Effects of Antihypertensive Therapy on Mechanics of Cerebral Arterioles in Rats

Michael A. Hajdu, Donald D. Heistad, and Gary L. Baumbach

The purpose of this study was to examine effects of antihypertensive treatment on structure and mechanics of cerebral arterioles and the incidence of stroke in stroke-prone spontaneously hypertensive rats (SHRSP). Treatment of hypertension was begun at 3 months of age with cilazapril (45 mg/kg/day), an angiotensin converting enzyme (ACE) inhibitor, or with hydralazine (18 mg/kg/day). Cilazapril and hydralazine reduced systolic arterial pressure (from 195±8 to 125±5 and 148±3 mm Hg, respectively [mean±SEM]; p<0.05). To examine structure and mechanics of cerebral arterioles, we measured pressure (servonull), external diameter, and cross-sectional area of the vessel wall (histologically) in pial arterioles of normotensive Wistar-Kyoto (WKY) rats and SHRSP that were untreated or that were treated for 3 months with cilazapril or with hydralazine. Arterioles were maximally dilated with EDTA. In WKY rats, cilazapril and hydralazine did not alter pial arteriolar pressure, external diameter, or cross-sectional area of the vessel wall. In SHRSP, both cilazapril and hydralazine reduced cross-sectional area of the vessel wall to levels not significantly different from WKY rats (from 1,911±155 to 1,244±101 and 1,138±59 μm² respectively, compared with 1,405±95 μm² for untreated WKY rats). Cilazapril was more effective than hydralazine in reducing pial arteriolar pressure (from 110±6 to 62±2 mm Hg with cilazapril versus 79±5 mm Hg for hydralazine compared with 60±4 mm Hg for untreated WKY rats). Cilazapril, but not hydralazine, attenuated reductions in external diameter of pial arterioles (from 91±4 to 100±4 μm for cilazapril versus 91±3 μm for hydralazine compared with 107±3 μm for untreated WKY rats). Stress-strain curves indicate that cilazapril was more effective than hydralazine in attenuating increases in distensibility of pial arterioles in SHRSP. Both treatments prevented the occurrence of stroke in SHRSP, whereas eight of 15 untreated SHRSP developed strokes. Thus, both an ACE inhibitor and hydralazine prevented hypertrophy of cerebral arterioles and stroke in SHRSP, even though the ACE inhibitor was more effective than hydralazine in lowering intra-arteriolar pressure. In contrast, only the ACE inhibitor attenuated increases in distensibility and "remodeling" (reduction in external diameter) of cerebral arterioles, perhaps due to its greater efficacy in reducing pial arteriolar pressure at the doses used in this study. These findings suggest that determinants of distensibility and vascular remodeling may be different from determinants of vascular hypertrophy. (Hypertension 1991;17:308–316)

Chronic hypertension alters the composition and mechanics of both large and small cerebral blood vessels. Large cerebral arteries undergo hypertrophy, with an increase in collagen content, and compliance is reduced in spontaneously hypertensive rats (SHR)1,2 and stroke-prone SHR (SHRSP).3,4 In contrast, compliance of cerebral arterioles is paradoxically increased in SHRSP.5 As the proportion of distensible components is increased,6 hypertrophy of the vessel wall,5 as the proportion of distensible components is increased.6

Recently, we have suggested that external diameter is reduced in cerebral arteries of SHRSP, even during maximal dilatation.7 We have termed this phenomenon "remodeling" to differentiate it from effects of vascular hypertrophy per se. Encroachment on the lumen of cerebral arterioles appears to be related primarily to reductions in external diameter.

Roche and Co. G.B. is the recipient of an Established Investigatorship Award from the American Heart Association.

This manuscript from the University of Iowa was sent to Henry W. Overbeck, Consulting Editor, for review by expert referees, for editorial decision, and final disposition.

Address for correspondence: Michael A. Hajdu, PhD, Department of Pathology, 122 Medical Laboratories, University of Iowa College of Medicine, Iowa City, IA 52242.
and not to hypertrophy per se. Thus, remodeling may be a major determinant of impaired maximal dilatation of cerebral arterioles in SHRSP.

Treatment of chronic hypertension attenuates the development of cerebral vascular hypertrophy. Effects of antihypertensive treatment on mechanics and remodeling of cerebral arterioles have not been examined.

The first goal of this study was to examine effects of the angiotensin converting enzyme (ACE) inhibitor cilazapril and of hydralazine on the development of hypertrophy of cerebral arterioles in SHRSP. Our hypothesis was that an ACE inhibitor would attenuate arteriolar hypertrophy because ACE inhibitors prevent vascular hypertrophy in several vascular beds and in large cerebral arteries. In contrast, hydralazine does not prevent hypertrophy in other vascular beds. The second goal was to determine whether antihypertensive treatment attenuates reductions in external, as well as internal, diameter of cerebral arterioles. Because reductions in external diameter can be accompanied by hypertrophy of the vessel wall, we predicted that if antihypertensive treatment prevented hypertrophy, it would also prevent remodeling. The third goal was to determine whether treatment of SHRSP with an ACE inhibitor or with hydralazine attenuates increases in distensibility of pial arterioles in SHRSP. Our hypothesis was that prevention of hypertrophy might prevent increases in arteriolar distensibility. The fourth goal was to examine effects of antihypertensive treatment on the development of stroke in SHRSP.

Methods

Mechanics

Experiments were conducted on male Wistar-Kyoto (WKY) rats and male SHRSP. At 3 months of age, both the WKY rats and SHRSP were divided into three treatment groups: a control group that drank distilled water (n=8 in WKY rats, n=12 in SHRSP), a group that received cilazapril (500 mg/l; n=4 in WKY rats, n=11 in SHRSP) through the drinking water, and a group that received hydralazine (100 mg/l; n=4 in WKY rats, n=9 in SHRSP) through the drinking water. Rats in the cilazapril and hydralazine groups drank approximately 30 and 60 ml water/day, whereas the dosages of cilazapril and hydralazine were approximately 45 and 18 mg/kg per day, respectively. Animals were allowed free access to food, housed at 25°C, and exposed to a 12-hour light/dark cycle each day. Systolic blood pressure was measured in all rats at 2-week intervals during the first month of the experiment and then monthly thereafter. Experiments were conducted when the animals reached approximately 6 months of age.

Animals were weighed and then anesthetized with sodium pentobarbital (5 mg/100 g body wt i.p.), intubated, and mechanically ventilated with room air and supplemental O2. Paralysis of skeletal muscle was obtained with gallamine triethiodide (20 mg/kg i.v.). Because the animals were paralyzed, we evaluated them frequently for adequacy of anesthesia. Additional anesthesia (1.7 mg/100 g body wt i.v.) was administered when pressure to a paw evoked a change in blood pressure or heart rate.

A catheter was inserted into a femoral vein for injection of drugs and fluids. A catheter was inserted into a femoral artery to record systemic arterial pressure and obtain blood samples for measurement of arterial blood gases, and a catheter was inserted into the other femoral artery to withdraw blood to produce hypotension.

Measurement of pial arteriolar pressure and diameter.

We measured pressure and diameter of first-order pial arterioles through an open skull preparation. The head was placed in an adjustable head holder, and a 1 cm incision was made in the skin to expose the skull. The skin edges were retracted with sutures, and ports were placed for inflow and outflow of artificial cerebrospinal fluid (CSF). A craniotomy was made over the left parietal cortex, and the dura was incised to expose cerebral vessels. The exposed brain was continuously sfused with artificial CSF, warmed to 37°-38°C, and equilibrated with a 5% CO2-95% N2 gas mixture. The composition of the CSF was (mM) KCl 3.0, MgCl2 0.6, CaCl2 1.5, NaCl 131.9, NaHCO3 24.6, urea 6.7, and dextrose 3.7.5 Pial arteriolar pressure was measured continuously with a micropipette connected to a servonull pressure measuring device (model 5, Instrumentation for Physiology and Medicine, Inc., San Diego, Calif.). Pipettes were sharpened to a beveled tip of 3-5 µm in diameter, filled with 1.5 M sodium chloride, and inserted into the lumen of a pial arteriole with a micromanipulator. The presence of the pipette tip in the vessel had no discernible effect on diameter of pial arterioles.

Pial vessels were monitored through an Olympus microscope (×10 objective) (Lake Success, N.Y.) attached to a closed-circuit video system consisting of a television camera, a time-date generator, a videotape recorder, and a video monitor. Final magnification of the video image was ×356. Pial arteriolar diameter was measured from videotapes using a Bioquant image analyzing system (R&M Biometrics, Inc., Nashville, Tenn.). The Bioquant system consists of an Apple Il computer, a videoboard, a digitizing pad, and software. We have determined previously that the precision of the Bioquant system ranges from 0.4 to 0.6 µm.

Experimental protocol. About 20-30 minutes after completion of surgery, measurements of pial arterioles were obtained under baseline conditions. Vascular smooth muscle was then deactivated by suffusion of pial vessels with artificial CSF containing EDTA (67 mM), which produces complete deactivation of smooth muscle in pial arterioles. To obtain pressure-diameter relations in deactivated pial arterioles, hemorrhage was used to reduce pial arteriolar pressure in decrements of 10 mm Hg at pressures between 70 and 10 mm Hg. After each pressure step,
arteriolar diameter achieved a steady state within 15 seconds. Inner diameter was measured approximately 30 seconds later.

After the last pressure step, blood was reinfused to restore pial arteriolar pressure to control levels. Suffusion of pial vessels with artificial CSF containing EDTA was stopped, and the maximally dilated arterioles were fixed at physiological pressure in vivo by suffusion of vessels with glutaraldehyde fixative (2.25% glutaraldehyde in 0.10 M cacodylate buffer) while pial arteriolar pressure was maintained at baseline levels. Arterioles were considered to be adequately fixed when blood flow through the arteriole had ceased.

After the animal was killed by an injection of potassium chloride, the arteriolar segment used for pressure–diameter measurements was removed with a microsurgical knife. Fixed arterioles were processed, embedded in Spurr’s medium while cross-sectional orientation was maintained, and sectioned at 1 μm. Sections were examined with a light microscope attached to the Bioquant image analyzing system described above. Lumen and total (lumen plus vessel wall) cross-sectional areas of the arteriole were measured with the digitizing pad by tracing the inner and outer edges of the vessel wall. Cross-sectional area of the arteriolar wall was calculated by subtraction of luminal cross-sectional area from total cross-sectional area.

Calculation of mechanical characteristics. Circumferential stress (σ) was calculated from

\[ \sigma = (PAP - PAD) / (2WT) \]

where PAP is pial arteriolar pressure, PAD, is inner diameter of pial arterioles, and WT is wall thickness. Pial arteriolar pressure was converted from millimeters of mercury to newtons per square meter (1 mm Hg = 1.334 × 10^2 N/m²). Because volume of the vessel wall does not change during changes in intravascular pressure,¹⁹,²₀ we assumed that cross-sectional area of the vessel wall remains constant with changes in arteriolar diameter. Thus, wall thickness can be calculated from cross-sectional area and inner pial arteriolar diameter:

\[ WT = [(4CSA/\pi + PAD^2)^{1/2} - PAD] / 2 \]

where CSA is cross-sectional area. Histological determinations of cross-sectional area were used in all calculations of wall thickness and circumferential stress.

Circumferential strain (ε) was calculated as

\[ \varepsilon = (PAD - PAD_0) / PAD_0 \]

where \( PAD_0 \) is original diameter. Original diameter has been defined as the diameter at very low or 0 mm Hg pressure with the vessel extended to in situ length.²⁰,²¹ Blood flow through pial arterioles at 10 mm Hg of pial arteriolar pressure was adequate to maintain an intact red blood cell column. Because reduction of pressure to 0 mm Hg stops blood flow and because passive vascular collapse is likely at 0 mm Hg, it was not possible to obtain reliable measurements of inner diameter of pial arterioles at 0 mm Hg. Therefore, we calculated strain using diameter at 10 mm Hg as the original diameter.

To obtain tangential elastic modulus, the stress–strain data from each animal were fitted to an exponential curve (\( y = ae^{bx} \)) using least-squares analysis:

\[ \sigma = \sigma_e e^{\beta \varepsilon} \]

where \( \sigma_e \) is stress at original diameter and \( \beta \) is a constant that is related to the rate of increase of the stress–strain curve. Tangential elastic modulus (Eₜ) was calculated at several different values of stress from the derivative of the exponential curve:

\[ E_t = d\sigma / d\varepsilon = \beta \sigma_e \varepsilon \]

Mortality and Stroke

At 4 weeks of age, 46 male SHRSP (in addition to those in which vascular mechanics were studied) were divided into three treatment groups: a control group that received 1% saline drinking water (n = 15), a group that received drinking water containing 1% saline and cilazapril (500 mg/l; n = 15), and a group that received drinking water containing 1% saline and hydralazine (100 mg/l; n = 16). Rats in the cilazapril and hydralazine groups drank approximately 30 and 60 ml water/day, respectively. Thus, the dosages of cilazapril and hydralazine were approximately 45 mg/kg per day and 18 mg/kg per day, respectively. Animals were allowed free access to food (Japanese rat chow, Funabashi Farms, Chiba-Ken, Japan), housed at 25°C, and exposed to a 12-hour light/dark cycle each day. Systolic blood pressure was measured in all rats with a tail-cuff measuring device (ITC, Woodland Hills, Calif.) every 2 weeks during the first 2 months of the study and then monthly thereafter.

Cages were inspected daily for rats that had died or were exhibiting abnormal behavior. When rats died, the brains were removed and placed in 10% buffered formalin. The brain of each rat was cut into eight to 10 coronal sections of equal thickness and examined grossly for evidence of hemorrhage, infarction, or both. The sections were then embedded in paraffin and sectioned at 5–7 μm, stained with hematoxylin and eosin, and examined microscopically. Lesions were classified as hemorrhages if the hemorrhage was apparent grossly and extensive ischemic damage was not seen histologically. Lesions were classified as infarcts when they demonstrated histological evidence of ischemia, which included cytoplasmic eosinophilia and nuclear pyknosis in neurons, loss of neurons, the presence of neutrophils, macrophages, and reactive astrocytes, vascular proliferation, and a decrease in tissue density. All surviving rats were killed at 8 months of age.

Statistical Analysis

Systolic pressures were compared with analysis of variance. Pressure–diameter curves were compared with repeated-measures analysis. Comparison of re-
TABLE 1. Baseline Values

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Cilazapril</th>
<th>Hydralazine</th>
<th>Untreated</th>
<th>Cilazapril</th>
<th>Hydralazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animals (n)</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>12</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>414±8</td>
<td>418±13</td>
<td>413±7</td>
<td>346±10*</td>
<td>325±8*</td>
<td>328±8*</td>
</tr>
</tbody>
</table>

**Before deactivation of smooth muscle**

| Mean arterial pressure (mm Hg) | 106±4 | 97±6 | 103±2 | 195±4* | 115±2† | 162±6†† |
| Pial arteriolar pressure (mm Hg) | 60±4 | 59±4 | 59±1 | 110±6* | 62±2† | 79±5†† |
| Mean Pulse | 24±2.1 | 21±3.2 | 22±3.2 | 36±1.8* | 19±1.9† | 18±1.9† |
| Pial arteriolar diameter (μm) | 54±2 | 54±4 | 55±4 | 44±3* | 43±4* | 39±2* |

**Arterial blood gases**

| PO2 | 115±10 | 103±5 | 108±7 | 110±3 | 108±6 | 116±5 |
| PH | 7.36±0.02 | 7.32±0.01 | 7.33±0.02 | 7.35±0.01 | 7.34±0.01 | 7.35±0.01 |
| PCO2 | 40±0.3 | 39±0.3 | 36±1.5* | 36±0.8* | 34±0.9* | 36±1.0* |

**After deactivation of smooth muscle**

| Pial arteriolar diameter (μm) | Internal | 98±3 | 95±5 | 96±3 | 78±4* | 91±4† | 81±2†† |
| External | 107±3 | 103±6 | 105±3 | 91±4* | 100±4† | 91±3†† |
| Cross-sectional area (μm²) | 1,405±95 | 1,353±209 | 1,407±58 | 1,911±155* | 1,244±101† | 1,388±159† |

All values are mean±SEM. Diameter was measured in deactivated arterioles at 70 mm Hg. PO2, partial pressure of oxygen; PCO2, partial pressure of carbon dioxide.

*p<0.05 vs. untreated Wistar-Kyoto (WKY) rats.
†p<0.05 vs. untreated stroke-prone spontaneously hypertensive rats (SHRSP).
‡p<0.05 vs. cilazapril-treated SHRSP.

measurements of stress to strain and tangential elastic modulus to stress was performed with regression analysis. Measurements of pressure, diameter, and cross-sectional area of the vessel wall were compared by using analysis of variance.

**Results**

**Vascular Mechanics**

**Before deactivation.** In WKY rats, weight and mean arterial pressure were not significantly altered by either cilazapril or hydralazine (Table 1). Treatment had no significant effect on weight in SHRSP (Table 1). Blood gases were similar in all animals, except that PCO2 was significantly elevated in the control and cilazapril-treated WKY rats. This difference is unlikely to have affected our results because all of the diameter measurements used in our calculations were taken after the vessel had been deactivated with EDTA. Systolic arterial pressure in SHRSP was reduced by both cilazapril and hydralazine (Figure 1). During the last month of treatment, reductions in systolic pressure were greater in the cilazapril group than in the hydralazine group. Furthermore, mean arterial pressure at the time of the terminal study was significantly less in the cilazapril group than in the hydralazine group (Table 1). Thus, at the doses that were used in this study, cilazapril was more effective than hydralazine in reducing arterial pressure in SHRSP.

In WKY rats, cilazapril and hydralazine had no significant effect on pial arteriolar pressure (Table 1). In SHRSP, cilazapril reduced pial arteriolar mean and pulse pressures in SHRSP to levels that were not significantly different from untreated WKY rats (Table 1). Hydralazine reduced mean pial arteriolar pressure significantly, but not to levels seen in untreated WKY rats. Treatment with both cilazapril and hydralazine, however, reduced pial pulse pressure to levels similar to untreated WKY rats (Table 1). Thus, both cilazapril and hydralazine were effective in reducing pial pressure in SHRSP, but cilazapril was more effective than hydralazine in reducing pial arteriolar mean pressure.

**Figure 1.** Line graph showing systolic blood pressure of stroke-prone spontaneously hypertensive rats in studies of vascular mechanics. U, untreated (n=12); H, hydralazine treated (n=11); C, cilazapril treated (n=9). Values are mean±SEM. *p<0.05 vs. untreated; †p<0.05 vs. hydralazine.
Diameters of pial arterioles before deactivation with EDTA were significantly less in SHRSP than in untreated WKY rats. Neither cilazapril nor hydralazine had significant effects on arteriolar diameter in WKY rats or SHRSP (Table 1).

After deactivation. During deactivation of pial arterioles with EDTA, internal and external diameters were significantly less in untreated SHRSP than in untreated WKY rats (Table 1). Cross-sectional area of the vessel wall was significantly greater in untreated SHRSP than in untreated WKY rats (Table 1). Cilazapril and hydralazine did not significantly alter diameter and cross-sectional area of the vessel wall in WKY rats. In SHRSP, cilazapril, but not hydralazine, increased internal and external diameter. Both cilazapril and hydralazine reduced cross-sectional area of the vessel wall in SHRSP. Thus at the doses given, an ACE inhibitor, but not hydralazine, attenuated reductions of internal and external diameter in SHRSP, whereas both an ACE inhibitor and hydralazine prevented hypertrophy of the vessel wall.

In WKY rats, cilazapril and hydralazine had no significant effect on the pressure-diameter relation (Figure 2), the stress–strain relation (Figure 3), or elastic modulus versus stress (Table 2) in deactivated pial arterioles. In SHRSP, the pressure–diameter relation was shifted upward by cilazapril, but not hydralazine (Figure 2). The stress–strain curves in both the cilazapril and hydralazine groups were shifted to the left of the curve in the untreated group, and the shift was significantly greater in the cilazapril group (Figure 3). The slope of tangential elastic modulus versus stress was less in untreated SHRSP than in untreated WKY rats (Table 2). Treatment with cilazapril, but not hydralazine, significantly increased the slope of tangential elastic modulus versus stress in SHRSP (Table 2). These findings suggest that, at the doses used in this study, cilazapril was more effective than hydralazine in attenuating increases in distensibility of cerebral arterioles in SHRSP.

Mortality and Stroke

In the untreated group, eight of 15 SHRSP died before 8 months of age (Figure 4, right panel). Evidence of cerebral infarction was found in five of eight rats that died and three of seven that survived 8 months. None of the brains showed significant hemorrhages. Cilazapril and hydralazine significantly reduced pressure in SHRSP (Figure 4, left panel). After 5 weeks of treatment, and continuing until the termination of the study, systolic blood pressure was significantly lower in the cilazapril group than in the...
Table 2. Slope of Tangential Elastic Modulus Versus Stress

<table>
<thead>
<tr>
<th>Rat strain</th>
<th>Untreated</th>
<th>Cilazapril</th>
<th>Hydralazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY</td>
<td>6.18±0.30</td>
<td>6.54±0.58</td>
<td>5.72±0.30</td>
</tr>
<tr>
<td>SHRSP</td>
<td>4.66±0.18*</td>
<td>5.40±0.30*</td>
<td>4.79±0.20*</td>
</tr>
</tbody>
</table>

All values are ×10⁵ N/m² (mean±SEM).
*p<0.05 vs. untreated Wistar-Kyoto (WKY) rats.
†p<0.05 vs. untreated stroke-prone spontaneously hypertensive rats (SHRSP).

Hydralazine group. All rats in the cilazapril and hydralazine groups survived until 8 months of age (Figure 4, right panel). There were no infarcts or hemorrhages found in any of the brains in either treatment group. Thus, cilazapril and hydralazine reduce systolic pressure and protect SHRSP from death and stroke.

Discussion

There were four major findings in this study. First, both cilazapril and hydralazine prevented hypertrophy of pial arterioles in SHRSP, even though the ACE inhibitor was more effective than hydralazine in reducing mean arteriolar pressure. Second, cilazapril but not hydralazine attenuated reductions in external diameter of pial arterioles in SHRSP. Third, cilazapril was more effective than hydralazine in attenuating increases in distensibility of cerebral arterioles in SHRSP. Differences in effects of treatment on distensibility and external diameter may be related to the different levels of mean arterial pressure that were obtained in SHRSP during treatment with cilazapril and hydralazine in the doses used in this study. Fourth, treatment of hypertension with either cilazapril or hydralazine reduced the incidence of stroke in SHRSP.

Consideration of Methods

An important consideration in this study is that hydralazine used was not as effective as cilazapril in reducing mean and systolic arterial pressure. The dose of hydralazine used in this study has been shown to normalize pressure in SHR,15-17.22 and when used in combination with hydrochlorothiazide, hydralazine reduces pressure in SHRSP to about the same level as found in WKY rats.23,24 We considered adding hydrochlorothiazide to hydralazine because hydrochlorothiazide enhances the antihypertensive effects of hydralazine. However, hydrochlorothiazide has important effects on the renin-angiotensin system.25,26 Angiotensin II stimulates hyperplasia of vascular smooth muscle cells in culture27,28 and is thought to stimulate vascular hypertrophy in vivo independently of its pressor effects.12 Because the goal of this study was to compare effects of an ACE inhibitor with a vasodilator, we chose not to add hydrochlorothiazide or other antihypertensive agents to hydralazine.

Treatment of hypertension with hydralazine also alters the renin-angiotensin system.29-31 Plasma renin activity is increased, perhaps as a result of increased activity of sympathetic nerves.31 An increase in renin and angiotensin levels, however, would be expected to stimulate12,27,28 rather than prevent vascular hypertrophy. Thus, prevention of cerebral vascular hypertrophy by hydralazine in this study occurred despite the propensity for hydralazine to stimulate the renin-angiotensin system. Although hydralazine did not lower mean arterial pressure as effectively as cilazapril at the dosage used, it was equally effective in preventing vascular hypertrophy.

The method we used to examine mechanics of pial arterioles takes into account several factors that could compromise our calculations of stress, strain, and tangential elastic modulus. These factors, which include plasma skimming, effectiveness of smooth muscle deactivation, compressibility of the wall, and definition of original diameter in the determination of strain, have been considered in detail previously and are unlikely to significantly affect the accuracy of our measurements.5

Hypertrophy

Hypertension is associated with hypertrophy of cerebral blood vessels.5,6,32 Mechanisms that may contribute to cerebral vascular hypertrophy in SHRSP include hypertension per se,33,34 genetic factors,35,36 neural influences,32,37,38 and humoral factors,28,39-41 The finding that reduction of hypertension reverses medial hypertrophy in aorta,11 large cerebral arteries,14 and cremaster arterioles42 of rats.
suggests that increases in pressure play an important role in the development of vascular hypertrophy during chronic hypertension. However, hypertrophy of non-cerebral vessels and increases in mean arterial pressure can occur independently. The ACE inhibitor captopril reduces hypertrophy of cremaster arterioles without reducing pressure in one-kidney, one clip hypertensive rats. Furthermore, angiotensin has been shown to stimulate hyperplasia of vascular smooth muscle cells in culture. These findings suggest that angiotensin may stimulate vascular hypertrophy independent of its pressor effect. In this study, therefore, prevention of arteriolar hypertrophy in SHRSP by cilazapril may have resulted from suppression of the trophic effects of angiotensin II as well as reductions in intravascular pressure. Our finding that hydralazine prevented hypertrophy of cerebral arterioles in SHRSP, even though it did not normalize mean arterial pressure, suggests that other factors in addition to mean arterial pressure may have contributed to hydralazine's effectiveness in preventing hypertension. One possibility relates to effects of antihypertensive treatment on pulse pressure. The finding in this study that hydralazine reduced pial arteriolar pulse pressure but not mean pressure in SHRSP to the same level found in untreated WKY rats suggests that increases in pulse pressure during chronic hypertension may be an important determinant of hypertrophy of cerebral arterioles. This possibility also is supported by the finding in a previous study that coarctation of the aorta, which decreases aortic pulse pressure but not mean pressure, reduces aortic mass distal to the site of coarctation. We cannot rule out the possibility, however, that the effect of antihypertensive treatment on pulse pressure is due to differences in the level of anesthesia, perhaps related to the different effects of cilazapril and hydralazine.

Remodeling

We have shown in a previous study that external, as well as internal, diameter is smaller in cerebral arterioles of 10-month-old SHRSP with established hypertension than in age-matched WKY rats. In contrast, external diameter is not significantly different in 3-month-old SHRSP and WKY rats. Furthermore, external diameter in SHRSP is significantly less at 10–12 months of age than at 3 months of age. Based on these findings, we suggested that arterioles of SHRSP undergo remodeling with a reduction in both internal and external diameter during the onset of chronic hypertension. The findings also indicate that diameter of cerebral arterioles are not inherently smaller in SHRSP than in WKY rats.

This study confirms our previous finding that external, as well as internal, diameter is reduced in SHRSP. The finding in this study that external diameter in SHRSP treated with cilazapril was greater than that in untreated SHRSP and was similar to that in untreated WKY rats suggests that antihypertensive therapy may attenuate reductions in external diameter of cerebral arterioles that would otherwise occur during chronic hypertension.

Of interest in this study is the finding that cilazapril, but not hydralazine, attenuates reductions in external diameter, even though both cilazapril and hydralazine prevent hypertrophy. This finding suggests that remodeling of cerebral arterioles may occur independent of hypertrophy. Furthermore, the finding that hydralazine did not significantly attenuate reductions in internal diameter of pial arterioles in SHRSP, despite prevention of hypertrophy, suggests that reductions in external diameter may make a greater contribution than vascular hypertrophy to encroachment on the lumen and reductions in internal diameter of cerebral arterioles in SHRSP.

Mechanics

Cilazapril, but not hydralazine, attenuates increases in distensibility of cerebral arterioles of SHRSP. This finding is somewhat unexpected since both treatments had similar effects on hypertrophy (cross-sectional area) of the vessel wall. We considered two factors that may contribute to differential effects of cilazapril and hydralazine on cerebral arteriolar distensibility. First, increases in distensibility of cerebral arterioles during chronic hypertension may be dependent on disproportionate alterations in the more distensible components of the vessel wall. We have suggested previously that distensibility of cerebral arterioles in SHRSP is increased despite hypertrophy because of a disproportionate increase in vascular smooth muscle and other distensible components in the vessel wall. It is possible, therefore, that cilazapril, but not hydralazine, prevents disproportionate increases in the more distensible components of the vessel wall and thus attenuates decreases in arteriolar distensibility.

Another possibility is that mean arterial pressure, which was lowered more effectively by cilazapril than hydralazine, is a major determinant of changes in distensibility. There is evidence in large arteries to support this concept. A variety of large arteries in which distensibility was altered during renal hypertension showed a partial recovery of distensibility after partial reversal of hypertension in dogs. In rats, reversal of renal hypertension with an ACE inhibitor completely reversed the decrease in distensibility of carotid arteries. Thus, mean arterial pressure may be an important determinant of arterial distensibility.

Stroke

Effects of antihypertensive treatment on the incidence of stroke in SHRSP have been examined previously. Enalapril, another ACE inhibitor, reduces stroke in SHRSP that are fed a high salt diet. In this study, stroke was prevented by both cilazapril and hydralazine, even though hydralazine was less effective than cilazapril in reducing mean arterial pressure. Thus, our data suggest that even moderate
reductions in mean arterial pressure are effective in preventing stroke in SHRSP. Furthermore, the finding that hydralazine was less effective than cilazapril in attenuating remodeling and increases in distensibility suggests that prevention of mechanical and structural alterations in cerebral arterioles may not be critical to the prevention of stroke during treatment of chronic hypertension.

Implications of Findings

We conclude that antihypertensive treatment with either cilazapril or hydralazine prevents cerebral arteriolar hypertrophy despite dissimilar effects on mean arterial pressure. Cilazapril, but not hydralazine, prevents changes in distensibility and maximal diameter of pial arterioles. An implication of these findings is that hypertrophy and reductions in external diameter of the cerebral arteriolar wall can occur independently. Hydralazine prevented hypertrophy of the vessel wall but did not increase external diameter. Treatment with cilazapril, on the other hand, prevented both hypertrophy and reductions in external diameter. Encroachment on the lumen of cerebral arterioles in SHRSP is primarily due to reductions in external diameter rather than hypertrophy.7 Thus, an important implication of the data is that a treatment that is effective in preventing arteriolar hypertrophy may not restore vasodilator capacity of cerebral arterioles. An ACE inhibitor may therefore be more effective than hydralazine in restoring dilator reserve of cerebral arterioles. It is important to consider, however, that differences in effects of treatment on vasodilator capacity of cerebral arterioles in SHRSP may be related to the different levels of mean arterial pressure that were obtained during treatment with cilazapril and hydralazine and not to different actions of cilazapril and hydralazine on the vessel wall.

Acknowledgments

We thank Jay Siems and Shams Ghoneim for technical assistance.

References


31. Kohlmann O, Bresnahan M, Gavras H: Central and peripheral indices of sympathetic activity after blood pressure lowering with enalapril (MK-421) or hydralazine in normotensive rats. Hypertension 1984;6(suppl 1):I-1–I-6


**KEY WORDS** • essential hypertension • angiotensin converting enzyme inhibitors • hydralazine • stroke • antihypertensive agents • arterioles
Effects of antihypertensive therapy on mechanics of cerebral arterioles in rats.
M A Hajdu, D D Heistad and G L Baumbach

Hypertension. 1991;17:308-316
doi: 10.1161/01.HYP.17.3.308

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/17/3/308

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/