Cerebral Arteriolar Structure in Mice Overexpressing Human Renin and Angiotensinogen

Gary L. Baumbach, Curt D. Sigmund, Frank M. Faraci

Abstract—We examined the hypothesis that the renin-angiotensin system plays an important role in vascular remodeling (defined as reduced external diameter) during chronic hypertension. We measured pressure, diameter, and cross-sectional area of the vessel wall in maximally dilated cerebral arterioles in transgenic mice that overexpress both human renin and human angiotensinogen and in spontaneously hypertensive mice, a model of chronic hypertension that is thought to develop independently of the renin-angiotensin system. Systemic arterial pressure under conscious conditions was increased by similar amounts in transgenically hypertensive mice (153±6 versus 117±4 mm Hg in controls; mean±SE, P<0.05) and spontaneously hypertensive mice (148±5 versus 112±5 mm Hg; P<0.05). The external diameter of maximally dilated cerebral arterioles was reduced in transgenically hypertensive mice (52±2 versus 66±3 μm; P<0.05), but not in spontaneously hypertensive mice (58±4 versus 60±4 μm; P>0.05). The cross-sectional area of the vessel wall was increased in both transgenically hypertensive mice (504±53 versus 379±37 μm²; P<0.05) and spontaneously hypertensive mice (488±40 versus 328±38 μm²; P<0.05). During maximal dilatation, the stress-strain curves in cerebral arterioles of transgenically hypertensive mice and spontaneously hypertensive mice were shifted to the right of the curves in corresponding controls, an indication that arteriolar distensibility was increased in the transgenically and spontaneously hypertensive groups. Thus, cerebral arterioles undergo remodeling and hypertrophy in transgenically hypertensive mice, but only hypertrophy in spontaneously hypertensive mice. These findings support the hypothesis that the renin-angiotensin system is an important determinant of vascular remodeling during chronic hypertension. (Hypertension. 2003;41:50-55.)

Key Words: renin-angiotensin system ■ mice ■ vasculature ■ remodeling ■ hypertrophy ■ hypertension, chronic

Chronic hypertension alters the 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,5,6 and endothelium-derived factors.7–9 A determinant of particular interest with respect to vascular remodeling has been the renin-angiotensin system. This interest was stimulated by previous studies in which we found that angiotensin-converting enzyme (ACE) inhibitors, but not hydralazine or propranolol, attenuate remodeling of cerebral arterioles in SHRSP.10,11 Because the ACE inhibitors lowered arterial pressure in SHRSP more effectively than hydralazine and propranolol, however, we were unable to draw definitive conclusions from these studies with regard to the direct effects of the ACE inhibitor on cerebral vascular remodeling and hypertrophy, as opposed to the effects of arterial pressure per se.

A major goal of this study was to examine further the hypothesis that the renin-angiotensin system plays an important role in vascular remodeling during chronic hypertension. To accomplish this goal, we examined structural characteristics of cerebral arterioles in 2 experimental models of hypertension. Transgenic mice that overexpress both human renin and human angiotensinogen (R+/A+)12–14 are a novel, defined model of hypertension. The other model was the BPH-2 mouse, a model of chronic hypertension that is thought to represent a non-renin-dependent mode of hypertension.15 We anticipated that if the renin-angiotensin system is an important determinant of vascular remodeling, cerebral arterioles would show evidence of remodeling in R+/A+ mice but not in BPH-2 mice.
Methods

Animals
The experimental protocol was approved by our institution’s animal care and use committee. All breeding and genotyping was performed in the transgenic animal facility (directed by C.D.S.), located in a virus- and pathogen-free animal care facility.

Transgenic Mice
Double transgenic mice (R+/A+) were generated by crossbreeding human renin (R+) mice with human angiotensinogen (A+) mice, as we have reported previously.13,14 The presence of the transgenes was assessed by gene- and species-specific polymerase chain reaction of DNA isolated from tail biopsy samples, as described previously.13,14 There are no differences in blood pressure between R+/A− and single transgenic mice (R+/A− or R−/A+) owing to the strict species specificity in the enzymatic reaction between renin and angiotensinogen.13 Because of this specificity, mouse renin does not cleave human angiotensinogen and human renin does not cleave mouse angiotensinogen.13 Because blood pressure is the same in all 3 mice, R−/A−, R+/A−, and R+/A+ mice were all used as controls in the present study. Control (n=11) and R+/A+ (n=12) mice averaged 6.5 months of age. The body weights of control and R+/A+ mice were 28±5 and 24±4 g, respectively.

BPH-2 Mice
Spontaneously hypertensive BPH-2 mice were maintained in the animal care facility. The BPH-2 mouse colony was established in Iowa by brother-sister mating of several breeding pairs obtained from the colony at the University of Kansas. The original derivation of the BPH-2 strain has been described previously.16,17 C57BL/6 mice (Harlan, Indianapolis, Ind) were used as controls. Control (n=10) and BPH-2 (n=10) mice averaged 7.5 months of age. The body weights of control and BPH-2 mice were 30±3 and 26±4 g, respectively.

Systemic Arterial Pressure in Conscious Mice
We and others have found that the most accurate measurements of arterial pressure in mice are obtained with chronic indwelling catheters in conscious animals. We therefore measured systemic arterial pressure in conscious mice using a method described previously.13 For chronic catheterization, mice were anesthetized with Avertin (0.2 to 0.3 mL, IP), shaved, and prepped with a 70% alcohol solution. Sterile catheters (0.040 in outer diameter×0.025 in inner diameter) were placed in the right carotid artery with the aid of a dissecting microscope. Mice were placed on a warming pad (39°C) during the surgical procedure and postoperatively until fully awake. All animals were given prophylactic antibiotics (penicillin G, 12 000 U, IM) and allowed to recover at least 24 hours before measuring systemic arterial pressure under conscious conditions.

In Vivo Preparation
Animals were weighed and anesthetized with sodium pentobarbital (5 mg per 100 g body weight [BW], IP), intubated, and mechanically ventilated with room air and supplemental O2. Additional anesthesia (1.7 mg per 100 g BW, 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. Catheters were inserted into both femoral arteries to continuously record arterial blood gases, and withdraw blood to produce hypotension (needed for studies of vascular mechanics).

Measurements in Cerebral Arterioles
We measured pressure and diameter in first-order arterioles on the cerebrum through an open skull preparation as described previously.3 A craniotomy was made over the left parietal cortex, and the dura was incised to expose cerebral vessels. Exposed brain was continuously suffused with artificial cerebrospinal fluid (CSF) warmed to 37 to 38°C and equilibrated with a gas mixture of 5% CO2 and 95% N2. Systolic, diastolic, mean, and pulse pressures were measured con-
addition, the slope of tangential elastic modulus versus stress was significantly less in R+/A+ mice and control mice (Figure 2, right). These findings suggest that hypertrophy of cerebral arterioles in R+/A+ mice was accompanied by an increase in passive distensibility of cerebral arterioles.

**BPH-2 Mice**

**Baseline Values**

Systemic arterial mean pressure was significantly greater in BPH-2 mice than in control mice in both the conscious and anesthetized states, even though anesthesia significantly reduced systemic arterial mean pressure in both groups (Table 2). Cerebral arteriolar systolic, diastolic, mean, and pulse pressures were significantly greater in BPH-2 mice than in control mice (Table 2). Furthermore, the levels of systemic arterial mean pressure and cerebral arteriolar pressures in BPH-2 mice (Table 2) were not significantly different \((P>0.05)\) from levels observed in R+/A+ mice (Table 1). The internal diameter before deactivation with EDTA and internal and external diameters after deactivation with EDTA were not significantly different in cerebral arterioles of BPH-2 mice and control mice (Table 2). Dilator reserve was not significantly different in BPH-2 mice from that in control mice \((25.2 \pm 2 \overline{2} \mu m; P>0.05)\). The cross-sectional area of the vessel wall was significantly greater in cerebral arterioles in BPH-2 mice than in control mice (Table 2). Thus, cerebral arterioles in BPH-2 mice underwent hypertrophy, but not remodeling or a reduction in dilator reserve.

**Vascular Mechanics**

Internal and external diameters in cerebral arterioles during maximal dilatation were similar in BPH-2 mice and control mice at all levels of arteriolar pressure between 10 and 40 mm Hg (Figure 3). The stress-strain curve in cerebral arterioles in BPH-2 mice was shifted to the right of the curve in cerebral arterioles of control mice (Figure 2, left). In addition, the slope of tangential elastic modulus versus stress was significantly less in BPH-2 mice and control mice (Figure 4, right). These findings suggest that distensibility was increased in the cerebral arterioles of BPH-2 mice.

**Discussion**

There are several new findings in this study. First, cerebral arterioles in R+/A+ mice undergo remodeling, with a

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**TABLE 1. Baseline Values in Renin-Angiotensinogen Mice**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Values</th>
<th>Controls</th>
<th>Transgenics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before deactivation of smooth muscle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic arterial mean pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unanesthetized</td>
<td>117±4</td>
<td>153±6*</td>
<td></td>
</tr>
<tr>
<td>Anesthetized</td>
<td>88±4</td>
<td>113±5*</td>
<td></td>
</tr>
<tr>
<td>Cerebral arteriolar pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>48±1</td>
<td>74±5*</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>36±2</td>
<td>53±4*</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>40±1</td>
<td>60±4*</td>
<td></td>
</tr>
<tr>
<td>Pulse</td>
<td>12±1</td>
<td>21±2*</td>
<td></td>
</tr>
<tr>
<td>Arterial blood gases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(pC_{O_2},) mm Hg</td>
<td>37±1</td>
<td>36±1</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.34±0.04</td>
<td>7.33±0.03</td>
<td></td>
</tr>
<tr>
<td>(pO_2,) mm Hg</td>
<td>124±6</td>
<td>136±8</td>
<td></td>
</tr>
<tr>
<td>Internal cerebral arteriolar diameter, mm</td>
<td>34±4</td>
<td>28±3</td>
<td></td>
</tr>
<tr>
<td><strong>After deactivation of smooth muscle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral arteriolar diameter, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal</td>
<td>62±3</td>
<td>45±2*</td>
<td></td>
</tr>
<tr>
<td>External</td>
<td>66±3</td>
<td>52±2*</td>
<td></td>
</tr>
<tr>
<td>Cross-sectional area of vessel wall, mm(^2)</td>
<td>379±37</td>
<td>504±53*</td>
<td></td>
</tr>
<tr>
<td>(E_t) vs stress</td>
<td>6.0±0.9</td>
<td>4.0±0.3*</td>
<td></td>
</tr>
</tbody>
</table>

Measurements of internal diameter before deactivation of smooth muscle were obtained at prevailing levels of arterial pressure. Measurements of internal diameter after deactivation of smooth muscle were made at an arteriolar mean pressure of 40 mm Hg. Values of external diameter after deactivation of smooth muscle were calculated from measurements of internal diameter at 40 mm Hg arteriolar pressure and histological measurements of cross-sectional area of the vessel wall. \(E_t\) vs stress indicates slope of tangential elastic modulus versus stress.

Values are mean±SEM in 11 control mice and 12 R+/A+ mice. *\(P<0.05\) vs control.

**Vascular Mechanics**

Internal and external diameters in cerebral arterioles during maximal dilatation were smaller in R+/A+ mice than in control mice at all levels of arteriolar pressure between 10 and 40 mm Hg (Figure 1). The stress-strain curve in cerebral arterioles of R+/A+ mice was shifted to the right of the curve in cerebral arterioles of control mice (Figure 2, left). In addition, the slope of tangential elastic modulus versus stress was significantly less in R+/A+ mice and control mice (Figure 2, right). These findings suggest that hypertrophy of cerebral arterioles in R+/A+ mice was accompanied by an increase in passive distensibility of cerebral arterioles.

**Figure 1.** Pressure-diameter relationships (internal diameter [left] and external diameter [right]) in cerebral arterioles during maximal dilatation with EDTA in control \((n=11)\) and R+/A+ mice \((n=12)\). Values are mean±SEM. *\(P<0.05\) versus control.

**Figure 2.** Stress-strain relationship (left) and stress versus tangential elastic modulus (right) in cerebral arterioles during maximal dilatation with EDTA in control \((n=11)\) and R+/A+ mice \((n=12)\). Values are mean±SEM. D indicates cerebral arteriolar diameter; D0, original cerebral arteriolar diameter.
undergo hypertrophy with an increase in distensibility, but do not undergo remodeling. These findings suggest that increases in arterial pressure per se are not sufficient to induce remodeling of cerebral arterioles. More importantly, the findings provide additional support for the hypothesis we proposed previously that the renin-angiotensin system may play an important role in cerebral vascular remodeling during chronic hypertension. In addition to these new findings and their implications regarding the renin-angiotensin system, this study is the first to measure arteriolar/microvascular pressure in any vascular bed in mice. Cerebral arteriolar mean pressure in normotensive mice was about 45% to 55% of systemic arterial mean pressure, a pressure reduction that is comparable to the drop in pressure between aorta and cerebral arterioles found in normotensive rats.5

Remodeling

We define remodeling as a reduction in external diameter of small resistance arteries and arterioles during chronic hypertension that cannot be attributed to altered distensibility of the vessel wall.1 Determinants of vascular remodeling during chronic hypertension are not yet well understood. Based on previous findings, we have proposed that the renin-angiotensin system may be a determinant of remodeling. In one study, we found that the ACE inhibitor, cilazapril, attenuated remodeling in cerebral arterioles in SHRSP, in contrast to hydralazine, which had no effect on cerebral arteriolar remodeling.10 We then observed in a subsequent study that remodeling of cerebral arterioles in SHRSP was attenuated nearly as effectively by a low dose of perindopril as by a high dose, even though the low dose of perindopril was half as effective as the high dose in lowering cerebral arteriolar pressure.11 In that same study,11 we also found that, in contrast to the low dose of perindopril, the β-adrenergic receptor 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.

We also, however, recognize the limitations of these studies.10,11 First, because hydralazine was significantly less effective than cilazapril in lowering arterial pressure in SHRSP, we were unable to unambiguously rule out the possibility that the effects of cilazapril on cerebral arteriolar

### Table 2. Baseline Values in BPH-2 Mice

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls</th>
<th>BPH-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before deactivation of smooth muscle</td>
<td></td>
<td></td>
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<tr>
<td>Systemic arterial mean pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unanesthetized</td>
<td>112±5</td>
<td>148±5*</td>
</tr>
<tr>
<td>Anesthetized</td>
<td>86±5</td>
<td>110±6*</td>
</tr>
<tr>
<td>Cerebral arteriolar pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>53±2</td>
<td>76±7*</td>
</tr>
<tr>
<td>Diastolic</td>
<td>41±3</td>
<td>57±6*</td>
</tr>
<tr>
<td>Mean</td>
<td>45±2</td>
<td>63±6*</td>
</tr>
<tr>
<td>Pulse</td>
<td>12±2</td>
<td>19±1*</td>
</tr>
<tr>
<td>Arterial blood gases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pCO₂, mm Hg</td>
<td>32±2</td>
<td>34±2</td>
</tr>
<tr>
<td>pH</td>
<td>7.36±0.02</td>
<td>7.35±0.03</td>
</tr>
<tr>
<td>pO₂, mm Hg</td>
<td>113±8</td>
<td>119±10</td>
</tr>
<tr>
<td>Internal cerebral arteriolar diameter, mm</td>
<td>32±4</td>
<td>29±2</td>
</tr>
<tr>
<td>After deactivation of smooth muscle</td>
<td></td>
<td></td>
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<tr>
<td>Cerebral arteriolar diameter, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal</td>
<td>55±3</td>
<td>54±4</td>
</tr>
<tr>
<td>External</td>
<td>58±4</td>
<td>60±4</td>
</tr>
<tr>
<td>Cross-sectional area of vessel wall, mm²</td>
<td>328±38</td>
<td>488±40*</td>
</tr>
<tr>
<td>E₁ vs stress</td>
<td>5.8±0.3</td>
<td>4.1±0.4*</td>
</tr>
</tbody>
</table>

Measurements of internal diameter before deactivation of smooth muscle were obtained at prevailing levels of arterial pressure. Measurements of internal diameter after deactivation of smooth muscle were made at an arteriolar mean pressure of 40 mm Hg. Values of external diameter after deactivation of smooth muscle were calculated from measurements of internal diameter at 40 mm Hg arteriolar pressure and histological measurements of cross-sectional area of the vessel wall. E₁ vs Stress: slope of tangential elastic modulus (E₁) versus stress.

Values are mean±SEM in 10 control mice and 10 BPH-2 mice. *P<0.05 vs control.

### Figure 3. Pressure-diameter relationships (internal diameter [left] and external diameter [right]) in cerebral arterioles during maximal dilatation with EDTA in control (n=10) and BPH-2 mice (n=10). Values are mean±SEM.

### Figure 4. Stress-strain relationship (left) and stress versus tangential elastic modulus (right) in cerebral arterioles during maximal dilatation with EDTA in control (n=10) and BPH-2 mice (n=10). Values are mean±SEM.
remodeling were secondary to reductions in arterial pressure rather than to direct effects of ACE inhibition. Second, 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. Finally, in addition to their ability to inhibit conversion of angiotensin I to angiotensin II, ACE inhibitors also inhibit inactivation of bradykinins. Thus, we cannot rule out the possibility that cilazapril and perindopril attenuated cerebral arteriolar remodeling in SHRSP by increasing availability of bradykinins rather than decreasing availability of angiotensin II.

We undertook the present study in an effort to further define the contributions of the renin-angiotensin system to cerebral arteriolar remodeling. The R+/A+ transgenic mouse is a well-defined model of angiotensin II–induced chronic hypertension. In addition, the genetic background of R+/A+ transgenic mice is nearly identical to that of the control animals because the mice used in these studies were derived from 6 to 7 generations of back-crossbreeding to the C57BL/6J. Because previous studies examining effects of hypertension in SHRSP versus Wistar Kyoto rats have used strains that are genetically diverse, the results are clouded by the presence of genes in the genetic background that may themselves promote vascular remodeling.

We found in this study that cerebral arterioles in R+/A+ mice undergo significant remodeling of the vessel wall. In contrast, cerebral arterioles in BPH-2 mice do not undergo remodeling. These findings provide additional support for the hypothesis that the renin-angiotensin system is a major determinant of vascular remodeling during chronic hypertension. The basis for this statement is that hypertension in R+/A+ results directly from overexpression of human renin and angiotensinogen, whereas hypertension in BPH-2 mice is thought to be independent of the renin-angiotensin system. Levels of tissue and plasma renin and renin activity are not significantly different in adult and juvenile BPH-2 mice relative to normotensive controls.

**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 angiotensin II were counteracted by simultaneous treatment with hydralazine. The cross-sectional area of the vessel wall in mesenteric resistance arteries of rats was increased by chronic infusion of angiotensin II, even when increases in arterial pressure were prevented by hydralazine.

The findings in this study do not provide convincing support for an essential role of the renin-angiotensin system in hypertrophy of cerebral arterioles. We found that cerebral arterioles undergo hypertrophy in BPH-2 mice, as well as in R+/A+ mice. Increases in systemic arterial mean pressure and cerebral arteriolar mean and pulse pressures were similar in the 2 groups of mice. Levels of renin-angiotensin activity, on the other hand, were presumably quite different. Whereas, activity of the renin-angiotensin system is known to be elevated in R+/A+ mice, activity in BPH-2 mice is thought to be normal. Thus, although increased activity of the renin-angiotensin system may contribute to the development of cerebral arteriolar hypertrophy in R+/A+ mice, it is likely that other factors, such as increases in arteriolar pressure, endothelial factors, or sympathetic nerves, play a more important role than renin-angiotensin in hypertrophy of cerebral arterioles in BPH-2 mice.

**Vascular Mechanics**

The 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. Furthermore, prevention of hypertension in cerebral arterioles of SHRSP by treatment with an ACE inhibitor or carotid clipping significantly attenuates increases in arteriolar distensibility. We were not surprised, therefore, by the finding in this study that distensibility, as well as the cross-sectional area of the vessel wall, was increased in cerebral arterioles of R+/A+ mice and BPH-2 mice.

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. Therefore, a possible explanation for the finding in this study of increased cerebral arteriolar distensibility in R+/A+ and BPH-2 mice is that hypertrophy of the vessel wall is accompanied by a disproportionate increase in the more compliant components of the vessel wall. Another possibility that cannot be ruled out is that matrix components in the arteriolar wall undergo qualitative alterations during chronic hypertension, which, in turn, lead to increases in passive distensibility.

**Perspectives**

We have proposed previously that one of the mechanisms that could result in remodeling may involve migration of smooth muscle cells within the vessel wall. Angiotensin II has been shown to stimulate migration of vascular smooth muscle in tissue culture. It is also of interest to note that nitric oxide inhibits angiotensin-stimulated migration of vascular smooth muscle. Angiotensin II also stimulates formation of superoxide, which, in turn, deactivates nitric oxide. Thus, angiotensin II may stimulate migration of vascular muscle directly and/or indirectly through removal of the inhibitory influence of nitric oxide. Enhanced migration of smooth muscle in the vessel wall could lead to remodeling with a reduction in external diameter by enabling adjacent smooth muscle cell processes to move past each other and increase the number of times each smooth muscle cell wraps itself around the vascular lumen (ie, an increase in wrapping distance). By increasing their wrapping distance, the migration of smooth muscle cells within the vessel wall would, in
effect, reduce vascular circumference, thereby reducing external diameter and producing encroachment of the tunica media into the lumen.

Another implication of this study relates to factors that may contribute to reductions in dilator reserve during chronic hypertension. Dilator reserve is defined as the difference in vessel diameter before and after maximal dilatation. We have proposed previously that remodeling with a reduction in external diameter may contribute to impairment of dilator reserve in the cerebral circulation during chronic hypertension.28 This concept is supported by the findings in this study that cerebral arterioles in R+/A+ mice undergo both remodeling and a reduction in vasodilator reserve, whereas cerebral arterioles in BPH-2 mice undergo neither. Furthermore, the finding that cerebral arterioles undergo hypertrophy of the vessel wall in both R+/A+ and BPH-2 mice suggests that hypertrophy per se may not play an important role in the impairment of dilator reserve during chronic hypertension.

Acknowledgments
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References
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