatment period ($p < 0.005$ for SBP and $p < 0.0001$ for DBP); values are shown in Table 2.

Pretreatment FMD% values of the hypertensives were significantly lower than the control group ($7.3 \pm 3.1\%$ vs. $15.3 \pm 4.8\%$, $p < 0.0005$). Flow-mediated dilatation was improved significantly after six months treatment in hypertensive patients (from $7.3 \pm 3.1\%$ to $16.0 \pm 2.9\%$, $p < 0.0005$) (see Table 2).

Endothelium-independent dilatation (GTN) was measured after sublingual nitroglycerin in all

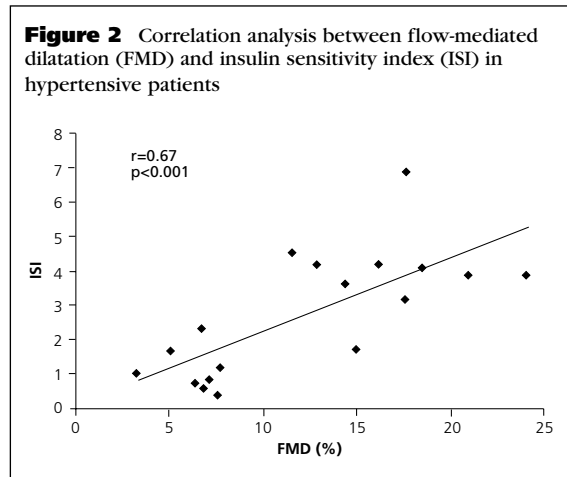
Figure 1 Flow-mediated dilatation (FMD) and insulin sensitivity index (ISI) values before and after treatment in hypertensive patients

participants and there were no significant differences between three groups ($17.3 \pm 3.4\%$, $18.4 \pm 9.8\%$ and $18.2 \pm 5\%$ for hypertensive patients before treatment, after treatment and controls, respectively).

Baseline ISI values of the hypertensive group were lower than the control group (1.18 ± 0.6 vs. 4.4 ± 0.9 , $p < 0.0001$) and improved after treatment in hypertensive patients (4.2 ± 1.0 , $p < 0.0001$) (see Table 2). Changes in FMD measurements and ISI calculations are shown in Figure 1. Calculated insulin sensitivity indices were found to be positively correlated with FMD measurements in hypertensives ($r = 0.67$, $p < 0.001$) (Figure 2). Changes in ISI and FMD values before and after treatment also showed a positive correlation in hypertensive patients ($r = 0.59$, $p < 0.05$).

Discussion

The relationship between insulin sensitivity, hypertension and endothelial function is quite complex. The vascular endothelium, by synthesis and release of various vasoactive substances, plays an important role in maintaining vascular tone. Local vascular control depends on a balance between dilators and constrictors, with endothelium-dependent NO being the best characterised and most important.¹⁹ Deficiency in the



endothelium-derived NO is regarded as a marker of endothelial dysfunction.^{20,21} Endothelial dysfunction can be seen in diabetes and states of insulin resistance, such as obesity, hypertension and dyslipidaemia,²⁰ and its presence may be predictive of the subsequent risk of cardiovascular events. Endothelium-dependent relaxation is impaired in hypertension,²² and abnormalities in endothelial function may account for excess cardiovascular risk in hypertensive patients.³ The endothelium also has a major role in the insulin sensitivity of tissues and some believe that endothelial dysfunction may lead to insulin resistance.⁵ Because insulin exerts vasodilatory actions by enhancing NO release, changes in vascular function are to be expected in states of reduced insulin sensitivity. Angiopathy in an insulin resistant state, whether secondary or primary, has been assumed to play a permissive role in the pathogenesis of hypertension.²³

Data suggest that insulin resistance and hyperinsulinaemia predispose to the development of hypertension.³ Half of all patients with hypertension can be considered to have insulin resistance.⁴ Insulin resistance and hyperinsulinaemia may potentiate the development of hypertension via enhanced renal sodium retention and sympathetic nervous system activation.³ Besides, insulin-mediated vasodilation is also impaired in insulin resistance syndrome.²⁴ Insulin resistance is associated with a number of metabolic abnormalities and endothelial dysfunction, which further increase cardiovascular risk.³ Increasing evidence indicates the benefit of interventions to improve insulin sensitivity and control of hypertension in reducing cardiovascular risk. ACE inhibition has been shown to improve both insulin resistance and endothelial function. ACE-Is prevent the production of Ang II and ACE-mediated breakdown of bradykinin.²⁵ Accumulation of bradykinin may lead to increased NO synthesis and activity, resulting in improved vasodilative response.²⁶ ACE inhibition also prevents superoxide anion generation, which results in increased activity of NO by preventing its breakdown.²⁵ Increased NO activity may not only produce greater relaxation of systemic and coronary arteries, but may also protect against

platelet activation and vascular inflammation.²⁵ Improvement in endothelial function by ACE inhibition has been demonstrated in both insulin-dependent and non-insulin-dependent diabetes mellitus, and in patients with coronary artery disease.^{10,12,27} Mancini *et al.* showed that six months of quinapril treatment improved endothelial dysfunction in normotensive patients with coronary artery disease.¹⁰ In Type 2 diabetic subjects, the ACE-I, enalapril, improved stimulated and basal NO-dependent endothelial function.²⁷ Angiotensin Type 1 (AT₁-) receptor antagonists have also been studied and proved to have similar beneficial effects, but ACE-Is are believed to have more pronounced effects, probably due to prevention of bradykinin breakdown.²⁸⁻³⁰ Data show that ACE-Is not only decrease BP, but also enhance insulin sensitivity, and this effect does not seem to be related to the AT₁-receptor.^{14,16}

Contrasting with these favourable results, Mullen *et al.* demonstrated no improvement in endothelial-dependent dilation in young subjects with Type 1 diabetes by treatment with enalapril.³¹ They pointed out the complex nature of vascular disease in insulin-dependent diabetes, which can affect both endothelial and smooth muscle function. Besides, differences may exist between ACE-Is in their effects on endothelial function, while some of the comparative studies have demonstrated improvement only with quinapril.^{11,32} Further studies will clarify the effects of different ACE-Is on vascular function in different disease states.

We studied the effect of ACE inhibition on endothelial function and insulin sensitivity in the same group of hypertensive patients. As compared with healthy subjects, flow-mediated dilatation and insulin sensitivity were impaired in the hypertensives and both of these parameters correlated with BP. After six months of treatment with enalapril, endothelium-dependent vasodilation and insulin sensitivity improved significantly. The mechanism of this beneficial action of ACE inhibition is not clear, though it might be related to NO via increasing bradykinin levels. In the present study, we did not measure bradykinin concentrations or muscle blood flow, but the data from the literature suggest that bradykinin and some vasoactive mediators, such as NO, might improve glucose metabolism by enhancing muscle blood flow and consequently the rate of insulin and glucose delivery to target tissues.^{33,34} Another possible mechanism may be explained by the effect of strict BP control, as reported by Muiesan *et al.*³⁵ In hypertensive patients long-term, effective pharmacological BP reduction may exert a beneficial effect on endothelial dysfunction.

Conclusions

We observed a strong association between endothelial dysfunction and insulin resistance in patients with essential hypertension. ACE inhibition had beneficial effects on insulin resistance and endothelial function, both of which are well-known atherosclerotic risk factors. Further studies are needed to clarify the mechanism of these

beneficial effects of ACE inhibition and the impact of improved endothelial dysfunction and insulin sensitivity on cardiovascular outcome.

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