Effects of an Angiotensin-Converting Enzyme Inhibitor and a β-Blocker on Cerebral Arterioles in Rats

Jean-Marc Chillon, Gary L. Baumbach

Abstract—We examined the effects of an angiotensin-converting enzyme inhibitor, perindopril, and a β-blocker, propranolol, on cerebral arterioles in stroke-prone spontaneously hypertensive rats (SHRSP). The structure and mechanics of cerebral arterioles were examined in untreated Wistar-Kyoto rats (WKY) and SHRSP that were untreated or treated for 3 months with a high (2 mg/kg per day) or a low (0.3 mg/kg per day) dose of perindopril or propranolol (250 mg/kg per day) alone or in combination with the low dose of perindopril. We measured pressure, external diameter, and cross-sectional area of the vessel wall (CSA) in maximally dilated (with EDTA) cerebral arterioles. Treatment of SHRSP with the high dose of perindopril or the combination of propranolol and the low dose of perindopril normalized cerebral arteriolar mean pressure (50 ± 1 [mean ± SEM] and 43 ± 2 mm Hg vs 50 ± 1 mm Hg in WKY and 94 ± 3 mm Hg in untreated SHRSP; \( P < 0.05 \)), pulse pressure (15 ± 1 and 16 ± 1 mm Hg vs 13 ± 1 mm Hg in WKY and 35 ± 1 mm Hg in untreated SHRSP; \( P < 0.05 \)), and CSA (1103 ± 53 and 1099 ± 51 \( \mu \text{m}^2 \), respectively, vs 1057 ± 49 \( \mu \text{m}^2 \) in WKY and 1281 ± 62 \( \mu \text{m}^2 \) in untreated SHRSP; \( P < 0.05 \)). In contrast, treatment of SHRSP with the low dose of perindopril or propranolol alone did not normalize arteriolar pulse pressure (24 ± 1 and 21 ± 1 mm Hg) and failed to prevent increases in CSA (1282 ± 77 and 1267 ± 94 \( \mu \text{m}^2 \)). Treatment with either dose of perindopril or the combination of propranolol and perindopril significantly increased external diameter in cerebral arterioles of SHRSP (99 ± 3, 103 ± 2, and 98 ± 3 \( \mu \text{m} \) vs 87 ± 2 \( \mu \text{m} \) in untreated SHRSP; \( P < 0.05 \)), whereas propranolol alone did not (94 ± 3 \( \mu \text{m} \); \( P > 0.05 \)). These findings suggest that effects of angiotensin-converting enzyme inhibitors on cerebral arteriolar hypertrophy in SHRSP may depend primarily on their effects on arterial pressure, particularly pulse pressure, whereas their effects on cerebral arteriolar remodeling (defined as a reduction in external diameter) may be pressure independent. (Hypertension. 1999;33:856-861.)

Key Words: hypertension, chronic ■ vascular remodeling ■ angiotensin ■ hypertrophy, vascular

Chronic hypertension alters structure and mechanics of cerebral arterioles. Cerebral arterioles in spontaneously hypertensive rats (SHR) and stroke-prone SHR (SHRSP) undergo both hypertrophy of the vessel wall and reduction in external diameter (remodeling).1,2 Despite hypertrophy, cerebral arterioles undergo a paradoxical increase in passive distensibility of the vessel wall during chronic hypertension in SHRSP.3 Because these alterations may contribute to the increased risk of stroke that accompanies chronic hypertension, it is important to examine determinants of these alterations in the cerebral circulation, as opposed to other vascular beds, so that we may better understand the link between chronic hypertension and stroke.

Alterations in vascular structure during chronic hypertension may result from a number of determinants including arterial pressure,4 neurohumoral factors,5–8 and endothelium-derived factors.9–11 A determinant of particular interest with respect to vascular remodeling has been the renin-angiotensin system. This interest was stimulated by a previous study in which we found that an angiotensin-converting enzyme (ACE) inhibitor but not hydralazine attenuates remodeling of cerebral arterioles in SHRSP.12 In contrast, both the ACE inhibitor and hydralazine prevented cerebral arteriolar hypertrophy. Because the ACE inhibitor lowered arterial pressure in SHRSP more effectively than hydralazine, however, we were unable to draw definitive conclusions from that study with regard to direct effects of the ACE inhibitor on cerebral vascular remodeling and hypertrophy, as opposed to direct effects of arterial pressure.

A major goal of this study, therefore, was to examine the hypothesis that effects of ACE inhibition on remodeling of cerebral arterioles may be largely independent of reductions in arterial pressure, in contrast to effects on hypertrophy, which may be largely pressure dependent. To accomplish this goal, we examined 5 groups of SHRSP: (1) an untreated group; (2) a group treated with a high dose of the ACE inhibitor perindopril to normalize arterial pressure relative to normotensive Wistar-Kyoto rats (WKY); (3) a group treated with a low dose of perindopril to minimize reductions in arterial pressure; (4) a group treated with the β-blocker...
propranolol to reduce arterial pressure independent of ACE inhibition; and (5) a group treated with a combination of propranolol and the low dose of perindopril. We anticipated that if effects of ACE inhibition on vascular remodeling are independent of arterial pressure, remodeling of cerebral arterioles in SHRSP would be attenuated as effectively by the low dose of perindopril as the high dose and would not be attenuated by propranolol alone. At the same time, if effects of ACE inhibition on vascular hypertrophy are pressure dependent, we would anticipate that the high dose of perindopril and propranolol alone or in combination with the low dose of perindopril would prevent cerebral arteriolar hypertrophy in SHRSP more effectively than the low dose of perindopril alone.

Methods

Experiments were conducted on male WKY rats and male SHRSP. At 3 months of age, the SHRSP were divided into 5 groups: an untreated group that drank tap water (n=16), a group that received a high dose of perindopril (2 mg/kg; n=18), a group that received a low dose of perindopril (0.3 mg/kg; n=18), a group that received propranolol alone (250 mg/kg, n=13), and a group that received a combination of propranolol plus the low dose of perindopril (n=16). Perindopril and propranolol were administered in the drinking water. WKY that drank tap water were used as normotensive controls (n=18). Animals were allowed free access to food and water, housed at 25°C, and exposed to 12 hours of light each day. Procedures followed in this study were in accordance with the institutional guidelines as set forth by the University of Iowa. After ~3 months of treatment, we examined mechanics of cerebral arterioles. Animals were weighed and anesthetized with sodium pentobarbital (5 mg/100 g body wt IP), intubated, and mechanically ventilated with room air and supplemental O₂. Paralysis of skeletal muscle was obtained with gallamine triethiodide (20 mg/kg IV). Because the animals were paralyzed, we evaluated them frequently for adequacy of anesthesia. Additional anesthesia (1.7 mg/100 g body wt IV) 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 Cerebral Arteriolar Pressure and Diameter

We measured pressure and diameter of first-order arterioles on the surface of the cerebrum¹³ through an open skull preparation.¹⁴ 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 suffused with artificial CSF, warmed to 37°C to 38°C, and equilibrated with a gas mixture of 5% CO₂–95% N₂. The composition of the CSF was (in mmol/L) KCl 3.0, MgCl₂ 0.6, CaCl₂ 1.5, NaCl 131.9, NaHCO₃ 24.6, urea 6.7, and dextrose 3.7.¹⁴

Systolic, diastolic, mean, and pulse pressures were measured continuously in cerebral arterioles with a micropipette connected to a Servo-null pressure measuring device (model 5, Instrumentation for Physiology and Medicine, Inc.). Pipettes were sharpened to a beveled tip of 3 to 5 μm in diameter, filled with 1.5 mol/L sodium chloride, and inserted into the lumen of a cerebral arteriole with a micromanipulator. The presence of the pipette tip in the vessel had no discernible effect on diameter of cerebral arterioles.

Arterioles were monitored through a Leitz microscope (NPI ×10 objective) connected to a closed-circuit video system with a final magnification of ×356. Images of arterioles were digitized with the use of a video frame grabber (Quick Image 24, MASS Microsystems) installed in a Macintosh computer (Quadra 900, Apple Computer). Arteriolar diameter was measured from the digitized images with the use of image analysis software (NIH Image, National Institutes of Health, Research Services Branch, NIMH). The precision of this system is 0.4 to 0.6 μm.

Experimental Protocol

Approximately 20 to 30 minutes after completion of surgery, measurements of cerebral arterioles were obtained under baseline conditions in 6-month-old rats. Vascular smooth muscle was then deactivated by suffusion of cerebral vessels with artificial CSF containing EDTA (67 mmol/L), which produces complete deactivation of smooth muscle in cerebral arterioles.¹⁴ Pressure-diameter relations were obtained in deactivated cerebral arterioles between cerebral arteriolar pressures of 60 and 10 mm Hg. Hemorrhage was used to reduce cerebral arteriolar pressure in decrements of 10 mm Hg at pressures down to 20 mm Hg of cerebral arteriolar pressure and decrements of 5 mm Hg at pressures between 20 and 10 mm Hg. After each pressure step, arteriolar diameter achieved a steady state within 15 seconds. Inner diameter was measured ~30 seconds later. Maximally dilated arterioles were fixed at physiological pressure in vivo by suffusion of vessels with glutaraldehyde fixative (2.25% glutaraldehyde in 0.10 mol/L cacodylate buffer) while maintaining cerebral arteriolar pressure at baseline levels. Arterioles were considered to be adequately fixed when blood flow through the arteriole had ceased. After the animal was killed with an injection of potassium chloride, the arteriolar segment used for pressure-diameter measurements was removed with a microsurgical knife. Fixed arterioles were processed for electron microscopy and embedded in Spurr’s low viscosity resin while cross-sectional orientation was maintained.

Cross-sectional area of the arteriolar wall was determined histologically from 1-μm sections with a light microscope interfaced with the video image analyzing system described above. Luminal and total (lumen plus vessel wall) cross-sectional areas of the arteriole were measured by tracing the inner and outer edges of the vessel wall. Cross-sectional area of the vessel wall was calculated by subtraction of luminal cross-sectional area from total cross-sectional area.

Calculation of Mechanical Characteristics

The assumption on which we based calculations of circumferential stress, circumferential strain, and tangential elastic modulus have been described in detail previously.¹⁴,¹⁵

Circumferential stress (σ) was calculated from cerebral arteriolar pressure (P), inner diameter of cerebral arterioles (Dᵢ), and wall thickness (WT): σ=(P-Dᵢ)/(2WT). Cerebral arteriolar pressure was converted from millimeters of mercury to Newtons per square meter (1 mm Hg=1.334×10⁻⁴ N/m²). Wall thickness was calculated from cross-sectional area of the vessel wall (CSA) and inner cerebral arteriolar diameter: WT=[(4CSA/π+Dᵢ²)/2]-Dᵢ/2. External diameter of cerebral arterioles (Dₑ) was calculated as Dₑ=Dᵢ+2WT. Histological determinations of cross-sectional area were used in all calculations of wall thickness and circumferential stress. Circumferential strain (ε) was calculated as ε=(Dₑ-Dᵢ)/Dᵢ, where Dᵢ is original diameter. We defined original diameter as the diameter at 10 mm Hg pressure.

To obtain tangential elastic modulus, the stress-strain data from each animal were fitted to an exponential curve (y=a₁eᵇ₁) with the use of least-squares analysis: σ=σₑeᵇₑ, where σₑ is stress at original diameter and bₑ is a constant that is related to the rate of increase of the stress-strain curve. Tangential elastic modulus (Eₑ) was calculated at several different values of stress from the derivative of the exponential curve: Eₑ=dsdε=βₑeᵇₑ.
Effects of Treatment on Cerebral Arterioles

Baseline Values in WKY, Unreated SHRSP, and SHRSP Treated With Perindopril or Propranolol Alone or in Combination

<table>
<thead>
<tr>
<th>Parameters</th>
<th>WKY</th>
<th>UnRxd</th>
<th>Per-L</th>
<th>Per-H</th>
<th>Prop</th>
<th>Prop+Per</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight, g</td>
<td>398±6</td>
<td>334±6*</td>
<td>333±6*</td>
<td>322±6*</td>
<td>278±6*</td>
<td>269±7†</td>
</tr>
<tr>
<td>Systemic mean pressure, mm Hg</td>
<td>102±2</td>
<td>196±4*</td>
<td>155±3*</td>
<td>116±2*</td>
<td>126±2*</td>
<td>105±3†</td>
</tr>
<tr>
<td>Arterial blood gases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pco₂, mm Hg</td>
<td>36±1</td>
<td>36±1</td>
<td>35±1</td>
<td>36±1</td>
<td>36±1</td>
<td>35±1</td>
</tr>
<tr>
<td>pH</td>
<td>7.36±0.01</td>
<td>7.36±0.01</td>
<td>7.34±0.01</td>
<td>7.36±0.01</td>
<td>7.38±0.01</td>
<td>7.39±0.01</td>
</tr>
<tr>
<td>P0₂, mm Hg</td>
<td>110±5</td>
<td>131±4</td>
<td>131±5</td>
<td>130±7</td>
<td>139±8</td>
<td>134±7</td>
</tr>
<tr>
<td>Cerebral arterioles before EDTA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure, mm Hg</td>
<td>50±1</td>
<td>94±3*</td>
<td>72±2*</td>
<td>50±1†</td>
<td>57±3†</td>
<td>43±2†</td>
</tr>
<tr>
<td>Pulse</td>
<td>13±1</td>
<td>35±1*</td>
<td>24±1†</td>
<td>15±1†</td>
<td>21±1†</td>
<td>16±1†</td>
</tr>
<tr>
<td>Internal diameter, μm</td>
<td>56±2</td>
<td>33±1*</td>
<td>40±1†</td>
<td>43±1†</td>
<td>38±1†</td>
<td>43±2†</td>
</tr>
<tr>
<td>Cerebral arterioles after EDTA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal diameter, μm</td>
<td>105±2</td>
<td>77±2*</td>
<td>90±2*</td>
<td>96±2*</td>
<td>85±2*</td>
<td>89±3†</td>
</tr>
<tr>
<td>External diameter, μm</td>
<td>111±2</td>
<td>87±2*</td>
<td>99±3*</td>
<td>103±2*</td>
<td>94±3*</td>
<td>98±3†</td>
</tr>
<tr>
<td>CSA of wall, μm²</td>
<td>1057±49</td>
<td>1281±62*</td>
<td>1282±77*</td>
<td>1103±53*</td>
<td>1267±94*</td>
<td>1099±51†</td>
</tr>
<tr>
<td>E₁ vs stress</td>
<td>7.2±0.5</td>
<td>5.5±0.2*</td>
<td>5.9±0.4</td>
<td>6.3±0.4</td>
<td>5.3±0.3*</td>
<td>5.6±0.3*</td>
</tr>
</tbody>
</table>

Measurements of internal diameter before deactivation of smooth muscle were obtained at prevailing levels of arterial pressure. Values of external diameter after deactivation of smooth muscle were calculated from measurements of internal diameter at 40 mm Hg cerebral arteriolar pressure and histological measurements of cross-sectional area (CSA) of the vessel wall. E₁ vs stress indicates slope of tangential elastic modulus (E₁) versus stress. Values are mean±SEM in 18 WKY, 16 untreated (UnRxd) SHRSP, 18 SHRSP treated with a high dose (2 mg/kg) of perindopril (Per-H), 18 SHRSP treated with a low dose of perindopril (Per-L), 13 SHRSP treated with propranolol (Prop), and 16 SHRSP treated with the combination of propranolol and the low dose of perindopril.

*P<0.05 vs WKY; †P<0.05 vs untreated SHRSP.

Statistical Analysis
ANOVA was used to compare systemic mean pressure, arteriolar pressures, diameters, cross-sectional area of the vessel wall, and slope of tangential elastic modulus versus stress. Probability values were calculated with a Student’s t test. Statistics were determined with the use of JMP statistics software (SAS Institute Inc) on a Macintosh computer.

Results

Baseline Values
Systemic mean arterial pressure and cerebral arteriolar mean and pulse pressures were significantly greater in untreated 6-month-old SHRSP than in age-matched WKY (Table). The low dose of perindopril reduced systemic and cerebral arteriolar pressures in SHRSP by ~50%, whereas the high dose nearly normalized systemic pressure and completely normalized cerebral arteriolar pressure (Table). Although propranolol alone did not reduce systemic and cerebral arteriolar mean pressures in SHRSP as effectively as the high dose of perindopril, it was significantly more effective than the low dose of perindopril (Table). Combining the low dose of perindopril with propranolol fully normalized systemic pressure in SHRSP and reduced cerebral arteriolar mean pressure to a level below those found in WKY (Table).

The high dose of perindopril as well as the low dose combined with propranolol effectively normalized cerebral arteriolar pulse pressure in SHRSP (Table). On the other hand, propranolol and the low dose of perindopril when given separately reduced cerebral arteriolar pulse pressure by only ~50% (Table).

Internal diameter of cerebral arterioles before deactivation with EDTA was significantly less in untreated SHRSP than in WKY (Table). Treatment of SHRSP with perindopril at both the low and high doses as well as propranolol both alone and combined with the low dose of perindopril significantly increased cerebral arteriolar diameter. Diameters were substantially less, however, in all of the treatment groups than in WKY (Table). Arterial blood gases (Pco₂, pH, and P0₂) were within normal limits in all groups examined (Table).

After deactivation of cerebral arterioles with EDTA, internal diameter of cerebral arterioles was significantly smaller in untreated SHRSP than in WKY (Table). Although none of the treatments fully normalized diameter of cerebral arterioles in SHRSP relative to WKY, internal diameter was significantly greater in SHRSP treated with both the low and high doses of perindopril than in untreated SHRSP (Table). In contrast, internal diameter was not significantly increased in SHRSP treated with propranolol alone (Table). Propranolol combined with the low dose of perindopril, on the other hand, significantly increased internal diameter in SHRSP (Table). Thus treatment with perindopril but not propranolol attenuated reductions in maximal dilatation of cerebral arterioles in SHRSP, even when given in a dose that reduced arteriolar pressure substantially less than propranolol.
Cross-sectional area of the vessel wall in cerebral arterioles was greater in untreated SHRSP than in WKY (Table). Both the high dose of perindopril and the combination of propranolol with the low dose of perindopril normalized cross-sectional area of the vessel wall in SHRSP (Table). In contrast, when given separately, neither the low dose of perindopril nor propranolol alone significantly altered cross-sectional area of the vessel wall in SHRSP (Table). Thus effects of perindopril and propranolol on hypertrophy of cerebral arterioles in SHRSP tended to parallel their effects on cerebral arteriolar pulse pressure.

Vascular Mechanics

After maximal dilatation of cerebral arterioles with EDTA, external diameter was significantly less in SHRSP than in WKY at all levels of cerebral arteriolar pressure between 60 and 10 mm Hg (Figure 1). Thus during chronic hypertension in SHRSP, cerebral arterioles undergo remodeling as defined by a reduction in external diameter. Both the low and high doses of perindopril significantly increased but did not fully normalize external diameter of cerebral arterioles in SHRSP at all levels of arteriolar pressure (Figure 1). Propranolol alone, on the other hand, did not significantly increase external diameter at any level of pressure (Figure 1). Furthermore, addition of propranolol to the low dose of perindopril resulted in no further increase in external diameter (Figure 1). These findings indicate that perindopril but not propranolol may attenuate remodeling of cerebral arterioles in SHRSP. The findings also suggest that attenuation of cerebral arteriolar remodeling by perindopril may be independent of its pressor effects.

The stress-strain curve in cerebral arterioles of untreated SHRSP was shifted to the right of the curve in WKY (Figure 2), and the slope of tangential elastic modulus versus stress was significantly less in untreated SHRSP than in untreated WKY (Table). Thus passive distensibility was increased in cerebral arterioles of SHRSP despite hypertrophy of the vessel wall. Treatment of SHRSP with the low dose as well as the high dose of perindopril attenuated the rightward shift of the stress-strain curve (Figure 2) and the decrease in the slope of tangential elastic modulus versus stress (Table). Treatment with propranolol alone did not alter the stress-strain relation (Figure 2) or the slope of tangential elastic modulus versus stress in cerebral arterioles of SHRSP (Table). Furthermore, effects of the low dose of perindopril on the stress-strain relation and the slope of elastic modulus versus stress were not enhanced further by the addition of propranolol (Figure 2). These findings suggest that perindopril but not propranolol may attenuate increases in distensibility of cerebral arterioles in SHRSP.

Discussion

There were 2 major findings in this study. First, both the high and low doses of perindopril attenuated reductions in external diameter of cerebral arterioles in SHRSP, even though the low dose of perindopril was substantially less effective in reducing arterial pressure. Furthermore, propranolol did not attenuate reductions in cerebral arteriolar external diameter.
when given alone and did not further attenuate reductions in external diameter when given in combination with the low dose of perindopril, even though it produced a substantial reduction in arterial pressure in SHRSP when given alone and a further reduction in pressure when given with perindopril. These findings suggest that ACE inhibition may attenuate remodeling of cerebral arterioles in SHRSP independent of its effects on arterial pressure. The findings also suggest that the renin-angiotensin system may be an important determinant of vascular remodeling during chronic hypertension. Second, both the high dose of perindopril and propranolol combined with the low dose of perindopril prevented hypertrophy and normalized pulse pressure in cerebral arterioles of SHRSP. In contrast, when given alone, neither the low dose of perindopril nor propranolol prevented cerebral arteriolar hypertrophy or normalized cerebral arteriolar pulse pressure. These findings suggest that effects of treatment with perindopril on hypertrophy of cerebral arterioles vessel wall in SHRSP are not due directly to ACE inhibition and instead may be the result of effects of treatment on arteriolar pulse pressure.

Remodeling

Determinants of cerebral arteriolar remodeling during chronic hypertension in SHRSP are not well defined. In a previous study, we found that the ACE inhibitor cilazapril attenuated remodeling in cerebral arterioles in SHRSP. In contrast, hydralazine had no effect on cerebral arteriolar remodeling. On the basis of these findings, we suggested that the renin-angiotensin system may be an important determinant of vascular remodeling during chronic hypertension. Because hydralazine was significantly less effective than cilazapril in lowering arterial pressure in SHRSP, however, we were unable to unambiguously rule out the possibility that effects of cilazapril on cerebral arteriolar remodeling were secondary to reductions in arterial pressure rather than to direct effects of ACE inhibition.

We undertook the present study in an effort to separate pressor and nonpressor effects of ACE inhibition on cerebral arteriolar remodeling. Several findings in this study support our previously proposed hypothesis that the renin-angiotensin system may contribute directly to vascular remodeling. First, remodeling of cerebral arterioles in SHRSP was attenuated nearly as effectively by the low dose of perindopril as by the high dose, even though the low dose of perindopril was half as effective as the high dose in lowering cerebral arteriolar pressure. Second, in contrast to the low dose of perindopril, the β-blocker (propranolol) did not significantly attenuate remodeling of cerebral arterioles in SHRSP, even though it was much more effective than the low dose of perindopril in lowering cerebral arteriolar pressure. Third, the effectiveness of the low dose of perindopril in attenuating cerebral arteriolar remodeling was not enhanced by the addition of propranolol, even though arteriolar pressure was reduced to levels significantly below those in WKY.

Although our findings in relation to effects of perindopril on remodeling of cerebral arterioles in SHRSP suggest an important role for angiotensin II (Ang II) as a determinant of remodeling, one other interpretation is possible. In addition to their ability to inhibit conversion of angiotensin I to Ang II, ACE inhibitors also inhibit inactivation of bradykinins. It cannot be ruled out, therefore, that perindopril may have attenuated cerebral arteriolar remodeling in SHRSP by increasing availability of bradykinins rather than decreasing availability of Ang II.

A potential concern in this study relates to effects of propranolol on body weight of SHRSP. Treatment with propranolol but not perindopril resulted in a significant reduction in body weight of SHRSP. If vessel size is proportional to body weight, then reduction of body weight during treatment with propranolol may have contributed to the finding of smaller external diameters in cerebral arterioles of SHRSP treated with propranolol than in SHRSP treated with the low and high doses of perindopril. We think that this possibility is unlikely, however, because external diameter of cerebral arterioles was greater in SHRSP treated with a combination of propranolol and perindopril than in SHRSP treated with propranolol only, even though body weight tended to be less in the group on combined treatment.

Hypertrophy

Determinants that may contribute to vascular hypertrophy during chronic hypertension include increases in arterial pressure and the renin-angiotensin system. Perhaps the best evidence obtained in vivo that supports a direct role for the renin-angiotensin system is provided by a study in which the pressor effects of Ang II were counteracted by simultaneous treatment with hydralazine. Cross-sectional area of the vessel wall in mesenteric resistance arteries of rats was increased by chronic infusion of Ang II, even when increases in arterial pressure were prevented by hydralazine.

The findings in this study do not provide convincing support for a role of the renin-angiotensin system in hypertrophy of cerebral arterioles in SHRSP. Whereas both the high dose of perindopril and the combination of propranolol with the low dose of perindopril prevented cerebral arteriolar hypertrophy in SHRSP, neither the low dose of perindopril nor propranolol alone had any effect on hypertrophy of cerebral arterioles. If ACE inhibition were contributing directly to prevention of arteriolar hypertrophy, it seems likely that the low dose of perindopril would have attenuated hypertrophy, even when given without the additional pressure lowering effects of propranolol.

An interesting finding in this study with respect to the possible role of arterial pressure as a determinant of vascular hypertrophy is that the effects of the various treatment regimens on cerebral arteriolar hypertrophy tended to parallel more closely their effects on cerebral arteriolar pulse pressure than mean pressure. The possibility that arterial pulse pressure, as opposed to mean pressure, systolic pressure, or diastolic pressure, may be an important determinant of vascular hypertrophy is supported by the previous findings that (1) reductions in cross-sectional area of the vessel wall in cerebral arterioles of WKY and SHRSP produced by carotid clipping correlate strongly with reductions in pulse pressure but not systolic pressure or mean pressure, and (2) creation of arteriovenous fistulas in Sprague-Dawley rats results in hypertension of cerebral arterioles and increases in cerebral arteriolar pulse pressure but not mean pressure or diastolic.
pressure. If there indeed is a relation between increases in pulse pressure and cerebral arteriolar hypertrophy, the stimulus for hypertrophy may be linked to cyclic strain. In vascular smooth muscle that is grown in culture, DNA synthesis and rate of growth are greater in cells that are subjected to cyclic strain than in cells that are grown under static conditions.21,22

Distensibility
Distensibility of fully relaxed cerebral arterioles is increased paradoxically in SHRSP, SHR, and rats with 1-kidney, 1-clip renal hypertension, despite hypertrophy of the arteriolar wall.2,14 Furthermore, prevention of hypertrophy in cerebral arterioles of SHRSP by treatment with an ACE inhibitor12 or carotid clipping19 significantly attenuates increases in arteriolar distensibility. We were surprised, therefore, by the finding in this study that treatment with the low dose as well as the high dose of perindopril attenuated increases in distensibility of cerebral arterioles in SHRSP, even though the low dose did not prevent hypertrophy.

We have proposed previously that increases in passive distensibility that accompany hypertrophy of cerebral arterioles may be due to a reduction in the proportion of stiff (collagen and basement membrane) to compliant (smooth muscle, elastin, and endothelium) components of the arteriolar wall in cerebral arterioles.2,3,5,19 Therefore a possible explanation for the finding in this study that treatment with the low dose of perindopril attenuated increases in cerebral arteriolar distensibility in SHRSP despite not preventing hypertrophy is that ACE inhibition alters proportional composition of the arteriolar wall, even when hypertrophy of the wall persists.

Conclusions
This study provides support for the concept that remodeling of cerebral arterioles during chronic hypertension may be independent of increases in arterial pressure. It also provides additional support for the hypothesis we proposed previously12 that Ang II may be an important determinant of cerebral arteriolar remodeling. Furthermore, this study suggests that in contrast to remodeling, hypertrophy of cerebral arterioles during chronic hypertension may be dependent primarily on increases in arterial pressure and in particular its pulsatile component.

Acknowledgments
This work was supported by the National Institutes of Health (grants HL–22149, NS–24621, and HL94–006), funds from the Iowa Affiliate of the American Heart Association, and funds from the Institut de Recherches Internationales Servier. Jean-Marc Chillon is the recipient of a Fellowship Award from the Iowa Affiliate of the American Heart Association. We thank Shams Ghoneim for technical assistance and Professor Jeffrey Atkinson for critical review of the manuscript.

References
Effects of an Angiotensin-Converting Enzyme Inhibitor and a \(\beta\)-Blocker on Cerebral Arterioles in Rats

Jean-Marc Chillon and Gary L. Baumbach

*Hypertension*. 1999;33:856-861
doi: 10.1161/01.HYP.33.3.856

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 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/33/3/856

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/