Effect of Long-Term Angiotensin-Converting Enzyme Inhibition on Endothelial Function in Patients with the Insulin-Resistance Syndrome

P. J. Bijlstra, P. Smits, J. A. Lutterman, and Th. Thien

Summary: Cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia are associated with an impaired endothelium-dependent vasodilation. In patients with type 2 diabetes mellitus, these risk factors are frequently clustered. We investigated whether long-term treatment with the angiotensin-converting enzyme (ACE) inhibitor perindopril can improve endothelium-dependent vasodilation in this particular group of patients. We selected 10 patients with type 2 diabetes and hypertension (age 59.4 ± 3.2 years, body mass-index 29.7 ± 1.5 kg \cdot m^{-2}, blood pressure 169 ± 6/92 ± 1 mm Hg, total cholesterol 6.6 ± 0.3 mM). Using venous occlusion plethysmography, we recorded the increases in forearm blood flow (FBF) in response to three vasodilator stimuli: (a) 5 min of forearm ischemia, (b) infusion of the endothelium-dependent vasodilator methacholine (Mch) into the brachial artery (0.03, 0.3, and 1.0 \mu g/min/100 ml), and (c) intraarterial infusion of the endothelium-independent vasodilator sodium nitroprusside (SNP 0.06, 0.2, 0.6 \mu g/min/100 ml). This procedure was repeated after 6 months of treatment with perindopril 4–8 mg/day. Forearm vascular resistance (FVR) was calculated by the quotient of the mean arterial pressure (MAP) and the FBF. Perindopril reduced blood pressure (BP) by 19/10 mm Hg (p < 0.05) and increased baseline FVR, but improved neither the maximal percentage decrease in vascular resistance induced by Mch (from -80 ± 2 to -82 ± 2%) nor that induced by SNP (from -73 ± 3 to -72 ± 3%). Perindopril decreased the FVR reached after the ischemic stimulus from 6.5 ± 1.2 to 4.8 ± 0.6 U (p < 0.05). Six months of treatment with perindopril improved neither the endothelium-dependent nor endothelium-independent vasodilation, but significantly reduced minimal FVR (p < 0.05). These observations suggest a reduction of structural vascular changes after long-term ACE inhibition.

Key Words: Endothelium-dependent vasodilation—Angiotensin-converting enzyme inhibition—Forearm blood flow—Insulin resistance—Diabetes—Hypertension—Plethysmography—Perindopril.

The clustering of type 2 diabetes mellitus, hypertension, and dyslipidemia has been described as the "insulin resistance (IR) syndrome," "Reaven's syndrome," or "syndrome X" (1). All components of this syndrome have been associated with an impaired endothelium-dependent vascular relaxation. In animal models, this was shown by Bucala and colleagues (2) and Tesfamariam and co-workers (3) for diabetes, by Tesfamariam and Halpern (4) and Boegehold (5) for hypertension, and by Osborne and colleagues (6) and Shimokawa and Vanhoutte (7) for hypercholesterolemia. Although human in vivo data on endothelium-dependent vasorelaxation are scarce, an impairment of endothelium-dependent vascular relaxation has repeatedly, though not consistently, been shown for hypertension (8–10) and hypercholesterolemia (11) as well as for type 2 diabetes (12). Consequently, the IR syndrome could be accompanied by an impaired endothelium-dependent vascular relaxation.

Besides decreasing blood pressure (BP), angiotensin converting enzyme (ACE) inhibitors have been reported to improve endothelium-dependent vasodilation and structural changes in the vascular
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wall in animal models (13,14) as well as in humans (15,16). However, no human data are yet available regarding the effect of ACE inhibitors on endothelium-dependent vasodilation in hypertensive, type 2 diabetic patients. An improvement in an impaired endothelium-dependent vasodilation could be of clinical importance in the management of patients with the IR syndrome.

To address this hypothesis, we assessed the endothelium-dependent forearm vasodilator response to infusion of the muscarinic receptor agonist methacholine (Mch) into the brachial artery (11), and the endothelium-independent vasodilator response to intraarterial infusion of sodium nitroprusside (SNP). To measure long-term effects of ACE inhibition, we performed experiments in exactly the same way before as well as after 6 months of ACE inhibition.

METHODS

Patients

After the study protocol was approved by the local ethics committee, 10 patients with type 2 diabetes mellitus with a duration of at least 4 years and a repeatedly measured BP of at least 140/90 mm Hg after 15 min of supine rest (measured by Critikon Dinamap device, type 1846 SX/P), were selected. Subjects with impaired renal function (plasma creatinine >130 μM), orthostatic hypotension, a decrease in systolic BP (SBP) after standing up of >20 mm Hg), or treatment with anticoagulant or nonsteroidal antiinflammatory drugs were excluded from the protocol. The use of antihypertensive and/or hypoglycemic drugs before selection was not an exclusion criterion. Subjects with impaired renal function (plasma creatinine >130 μM), orthostatic hypotension (a decrease in systolic BP (SBP) after standing up of >20 mm Hg), or treatment with anticoagulant or nonsteroidal antiinflammatory drugs were excluded from the protocol.

Protocol

All subjects participated in two tests from 1330 to 1730 h, one before and one during treatment with the ACE inhibitor perindopril. These tests were performed in a quiet, temperature-controlled (22°C) room to ensure that FBF recordings predominately referred to forearm muscle perfusion and to exclude FBF fluctuations due to changes in temperature (17). All participants were asked to abstain from alcohol and caffeine or smoking for at least 24 h before the test. The patients receiving oral hypoglycemic therapy were asked not to use those drugs for at least 24 h before the test until the end of the test. The eventual remaining medication was continued. Subjects receiving insulin had their regular subcutaneous morning dose. All subjects were asked to have their usual breakfast but not to eat for at least 2 h before the test was performed.

After forearm volume (FAV) was measured by water displacement, the subjects remained in the supine position. Under local anesthesia, the left antecubital brachial artery was cannulated with a 20-gauge Angiocath (De seret Medical, Beckton Dickinson, Sandy, UT, U.S.A.) for intraarterial drug infusion with an automated syringe infusion pump (type STC-521, Terumo, Tokyo, Japan) as well as for BP and heart rate (HR) monitoring (type 78353B, Hewlett-Packard GmbH, Böblingen, Germany). Plasma glucose levels were monitored during the tests at half-hour intervals (Accutrend, type 1284851, Boehringer, Mannheim, Germany) and, if necessary, corrections were made by infusing glucose 5% or insulin intravenously in the contralateral arm.

FBF recordings were started after a 45-min equilibration period. We measured FBF at both forearms by ECG-triggered venous occlusion mercury-in-silastic strain-gauge plethysmography (Hokanson EC4, D. E. Hokanson, Washington). To ensure that FBF recordings referred only to the forearm skeletal muscle circulation, the hand circulation was occluded during recordings by a wrist cuff inflated 100 mm Hg above the SBP (18).

We investigated vasodilator responses to three different stimuli. Each of these stimuli was preceded by 5 min of intraarterial infusion of placebo, during which baseline values of all parameters were recorded. First we assessed structural changes in the vascular wall by measuring the postocclusive reactive hyperemic (PORH) response of the forearm vascular bed to 5 min of forearm ischemia (19) while infusing placebo, achieving this by inflating a cuff around the upper arm to 100 mm Hg above the SBP. This response is considered a measure of the maximal vasodilator capacity, which indicates structural changes in the vessel wall on arteriolar and lower level (19).

Fifteen minutes later, new baseline recordings were obtained; subsequently endothelium-dependent vasodilator responses to intraarterial infusion of Mch were recorded. Three increasing dosages of Mch were given (0.03, 0.3, and 1.0 μg/min/100 ml FAV, 5 min/dose). Forty-five minutes later, we obtained new baseline recordings and then recorded the vasodilator responses to intraarterial infusion of three increasing dosages of SNP (0.06, 0.2, and 0.6 μg/min/100 ml FAV, 5 min/dose). This procedure was repeated in exactly the same way after 6 months of treatment with perindopril 4–8 mg/day. During these 6 months, preexisting concomitant medication was not altered, and the patients made a monthly control visit to the outpatient clinic. Moreover, blood samples were taken to monitor possible side effects. The dosage of perindopril was increased from 4 to 8 mg/day unless BP decreased >20 mm Hg or had decreased to <120/80 mm Hg.

Drugs

Mch was prepared freshly for each experiment by our pharmaceutical laboratory in a solution in NaCl 0.9%. SNP was purchased from Hoffmann La Roche (Mijdrecht, The Netherlands). Protected from light, it was dissolved in 5% glucose just before administration. Saline 0.9% was used as placebo in the baseline recordings and the PORH test, except for the baseline recordings preceding the SNP test, for which 5% glucose was used. All infusions were administered at a rate of 100 μl/min/100 ml FAV.

Statistics and calculations

Each drug and each dosage was administered for 5 min, during which time all relevant registrations were made. Each minute, three FBF curves were recorded. For the calculations of the baseline FBF, all recorded curves were used. For the PORH response, only the highest FBF was used. The mean FBF values for each dosage of Mch and SNP were calculated by averaging the values from the last 2 min per dosage, when a steady state was achieved. The FBF ratio was calculated as the quotient of
the FBF from the experimental and nonexperimental side (8,20). Absolute and percentage changes for each stimulus were calculated from the preceding baseline value. The FVR was calculated by the quotient of the mean arterial pressure (MAP) and the FBF.

Differences in baseline levels and responses to ischemia before and after treatment with perindopril were evaluated by a paired Student's t test. The vasodilator responses to the various drugs and dosages were compared by a multivariate analysis of variance (MANOVA) with repeated measures. Differences were considered statistically significant at p < 0.05. All results are mean values ± SE, unless indicated otherwise.

RESULTS

Subjects

Three male and 7 female patients with a mean age of 59.4 ± 3.2 years gave their informed consent. The average weight was 82.7 ± 5.8 kg, and the mean body mass index was 29.7 ± 1.5 kg/m². The FAV averaged 1,031 ± 80 ml. The mean duration of diabetes was 11.1 ± 2.3 years, that of hypertension was 11.3 ± 3.4 years, and mean fasting blood glucose was 12.2 ± 1.5 mM. The average glycosylated hemoglobin was 8.7 ± 0.5%, with reference values of 4.2–6.3%. Fasting insulin concentration averaged 19.7 ± 3.7 mU/L (reference values 8–20 mU/L). Diabetes was controlled by diet and oral hypoglycemic drugs in 5 patients, 4 patients used subcutaneous insulin preparations, and 1 patient was not treated with either diet or medication. Four patients had an increased albumin excretion ratio (>20 μg/min), 4 patients had diabetic retinopathy, and 5 had decreased vibration perception. Five patients were already receiving antihypertensive drug therapy: used β-blockers (3) and thiazide diuretics (2); 1 also was treated with nitrates and 1 with a calcium antagonist, but none were receiving ACE inhibitors.

Effects of ACE inhibition on baseline parameters

Table 1 and Fig. 1 show the baseline characteristics of the patients before and after 6 months of treatment with 4–8 mg of the ACE inhibitor perindopril. Perindopril significantly reduced the baseline BP from 169.4 ± 5.9/92.6 ± 2.12 to 150.0 ± 4.3/83.0 ± 3.1 mm Hg, as measured by Dinamap device (p < 0.05) and from 174.6 ± 7.1/80.8 ± 2.2 to 145.6 ± 6.3/75.8 ± 2.7 mm Hg as measured intraarterially (p < 0.05).

The baseline pulse pressure was significantly reduced (p < 0.01). The baseline HR tended to be lower after 6 months of treatment (p = 0.08). After 6 months of ACE inhibition, the baseline FBF was significantly lower at the experimental left side (p < 0.05) while the FBF ratio remained unchanged. Moreover, the baseline FVR before treatment was significantly increased by the perindopril treatment (p < 0.05) (Fig. 1).

Table 1 shows that fasting plasma glucose concentrations showed no significant changes during the 6 months of treatment. This absence of changes also accounts for HbAlc, and fasting insulin concentrations. During treatment, plasma cholesterol decreased from 6.62 ± 0.35 to 6.31 ± 0.34 mM (p = 0.13), triglycerides decreased from 2.74 ± 0.65 to 2.25 ± 0.56 mM (p = 0.05), high density lipoprotein cholesterol increased from 1.4 ± 0.08 to 1.23 ± 0.07 mM (p = 0.07), and low density lipoprotein cholesterol increased from 4.17 ± 0.30 to 4.38 ± 0.29 mM (p = 0.58). Moreover, albumin excretion ratio decreased significantly during 6 months of ACE inhibition (p < 0.05).

In only 1 patient was it necessary to increase the perindopril dosage from 4 to 8 mg/day to achieve an adequate BP reduction. One patient developed a cough during treatment, but was able to continue the medication. There were no other side effects.

Effects of ACE inhibition on the forearm vasodilator responses to the three stimuli

Table 2 and Fig. 2 show the absolute values for FBF and FVR; Fig. 3 shows the percentage of decrement from baseline in FVR.

### TABLE 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>p-Value</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>8.7 ± 1.6</td>
<td>0.60</td>
<td>8.6 ± 1.7</td>
</tr>
<tr>
<td>AER (μg/min)</td>
<td>17.5 ± 11.3</td>
<td>0.03</td>
<td>9.5 ± 5.3</td>
</tr>
<tr>
<td>Creat (μM)</td>
<td>77.9 ± 12.1</td>
<td>0.95</td>
<td>78.0 ± 15.4</td>
</tr>
<tr>
<td>K* (mM)</td>
<td>4.4 ± 0.3</td>
<td>0.87</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>Gluc (mM)</td>
<td>12.2 ± 3.1</td>
<td>0.29</td>
<td>11.8 ± 3.3</td>
</tr>
<tr>
<td>Ins (μU/L)</td>
<td>19.7 ± 11.6</td>
<td>0.60</td>
<td>19.0 ± 12.6</td>
</tr>
<tr>
<td>Gluc/ins (mmol/U)</td>
<td>0.76 ± 0.53</td>
<td>0.07</td>
<td>0.65 ± 0.45</td>
</tr>
</tbody>
</table>

Values are means ± SD; p-values derived from paired Student’s t test.

HbA1c, glycosylated hemoglobin; AER, albumin excretion ratio; Creat, serum creatinine concentration; K*, serum potassium concentration; Gluc, plasma glucose concentration; Ins, plasma insulin concentration; Gluc/ins, quotient of glucose and insulin plasma concentrations.

FIG. 1. The baseline individual and mean (± SE) values of the pulse pressure (PP), the forearm vascular resistance (FVR), the mean arterial pressure (MAP), and the heart rate (HR) before and after 6 months of angiotensin-converting enzyme inhibition by perindopril, with indication of p-values from paired Student’s t tests.

TABLE 2. Mean (±SE) of the hemodynamic parameters throughout the test before as well as after treatment with perindopril

<table>
<thead>
<tr>
<th>Condition</th>
<th>MAP (mm Hg)</th>
<th>FBF(L) (ml/100 ml FAV/min)</th>
<th>FBF ratio (L/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>117.5 ± 2.5</td>
<td>3.5 ± 0.5</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>PORH</td>
<td>111.8 ± 4.4</td>
<td>19.7 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>119.8 ± 3.6</td>
<td>3.3 ± 0.4</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>Mch 0.03</td>
<td>116.8 ± 3.7</td>
<td>6.7 ± 0.8</td>
<td>2.4 ± 0.2</td>
</tr>
<tr>
<td>Mch 0.3</td>
<td>117.5 ± 3.8</td>
<td>13.1 ± 1.4</td>
<td>5.3 ± 0.6</td>
</tr>
<tr>
<td>Mch 1.0</td>
<td>116.9 ± 3.7</td>
<td>17.9 ± 1.8</td>
<td>8.5 ± 1.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>123.2 ± 3.7</td>
<td>3.5 ± 0.5</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>SNP 0.06</td>
<td>122.4 ± 3.8</td>
<td>5.1 ± 0.8</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>SNP 0.2</td>
<td>120.1 ± 3.7</td>
<td>8.0 ± 1.1</td>
<td>3.3 ± 0.4</td>
</tr>
<tr>
<td>SNP 0.6</td>
<td>117.8 ± 3.6</td>
<td>14.0 ± 2.5</td>
<td>5.7 ± 1.2</td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>105.6 ± 3.5</td>
<td>2.5 ± 0.3</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>PORH</td>
<td>102.6 ± 3.6</td>
<td>22.4 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>112.0 ± 6.4</td>
<td>2.6 ± 0.4</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>Mch 0.03</td>
<td>111.9 ± 4.0</td>
<td>5.0 ± 0.7</td>
<td>2.2 ± 0.2</td>
</tr>
<tr>
<td>Mch 0.3</td>
<td>109.8 ± 3.3</td>
<td>12.4 ± 2.3</td>
<td>5.0 ± 0.7</td>
</tr>
<tr>
<td>Mch 1.0</td>
<td>110.4 ± 3.5</td>
<td>16.4 ± 3.1</td>
<td>7.0 ± 0.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>118.9 ± 4.0</td>
<td>2.5 ± 0.3</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>SNP 0.06</td>
<td>117.8 ± 3.1</td>
<td>4.9 ± 0.6</td>
<td>2.3 ± 0.3</td>
</tr>
<tr>
<td>SNP 0.2</td>
<td>118.2 ± 3.5</td>
<td>7.7 ± 1.0</td>
<td>3.4 ± 0.5</td>
</tr>
<tr>
<td>SNP 0.6</td>
<td>117.2 ± 3.6</td>
<td>10.4 ± 1.7</td>
<td>4.9 ± 0.8</td>
</tr>
</tbody>
</table>

PORH, postocclusive reactive hyperemia; MAP, mean arterial pressure; FBF, forearm blood flow; Mch, methacholine; SNP, sodium nitroprusside; MAP, mean arterial pressure; FBF(L), forearm blood flow at the experimental side; FBF(L/R), the ratio of the FBF at the experimental and nonexperimental side, before and after treatment with perindopril.

Baseline values are shown as placebo. Responses to three stimuli are shown: (a) PORH, 5-min forearm ischemia; (b) Mch 0.03, 0.3, and 1.0, three increasing dosages of methacholine; and (c) SNP 0.06, 0.2, and 0.6, three increasing dosages of sodium nitroprusside.

* p < 0.05 versus before perindopril, paired t test.

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The minimal FVR during Mch infusions was not significantly altered by 6 months of ACE inhibition (7.8 ± 1.5 before 9.4 ± 1.7 AU after treatment). However, absolute decrements in FVR in response to Mch were significantly greater after perindopril (p < 0.05), but the percentage changes in FVR from baseline were not. Neither did the absolute values of FBF ratio, absolute responses from baseline, or the percentage responses to Mch from baseline of FBF ratio change significantly with long-term ACE inhibition.

Endothelium-independent vasorelaxation

Before and after 6 months of perindopril treatment (Table 2 and Fig. 2), the three dosages of SNP percentage increases (Table 2 and Fig. 2). The minimal FVR during Mch infusions was not significantly altered by 6 months of ACE inhibition (7.8 ± 1.5 before 9.4 ± 1.7 AU after treatment). However, absolute decrements in FVR in response to Mch were significantly greater after perindopril (p < 0.05), but the percentage changes in FVR from baseline were not. Neither did the absolute values of FBF ratio, absolute responses from baseline, or the percentage responses to Mch from baseline of FBF ratio change significantly with long-term ACE inhibition.

Endothelium-dependent vasorelaxation

Before and after 6 months of perindopril treatment (Table 2 and Fig. 2), the three dosages of SNP
increased FBF dose dependently to the same extent. Absolute changes in FBF from baseline in response to SNP infusions were not significantly different after the treatment with perindopril, nor were the percentage changes from baseline.

Neither the levels of FVR reached in response to the three dosages of SNP nor the absolute nor the percentage changes from baseline in FVR were significantly altered by 6 months of ACE inhibition. The same was true of the values achieved and changes from baseline of the FBF ratio.

By relating the changes in FVR during Mch and SNP infusion to the maximal vasodilator response during PORH, we corrected for changes in baseline values, because minimal FVR reached after ischemia is independent of baseline values (21). Nonetheless, no improvements were noted in either endothelium-dependent or endothelium-independent vasodilation.

Systemic changes during the experiments

Table 2 shows that there were no significant changes in baseline FBF ratio. Before treatment with perindopril, baseline FBF ratio ranged from 1.2 ± 0.1 to 1.3 ± 0.1. After 6-month treatment, there was a similar range of 1.0 ± 0.1 to 1.1 ± 0.1. Increases in FBF ratio during Mch and SNP infusion were strictly coupled to increases in FBF at the experimental side and were certainly not related to changes in control arm blood flow, indicating that systemic changes could not have influenced the results.

During the experiments, SBP and diastolic BP (DBP) increased significantly (p < 0.05). Before treatment, the SBP increased from 174.6 ± 7.1 to 182.7 ± 6.4 mm Hg. Likewise DBP increased from 80.8 ± 2.1 mm Hg during the first baseline recording to 87.4 ± 3.1 mm Hg during the third with placebo. The MAP showed an increase of 5.8 mm Hg (p = NS). After 6 months of treatment with perindopril equal and significant increases again occurred in SBP (145.6 ± 6.3–165.8 ± 9.2 mm Hg), DBP (75.7 ± 2.7–85.1 ± 1.8 mm Hg), and MAP (105 ± 3–118 ± 4 mm Hg) (p < 0.05). The HR showed only slight and insignificant alterations throughout the experiments.

During the experiments, the plasma glucose concentration was monitored. Before treatment the average plasma glucose level was 13.8 ± 1.3 mM at the beginning of the experiments and 10.7 ± 0.8 mM at the end, whereas after 6 months of ACE inhibition these values were 9.8 ± 1.0 and 9.0 ± 0.7 mM. At the actual timepoints of FBF measurements, plasma glucose concentrations remained within a range of 5–15 mM. The average intravascular plasma glucose variation during the tests was 2.9 mM, with a minimum of 0.7 and a maximum fluctuation of 7.3 mM.

DISCUSSION

Responses to vasodilator stimuli

The improvements after 6 months of ACE inhibition of the absolute and relative responses to ischemia (PORH) could be related to an improvement in vascular structural changes (19). According to findings in comparable studies, these changes are probably due to the ACE inhibition and not to BP reduction itself (22). Because the minimal vascular resistance as reached after ischemia is independent of baseline (23), the perindopril-induced decrease in baseline FBF cannot account for this improvement.

For the particular group of patients in our study, the minimal FVR was shown to be significantly higher as compared with that of a healthy control group (24). The decrease in the minimal FVR is therefore an improvement toward normal. This result is in accordance with the study of De Cesaris and colleagues (16), who suggested that long-term treatment with an ACE inhibitor can induce a regression of structural changes in large arteries in patients with hypertension. Therefore, our data strongly suggest a reduction of structural vascular changes, although firm conclusions cannot be drawn because our ischemic stimulus is not the optimal stimulus to assess minimal vascular resistance (23).

Although there have been contradictory reports on endothelium-dependent vasodilation in patients with type 1 diabetes mellitus (25,26), McVeigh and co-workers (12) reported impaired endothelium-dependent vasodilation in type 2 diabetic patients. As compared with healthy volunteers, our study population also showed an impaired endothelium-dependent vasodilation (24), which is supported by data of Creager and associates (11), who also used Mch as an endothelium-dependent vasodilator.

ACE inhibitors have been reported to improve endothelial function in the animal model (13,14) and, at least in the short-term, to improve endothelium-dependent vasodilation in human single-dose studies (15,27). In contradiction to our expectations, 6 months of ACE inhibition with perindopril 4 mg/day did not improve endothelium-dependent vasodilation. Probably this cannot be explained by noncompliance of the patients, because other relevant parameters such as BP and albumin excretion ratio both were significantly reduced by perindopril. Another theoretical explanation is the absence of a sulfhydryl group in perindopril. Several studies have shown that a sulfhydryl group contributes significantly to the potentiation of endothelium-dependent vasodilation (28,29). However, it has to be emphasized that some of these positive results were obtained with ACE inhibitors without a sulfhydryl group (16). Recently, Panza and colleagues (30) reported that reducing BP caused no improvement in endothelium-dependent vasodilation in hypertensive patients. Schiffrin and co-

workers (22) investigated vascular reactivity and structure in subcutaneous gluteal biopsies before and after 1 year of treatment of a group of hypertensive patients with either a β-blocker or an ACE inhibitor. Endothelium-dependent vasodilation was not improved in either group, but in the ACE-inhibited group structural changes were reduced. Apparently, potentiation of endothelium-dependent vasodilation does not occur after chronic treatment with nonsulphydryl group-containing ACE inhibitors.

Changes in baseline parameters
Figure 1 shows reductions in the baseline pulse pressure, MAP, and the HR, as well as an increase of FVR by 6 months of ACE inhibition with perindopril. These changes can be considered a trend toward normalization. High insulin levels have been reported to have vasodilator effects (31). However, it is unlikely that insulin played a role in these changes since fasting insulin concentrations were not altered by 6 months of ACE inhibition. Despite the reduced BP, baseline FVR surprisingly was significantly greater after treatment. Our results do not allow conclusions regarding the mechanisms that could explain the combination of BP decrease and FVR increase. The changes in the parameters shown in Fig. 1 might suggest changes in cardiac output or peripheral resistance, but unfortunately these were not measured. Furthermore, the microalbuminuria was significantly reduced. Serum creatinine and potassium had not changed during the 6 months of ACE inhibition, and there was no clinically relevant effect on lipids. Together, these findings are indicative of a reduction in cardiovascular risk.

Systemic parameters during the experiments
During the tests, all patients had a slight decrease in plasma glucose concentration that occurred before as well as after 6 months of ACE inhibition in an almost identical way. Fasting glucose and insulin levels as well as their ratio showed only slight changes during the 6 months of treatment. Moreover, HbA1c had not changed during treatment. Therefore, we found no arguments for an influence of perindopril on glucose metabolism, which is in accordance with the literature (32).

All values of plasma glucose concentrations were between 4.4 and 15.1 mM during measurements. Furthermore, the average intraindividual plasma glucose fluctuation during the tests was very low; therefore, it is unlikely that plasma glucose concentrations influenced the results.

Table 2 shows that the BP slightly increased during the course of the test. This increase in BP occurred during the equilibration period between the last dosage of Mch and the third baseline recording. We emphasize that these alterations in BP were similar before and after treatment and therefore could not have affected the final results.

Study limitations
The absence of a placebo group and a patient control group are limitations of the study. Yet control groups would have been of greater importance if perindopril had had significant effects on endothelium-dependent vasodilation.

We conclude that 6 months of ACE inhibition with perindopril 4 mg/day did not specifically improve endothelium-dependent vasodilation but improved the hyperemic response to an ischemic stimulus, which may indicate an improvement in structural changes in the vascular wall.

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REFERENCES


