Effects of a β-Blocker or a Converting Enzyme Inhibitor on Resistance Arteries in Essential Hypertension

Ernesto L. Schiffrin, Li Yuan Deng, Pierre Larochelle

Abstract Seventeen male untreated mild essential hypertensive patients aged 41±2 years agreed to participate in a double-blind randomized trial to test the effects of antihypertensive treatment on the structure and function of subcutaneous resistance arteries. Patients were treated with either 50 to 100 mg/d atenolol or 2.5 to 5 mg/d cilazapril. Blood pressure before treatment was 148±6/99±1 and 147±2/99±1 mm Hg, respectively. At 1 year of treatment blood pressure was 131±4/85±2 and 132±2/87±1 mm Hg, respectively. Resistance arteries (200 to 400 μm lumen diameter) dissected from subcutaneous gluteal biopsies obtained before treatment and at 1 year showed that the media-lumen ratio of arteries from patients treated with cilazapril was reduced to 6.31±0.21% from 7.54±0.31% before treatment (P<.05), still slightly but significantly larger (P<.05) than the media-lumen ratio of resistance arteries of normotensive control subjects (5.15±0.30%). In contrast, arteries from patients treated with atenolol there was no significant change with treatment (7.97±0.60% before and 8.07±0.45% after 1 year of treatment). Active wall tension responses to endothelin-1 were blunted in hypertensive patients and normalized in the cilazapril-treated patients. Depressed active media stress responses to norepinephrine, arginine vasopressin, and endothelin-1 were accordingly normalized in the patients receiving cilazapril as the media width became thinner but were unchanged in those taking atenolol. These results suggest that treatment for 1 year with the converting enzyme inhibitor cilazapril corrects in part the structural and functional abnormalities present in subcutaneous resistance arteries of patients with mild essential hypertension. (Hypertension. 1994;23:83-91.)

Key Words • angiotensin converting enzyme inhibitors • adrenergic beta receptor blockers • hypertrophy • blood vessels • hypertension, essential

Normalization of elevated blood pressure in hypertensive patients has been clearly shown to improve survival and decrease the incidence of stroke and renal and heart failure.1-3 However, most clinical trials of antihypertensive treatment have failed to show significant beneficial effects on myocardial ischemia, although meta-analyses have indeed allowed benefit to be demonstrated, albeit to a lesser degree than on the incidence of stroke.4,5 The reasons for this relative lack of success have been a matter of discussion but remain unclear. One possible explanation could be that altered vascular structure in hypertensive patients is not normalized by antihypertensive therapy. Persistent abnormalities in blood vessels, particularly in coronary arteries and arterioles, may play a role in this outcome. Alteration of large blood vessels in hypertensive patients has been clearly documented and is mainly associated with atherosclerosis.6 However, the increased peripheral resistance that characterizes high blood pressure in animals and humans is above all the consequence of alterations in the smaller arteries and arterioles, called resistance arteries.7,8 These comprise arteries smaller than 300 μm and arterioles smaller than 100 μm in lumen diameter.9 Several studies have investigated small resistance arteries in humans. The approach used has been to dissect these resistance arteries from biopsies of subcutaneous fat. This is an invasive but minor procedure, which patients find acceptable.10 These studies have demonstrated that in hypertensive patients these subcutaneous resistance arteries present a number of changes compared with those of normotensive control subjects.11-13 These differences are structural and functional. Structural differences include a reduced lumen and external diameter, a thickened media, and consequently an exaggerated media-lumen ratio. Functional differences include decreases in media stress responses to most agonists (norepinephrine, serotonin, vasopressin, and endothelin-1 but not angiotensin II); a shift to the left in the dose-response curve to norepinephrine in the presence of cocaine; a decrease in the sensitivity to calcium, suggesting depressed signal transduction; and an increased rate of relaxation. It is unclear how these abnormalities relate to the enhancement in the resistance to flow. However, it is clear that the structural abnormalities, particularly as a result of the increased media-lumen ratio, amplify vasoconstrictor responses, thus contributing significantly to exaggerated vascular tone.14

Studies in animals and humans have attempted to establish whether antihypertensive therapy may correct structural and functional abnormalities in resistance vessels. In humans, Heagerty et al15 found that antihypertensive treatment for 13 months produced some
regression of the wall media thickness, with reduction of the media-lumen ratio, whereas Aalkjaer et al, using various antihypertensive agents, were unable to demonstrate normalization of vascular structure after a median follow-up period of 14 months. In both studies there was no evidence of improvement in the functional alterations of resistance arteries of hypertensive patients. In animals such as spontaneously hypertensive rats, treatment with angiotensin I converting enzyme inhibitors or angiotensin II receptor antagonists has been shown to induce some regression of the vascular changes that are characteristic of hypertension in rats, namely, the increased media-lumen ratio and thickened media.

We decided to assess whether a prospective trial comparing two different antihypertensive agents over a prolonged period of time would allow us to establish if some but not other antihypertensive drugs may indeed induce regression of vascular changes in hypertensive patients, which might be obscured in studies in which the effects of several drugs are examined together. For this reason we performed a double-blind randomized trial that compared the effects of an angiotensin I converting enzyme inhibitor—cilazapril, which is marketed in Europe and Canada and is similar to other converting enzyme inhibitors—and a β-blocker, atenolol, on vascular structure and function of resistance vessels in mild essential hypertensive patients who were either untreated previously or had not received antihypertensive medication for at least 6 months. Patients were treated for 1 year, and resistance arteries dissected from gluteal subcutaneous fat biopsies before and after 1 year of treatment were studied.

Methods

Materials

Norepinephrine was obtained from Sigma Chemical Co, St Louis, Mo. Arginine vasopressin, isolecuine angiotensin II, and human endothelin-1 were bought from Peninsula Laboratories, Belmont, Calif. Cocaine HCl powder was provided by the pharmacy of Hôtel-Dieu Hospital and was obtained from Atlas Laboratories, Montreal, Quebec, Canada. All agents used were of the highest reagent grade available.

Patients

The protocol was approved by the Ethics Committees of the Clinical Research Institute and Hôtel-Dieu Hospital of Montreal. Written informed consent to participate in the study was obtained from each subject. Normotensive control subjects and patients with essential hypertension aged 25 to 50 years were recruited between November 1990 and February 1992. All subjects studied were male because of requirements of the Health Protection Branch, Health and Welfare Canada, relating to the potential teratogenicity of nifedipine, which would be used if goal blood pressure was not achieved with the drugs being studied. Control subjects had a normal physical examination, complete blood count and blood chemistries (sequential multiple analysis 20), and urinalysis. Their systolic blood pressure was less than 140 mm Hg or diastolic blood pressure less than 85 mm Hg. Patients were considered hypertensive when on more than two occasions their recumbent systolic blood pressure was greater than 140 mm Hg or diastolic blood pressure was greater than 90 mm Hg. They were untreated or had not received antihypertensive medication for at least 6 months. The diagnosis of essential hypertension was established by absence of clinical evidence of secondary hypertension; normal serum electrolytes, creatinine, and urinalysis; a normal abdominal echogram; and, where indicated, renal scintiscan, renal arteriogram, and computed abdominal tomography. Patients were excluded if they smoked more than five cigarettes per day, their fasting blood glucose level was abnormal, they had a serum creatinine concentration greater than 150 μmol/L, or they had any other systemic disease.

Subjects arrived between 7:30 and 9 AM, having fasted since the previous evening. Blood pressure (standard mercury sphygmomanometer) was measured after subjects had rested 15 minutes in the sitting position. Diastolic blood pressure was read as phase V of the Korotkoff sounds. After 2 hours in the supine position, venous blood was withdrawn for determination of plasma renin activity (into tubes containing a final concentration in blood of 5 mmol/L potassium edetate), serum electrolytes, creatinine, and glucose. An echocardiogram was obtained in the hypertensive patients and read by a cardiologist unaware of the protocol. Twenty-four-hour ambulatory blood pressure monitoring was recorded at hourly intervals during daytime activities (8 AM to 10 PM) in the hypertensive patients with a model 90207 ambulatory blood pressure recorder (SpaceLabs Inc, Redmond, Wash). Gluteral biopsies of subcutaneous fat of 1.5×0.5×0.5 cm were obtained by a surgeon with patients under local anesthesia. Results of the comparison of normotensive subjects and some of these hypertensive patients before treatment have already been published.

Treatmen Protocol

 Patients were randomized to treatment with either atenolol or cilazapril in a double-blind fashion. They were seen at 2-week intervals twice before treatment was started, during which time they received placebo. Drug titration was done at 2-week intervals, with atenolol provided in identical 50- and 100-mg tablets and cilazapril in 2.5- and 5-mg tablets. If patients did not achieve goal blood pressure, long-acting nifedipine was added at a dose of 10 or 20 mg twice daily. Only three patients required addition of nifedipine. Patients were then seen at monthly intervals. At the end of 1 year of treatment the patients underwent a second biopsy of gluteal subcutaneous fat as well as a second echocardiogram and ambulatory blood pressure recording. Blood chemistries and urinalysis were done at 4-month intervals.

Preparation of Small Subcutaneous Arteries

Arteries were dissected from the gluteal fat under a dissecting microscope immediately after the biopsy was obtained, and 1, 2, or up to 4 small arteries were isolated. Vessels were mounted as a ring preparation on an isometric myograph (Living Systems Instrumentation, Burlington, Vt) by threading onto two tungsten wires (20 μm diameter). The wires were attached to a force transducer and micrometer, respectively. The physiological salt solution (PSS) used had the following composition (mmol/L): NaCl, 120; NaHCO3, 25; KCl, 4.7; KH2PO4, 1.18; MgSO4, 1.18; CaCl2, 2.5; EDTA, 0.026; and glucose, 5.5.

Protocol for Study of Arteries

The vessels were warmed to 37°C and allowed to equilibrate in PSS for approximately 30 minutes with the vessel internal circumference set to give a wall tension of 0.2 mN/mm. The resting tension—internal circumference relation was determined, and vessels were set to L0, where L0=0.9 Lmax and Lmax is the internal circumference the vessels would have had in vivo when relaxed and under a transmural pressure of 100 mm Hg. Vessel wall and media thicknesses were measured at 12 sites that were then averaged, using a Leitz-Diavert inverted light microscope at ×320 magnification, which provides a resolution of 0.4 μm. Lower magnification was used for measurement of the distance between the wires and length of the blood vessel. The vessels were maintained in PSS at 37°C for a further 90 minutes and were then stimulated as follows: (1) three stimulations (2 minutes for each) with PSS in which NaCl was substituted with KCl on an equimolar basis (K-PSS)
TABLE 1. Clinical and Laboratory Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensive Subjects</th>
<th>Atenolol</th>
<th>Cilazapril</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Treatment</td>
<td>After Treatment</td>
<td>Before Treatment</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.8±0.8*</td>
<td>27.1±1.5</td>
<td>27.3±1.1</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>112.5±2.4*</td>
<td>148±6.5</td>
<td>130±3.6†</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>76.8±1.8*</td>
<td>99±0.8</td>
<td>94±0.9</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>88.9±1.6*</td>
<td>115.4±2.4</td>
<td>115.4±0.9</td>
</tr>
<tr>
<td>ASBP, mm Hg</td>
<td>...</td>
<td>151.3±5.5</td>
<td>133.4±3.3†</td>
</tr>
<tr>
<td>ADBP, mm Hg</td>
<td>...</td>
<td>99±3.0</td>
<td>85.7±1.6†</td>
</tr>
<tr>
<td>Serum Na⁺, mmol/L</td>
<td>140.5±0.6</td>
<td>137.8±0.5</td>
<td>139.5±0.46</td>
</tr>
<tr>
<td>Serum K⁺, mmol/L</td>
<td>4.48±0.15</td>
<td>4.40±0.22</td>
<td>4.12±0.05</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>99.3±2.8</td>
<td>90.2±3.2</td>
<td>91.9±4.2</td>
</tr>
<tr>
<td>Supine PRA, ng Ang I·mL⁻¹·h⁻¹</td>
<td>1.85±0.34</td>
<td>1.42±0.28</td>
<td>0.99±0.24</td>
</tr>
<tr>
<td>Supine epinephrine, ng/mL</td>
<td>...</td>
<td>0.04±0.01</td>
<td>0.04±0.01</td>
</tr>
<tr>
<td>Supine norepinephrine, ng/mL</td>
<td>0.25±0.04</td>
<td>0.20±0.03</td>
<td>0.23±0.03</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; ASBP, ambulatory systolic blood pressure; ADBP, ambulatory diastolic blood pressure; PRA, plasma renin activity; and Ang I, angiotensin I.

*P<.01 vs hypertensive patients.
†P<.01 vs before treatment.

and two stimulations with K-PSS containing 10 μmol/L norepinephrine; (2) two cumulative concentration-response curves to norepinephrine (from 0.01 to 10 μmol/L, 3 minutes per concentration), the second one obtained in the presence of 3 μmol/L cocaine·HCl; (3) a cumulative concentration-response curve to vasopressin (from 0.01 to 30 mmol/L, 3 minutes per concentration); (4) a cumulative concentration-response curve to angiotensin II (from 0.1 to 300 mmol/L, 3 minutes per concentration); and (5) a cumulative concentration-response curve to endothelin-1 (from 0.01 to 1 μmol/L, 6 minutes per concentration). After each activation, the vessels were washed with PSS for 15 minutes. Relaxation of blood vessels precontracted with 10 μmol/L norepinephrine was performed with acetylcholine (1 mmol/L to 10 μmol/L).

Biochemical Methods

Plasma renin activity was measured by radioimmunoassay of angiotensin I generated during a 2-hour incubation of plasma at 37°C and pH 5.5 in the presence of 8-hydroxyquinoline and sodium edetate. 23 Plasma catecholamines were measured by a radioenzymatic method. 24 Serum sodium, potassium, and creatinine were measured by automated methods.

Analysis of Data

Wall and media thicknesses of blood vessels were obtained assuming a constant wall and media volume, from wall and media cross-sectional area calculated from wall and media thickness measured in unstretched vessels. Using the lumen diameter of the stretched vessel (at Lw=0.9 Lmax), the wall and media thicknesses could be calculated from the respective cross-sectional areas using the equation:

$$\text{Wall or Media Thickness} = \frac{-L_w(2+4\pi A)^{1/2}}{2\pi}$$

where A is the wall or media cross-sectional area of the unstretched vessel (A=Lwm+w, where Lw is the inner circumference of the unstretched blood vessel, and m is the unstretched wall or media width). The computed wall thickness and measured lumen of stretched vessels (at 0.9 Lmax) were used to calculate outer diameter. The responses of blood vessels are expressed as active wall tension, which is the increase in wall force to stimulation divided by twice the length of the vessel segment. Active media stress is the active wall tension divided by the media thickness. From concentration-response curves, the concentration in moles per liter producing 50% of maximal response (EC50) was determined. The sensitivity to each agonist was expressed as pD2 = -log (EC50).

Results

Patient Characteristics and Blood Pressure Response

Patient demographics are depicted in Table 1. Twelve age-matched male normotensive subjects (39.6±1.7 years old) of slightly lower weight than the hypertensive patients were studied. The 8 patients randomized to atenolol and the 9 patients randomized to cilazapril treatment were similar in relation to age (42.4±1.6 and 39.1±2.3 years, respectively), body mass index, blood pressure before treatment, and blood biochemistry. Twenty-four-hour ambulatory blood pressure monitoring performed before treatment in 7 patients of the atenolol group and 6 of the cilazapril group showed similar results. Twenty-four-hour monitoring of blood pressure was not performed in the remaining patients because of a technical problem. Echocardiographic indexes were similar before treatment in both groups of
was below 140 mm Hg and diastolic below 90 mm Hg for the blood pressures of both groups. *P<.0001 vs following year. There were no statistically significant differences between the blood pressures of both groups.

Morphological Characteristics of Resistance Vessels

Resistance blood vessels dissected from biopsies of gluteal subcutaneous fat before treatment in the total group of hypertensive patients exhibited a significantly greater media-lumen ratio than those of normotensive control subjects (Table 3), as described in a previous study. The arteries dissected before antihypertensive therapy were started in the group of patients randomized to treatment with atenolol were smaller than those of patients randomized to treatment with cilazapril (Table 3). However, because media width is directly correlated to lumen diameter, media-lumen ratio remains relatively unchanged with differences in lumen diameter within the small range of diameters (200 to 400 μm) of the resistance arteries of the hypertensive patients examined in this study (r = −0.05, not significant). Thus, in view of the slight heterogeneity in vessel diameter in both groups, which may result from sampling vessels at random points in the vasculature, media-lumen ratio is the morphological parameter compared between groups rather than lumen diameter or media width (shown in Table 3) or media cross-sectional area (not shown).

After 1 year of equally effective antihypertensive treatment (Fig 1), the subcutaneous resistance arteries of the patients treated with cilazapril exhibited a media-lumen ratio which was significantly smaller than that of the arteries of untreated patients or of those treated with atenolol but was slightly but significantly greater than that of the control subjects (Table 3). The media-lumen ratio of resistance arteries of atenolol-treated patients was nearly identical before and after treatment. The arteries dissected after treatment had a significantly smaller lumen diameter in the cilazapril group and tended to have a larger diameter (although not reaching statistical significance) in the atenolol group relative to before treatment.

Function of Resistance Arteries

Wall tension responses to norepinephrine, vasopressin, and angiotensin II were similar in normotensive subjects and hypertensive patients and did not change significantly with treatment (Table 4). Wall tension responses to endothelin-1 were depressed in vessels from hypertensive patients and became normal in the group treated with cilazapril but remained depressed in the atenolol-treated group. Media stress responses of subcutaneous small arteries to norepinephrine, vasopressin, and endothelin-1 were significantly depressed in both hypertensive groups compared with normotensive subjects, whereas responses to angiotensin II were similar (Table 4). Because the media was thinner after 1 year of treatment in the group of patients treated

### Table 2. Echocardiographic Indexes of Hypertensive Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Atenolol Before Treatment</th>
<th>Atenolol After Treatment</th>
<th>Cilazapril Before Treatment</th>
<th>Cilazapril After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD, mm</td>
<td>40.0±2.8</td>
<td>39.1±1.7</td>
<td>38.1±1.9</td>
<td>39.0±1.9</td>
</tr>
<tr>
<td>LVDD, mm</td>
<td>47.7±1.2</td>
<td>49.0±1.8</td>
<td>49.4±2.1</td>
<td>51.4±1.7</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>41.5±3.0</td>
<td>35.0±3.9</td>
<td>42.0±2.9</td>
<td>40.0±2.6</td>
</tr>
<tr>
<td>IVSDd, mm</td>
<td>11.2±0.8</td>
<td>10.7±0.8</td>
<td>11.7±0.8</td>
<td>10.7±1.1</td>
</tr>
<tr>
<td>LPWd, mm</td>
<td>9.7±0.6</td>
<td>9.7±0.3</td>
<td>10.4±0.9</td>
<td>9.6±0.7</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>109.9±6.4</td>
<td>109.8±12.5</td>
<td>124.8±11.7</td>
<td>117.7±15.9</td>
</tr>
</tbody>
</table>

LAD indicates left atrial dimension; LVDD, left ventricular diastolic dimension; IVSDd, interventricular septum diastolic dimension; LPWd, left posterior wall width in diastole; and LVMI, left ventricular mass index (calculated according to the Penn convention).
TABLE 3. Morphological Characteristics of Resistance Arteries

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensive Subjects</th>
<th>Atenolol Before Treatment</th>
<th>Atenolol After Treatment</th>
<th>Cilazapril Before Treatment</th>
<th>Cilazapril After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumen diameter, μm</td>
<td>374±31*</td>
<td>219±30</td>
<td>267±35</td>
<td>306±27</td>
<td>223±25†</td>
</tr>
<tr>
<td>Media width, μm</td>
<td>18.8±1.6</td>
<td>16.7±1.4</td>
<td>21.3±3.2</td>
<td>23.3±2.8</td>
<td>13.9±1.6†</td>
</tr>
<tr>
<td>Media-lumen ratio, %</td>
<td>5.15±0.30</td>
<td>7.97±0.60†</td>
<td>8.07±0.45‡</td>
<td>7.54±0.31*</td>
<td>6.31±0.21†‡</td>
</tr>
</tbody>
</table>

Resistance arteries were successfully dissected and studied in 12 normotensive subjects, 6 patients in the atenolol group before treatment, 8 patients in the atenolol group after treatment and in the cilazapril group before treatment, and 9 patients in the cilazapril group after treatment.

*P<.05 vs both hypertensive groups combined before or after treatment.
†P<.05 vs before treatment.
‡P<.05 vs normotensive subjects.

with cilazapril, media stress responses to all agents were similar to those of normotensive subjects and significantly greater than before treatment. In contrast, the group of patients treated with atenolol did not exhibit changes after treatment with respect to results before treatment. Relative to responses of normotensive subjects, media stress responses to vasoconstrictors of vessels of atenolol-treated patients remained depressed.

Endothelial function was explored by examining the endothelium-dependent relaxation of norepinephrine-precontracted arteries in response to increasing doses of acetylcholine. Contraction induced by 10 μmol/L norepinephrine, on which the acetylcholine dose-response curve was superimposed, was similar in normotensive subjects and in both groups of hypertensive patients before and after either treatment (Table 4). Relaxation induced by acetylcholine was similar in the cilazapril and atenolol groups (81.0±8.6% and 84.1±6.5%, respectively) before and after treatment (88.2±5.9% and 75.9±9.1%, respectively) (Fig 2). Relaxation in the hypertensive patients before treatment was slightly but significantly less (P<.05) than that of the normotensive subjects similarly investigated (95.3±1.2%).

TABLE 4. Responses of Resistance Arteries to Vasoconstrictors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Agent</th>
<th>Normotensive Subjects</th>
<th>Atenolol Before Treatment</th>
<th>Atenolol After Treatment</th>
<th>Cilazapril Before Treatment</th>
<th>Cilazapril After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active wall tension, mN/mm</td>
<td>NE</td>
<td>3.94±0.41</td>
<td>2.78±0.21</td>
<td>3.00±0.29</td>
<td>4.10±0.78</td>
<td>3.61±0.74</td>
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<tr>
<td></td>
<td>NE+Co</td>
<td>3.99±0.40</td>
<td>2.91±0.26</td>
<td>3.02±0.30</td>
<td>4.02±0.68</td>
<td>3.80±0.69</td>
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<tr>
<td></td>
<td>AVP</td>
<td>3.83±0.55</td>
<td>3.11±0.31</td>
<td>3.20±0.29</td>
<td>3.53±0.59</td>
<td>4.07±0.69</td>
</tr>
<tr>
<td></td>
<td>Ang II</td>
<td>2.05±0.45</td>
<td>1.67±0.22</td>
<td>1.71±0.28</td>
<td>2.51±0.36</td>
<td>2.66±0.54</td>
</tr>
<tr>
<td></td>
<td>ET-1</td>
<td>4.78±0.32*</td>
<td>2.86±0.45†</td>
<td>3.47±0.27†</td>
<td>3.01±0.38†</td>
<td>4.34±0.73†‡</td>
</tr>
<tr>
<td>Active media stress, kPa</td>
<td>NE</td>
<td>232±30*</td>
<td>174±21</td>
<td>156±19†</td>
<td>176±16</td>
<td>221±17†</td>
</tr>
<tr>
<td></td>
<td>NE+Co</td>
<td>236±31</td>
<td>181±22†</td>
<td>159±21†</td>
<td>173±13†</td>
<td>236±13†</td>
</tr>
<tr>
<td></td>
<td>AVP</td>
<td>230±35</td>
<td>190±19†</td>
<td>170±22†</td>
<td>159±20†</td>
<td>255±21†</td>
</tr>
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<td></td>
<td>Ang II</td>
<td>122±28</td>
<td>101±12</td>
<td>96±18</td>
<td>115±14</td>
<td>164±12‡</td>
</tr>
<tr>
<td></td>
<td>ET-1</td>
<td>271±25</td>
<td>178±29†</td>
<td>174±13†</td>
<td>139±20†</td>
<td>282±38‡</td>
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<tr>
<td>pD2</td>
<td>NE</td>
<td>6.62±0.13</td>
<td>6.28±0.21</td>
<td>6.67±0.13</td>
<td>6.61±0.11</td>
<td>6.91±0.11</td>
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<tr>
<td></td>
<td>NE+Co</td>
<td>6.81±0.10</td>
<td>6.53±0.17</td>
<td>6.73±0.15</td>
<td>6.60±0.11</td>
<td>6.92±0.13</td>
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<tr>
<td></td>
<td>AVP</td>
<td>8.91±0.07</td>
<td>8.90±0.06</td>
<td>8.75±0.15</td>
<td>8.65±0.16</td>
<td>8.89±0.15</td>
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<td></td>
<td>Ang II</td>
<td>8.46±0.07</td>
<td>8.35±0.12</td>
<td>7.94±0.12‡</td>
<td>8.28±0.08</td>
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<tr>
<td></td>
<td>ET-1</td>
<td>8.23±0.11</td>
<td>7.85±0.15†</td>
<td>7.78±0.18†</td>
<td>7.68±0.10†</td>
<td>8.26±0.16†‡</td>
</tr>
</tbody>
</table>

NE indicates norepinephrine; Co, cocaine; AVP, arginine vasopressin; Ang II, angiotensin II; and ET-1, endothelin-1.

*P<.05 vs both hypertensive groups combined before treatment.
†P<.05 vs normotensive patients.
‡P<.05 vs before treatment.
Discussion

This double-blind randomized clinical trial on the effect of two antihypertensive drugs, the \( \beta \)-blocker atenolol and the angiotensin I converting enzyme inhibitor cilazapril, on the structure and function of resistance arteries of hypertensive patients suggests that certain drugs may have specific effects on blood vessels in hypertension, presumably independently of the beneficial action of lowering blood pressure. The results of the study show that although structural characteristics, namely, the media-lumen ratio, and functional characteristics, the responses to several vasoconstrictor agents, regressed toward normal under cilazapril treatment, they remained unchanged under atenolol treatment. These results do not allow us to establish whether the vascular effects of cilazapril, an angiotensin I converting enzyme inhibitor marketed in Canada and Europe and similar to other drugs of its class, will also be produced by other angiotensin I converting enzyme inhibitors nor whether the lack of effect of atenolol is shared by other \( \beta \)-blockers.

The mechanism for the effect of cilazapril on vascular structure is unclear but could be related to the reduction in angiotensin II concentrations in plasma and tissues occurring as a result of treatment with converting enzyme inhibitors. Previous studies have demonstrated in vitro that angiotensin II is a mitogen, which could be responsible for smooth muscle hyperplasia, and that it increases protein synthesis, which can result in hypertrophy of vascular smooth muscle. Infusion of angiotensin II into rats results in increased media-lumen ratio due to remodeling of the media thickness but little significant change in functional abnormalities. Aalkjaer et al have shown in another study that in 13 hypertensive patients with a mean age of 53 years, treated with different antihypertensive agents for 3 to 66 months (median of 14 months), vascular structural and functional changes in hypertensive patients were not normalized. These studies, however, used several antihypertensive agents, thus potentially diluting the specific beneficial effects of individual drugs. Taken together, these previous reports, as well as the experimental animal data and the present study allow us to conclude that regression of structural vascular abnormalities at the level of resistance arteries can occur in hypertensive patients treated effectively for 1 year with converting enzyme inhibitors such as cilazapril.

We have previously reported that resistance arteries of the mesenteric circulation of most hypertensive models in the rat exhibit the characteristic of having not only a smaller lumen and greater media-lumen ratio but also a smaller outer diameter. This phenomenon was first described by Baumbach and Heistad in pial arteries of stroke-prone spontaneously hypertensive rats and was called "remodeling." The nature of vascular remodeling in hypertension is controversial and may be different in experimental animals, in which growth or hypertrophy or hyperplasia may play an important role.
in producing an increase in the media mass, whereas in human essential hypertension the predominant phenomenon in resistance arteries appears to be mainly a rearrangement of cellular and interstitial elements resulting in a smaller vessel (remodeling) with little vascular hypertrophy. When considered together, both groups of hypertensive patients exhibited this remodeling of their subcutaneous resistance arteries compared with normotensive control subjects. The resistance arteries of the cilazapril-treated patients had a smaller outer diameter after treatment compared with before treatment and compared with normotensive subjects or the arteries of the atenolol-treated patients. As a result of random sampling, possibly at different points in the vasculature, it is unclear whether this is indicating a sampling bias or whether it is the result of treatment. In contrast to resistance arteries from the mesenteric circulation of the rat, which are obtained from exactly the same spot in each rat, resistance arteries in these patients are obtained by dissection of a skin biopsy in which the artery or two or occasionally three that are found in the sample are used for the study without consideration of diameter (as long as they are between 200 and 400 μm in lumen diameter). As a result, the lumen diameter, or for that matter the media width and media cross-sectional area of the arteries (the latter correlating directly to vessel diameter), may be valid parameters only when many patients are examined. In contrast, because media width increases with increasing lumen diameter, media-lumen ratio is a parameter that is independent of vessel diameter within the limited range of diameters studied (see Reference 30 and this study). Thus, media-lumen ratio is a valid parameter, not subject to sample bias, and the only one adequate for evaluation of regression of vascular changes in a study such as the present one, whereas media width, media cross section, and lumen diameter may not be. On the other hand, if the smaller outer diameter of vessels from cilazapril-treated patients were the result of a drug effect and not of sampling bias, which remains to be proved, it could be a consequence of the inhibition of generation of angiotensin II and reduction of its trophic, proliferative, or hypertrophic effect. It could be the equivalent at the level of these subcutaneous small arteries from hypertensive patients of findings in renin-dependent two-kidney, one clip Goldblatt hypertensive rats, in which another converting enzyme inhibitor, captopril, produced an increase in the rarefaction of muscular arterioles, an atrophic response probably resulting from the disappearance of the trophic effect of angiotensin II under the effects of converting enzyme inhibition.

Treatment with cilazapril resulted in a correction to normal of wall tension development of these small subcutaneous arteries in response to endothelin-1. The mechanism underlying this effect is unclear. We have previously reported in renal hypertensive rats that cilazapril treatment normalized depressed endothelin-1 responses in resistance arteries at the same time that media-lumen ratio was normalized together with effective lowering of blood pressure. Responses to other agents were also improved, mainly when media stress responses were evaluated, as in this study. As the wall media was thinner, the calculated media stress may exaggerate the improvement in responses to agents other than endothelin-1. If media stress rather than tension reflects myofilament contractility, this may indicate that correction of structural abnormalities may be associated with nonspecific regression of smooth muscle contractility to normal, thus reverting the generalized depression in smooth muscle function found in previous studies of vessels from hypertensive animals or humans.

In studies examining large arteries in experimental and human hypertension, endothelial function has been shown to be altered, particularly in relation to acetylcholine-induced relaxation. In the current study acetylcholine relaxed norepinephrine precontracted blood vessels slightly but significantly less in both groups of hypertensive patients than in the normotensive subjects. Thus, in mild essential human hypertension, endothelium-dependent relaxation induced by acetylcholine in resistance arteries may be only slightly reduced or even normal, as found by other investigators using techniques similar to those of this study. In the present work we did not examine endothelium-dependent relaxation stimulated by other agonists such as bradykinin. The absence of contractions in response to acetylcholine suggests that in these small arteries there is no generation of endothelium-derived contracting factor, an endoperoxide or other product of the enzyme cyclooxygenase, which is released in response to high doses of acetylcholine in large and small arteries of spontaneously hypertensive rats. Although treatment did not produce any significant changes, there appeared to be a trend toward an increased relaxation after 1 year of treatment in the arteries of the cilazapril-treated patients (from 81% to 88%) compared with the atenolol-treated group (from 84% to 76%), although this did not achieve statistical significance. These findings agree in part with a previous study in which cilazapril was shown to improve endothelium-dependent relaxation of aorta in spontaneously hypertensive rats, apparently through increase in the release or action of endothelium-derived relaxing factor.

Although in this study we found changes in the structure and function of resistance arteries with treatment, no change occurred in echocardiographic indexes. The patients studied exhibited little evidence of cardiac hypertrophy. Indeed, five patients in the group treated with cilazapril had a slight increase in left ventricular mass, whereas only three in the group treated with atenolol had increased left ventricular mass and one a thickened posterior wall. This relates to the mild characteristic of the blood pressure elevation in the group of patients recruited for this study, in part a result of the requirement that patients should have been untreated for at least 6 months when entered into the study. As a result, it would not be expected to find significant echocardiographic changes despite effective treatment. On the other hand, the presence of vascular abnormalities at the level of resistance arteries in the presence of only mild manifestations of left ventricular hypertrophy is not surprising, because increased media thickness is already present in subcutaneous resistance arteries with a lumen diameter of 200 to 300 μm from normotensive offspring of hypertensive parents.

In conclusion, this study demonstrates that administration of cilazapril, an angiotensin I converting enzyme inhibitor, with effective control of blood pressure for a year, produces regression of structural and functional
abnormalities of resistance arteries in mild essential hypertension. In contrast, the β-blocker atenolol does not significantly affect the alterations in resistance blood vessel structure and function. Whether this "reverse remodeling" translates into improvement in outcome of hypertensive patients treated with cilazapril or other converting enzyme inhibitors remains to be determined.

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Effects of a beta-blocker or a converting enzyme inhibitor on resistance arteries in essential hypertension.

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