Remodeling of Cerebral Arterioles in Chronic Hypertension

Gary L. Baumbach and Donald D. Heistad

Chronic hypertension impairs dilatation of cerebral arterioles. Impairment of dilatation generally has been attributed to hypertrophy of the vessel wall with encroachment on the vascular lumen. In this study, we tested the hypothesis that a reduction in external diameter may contribute to encroachment on the vascular lumen during chronic hypertension. We examined 10–12-month-old, anesthetized Wistar-Kyoto (WKY) rats and stroke-prone spontaneously hypertensive rats (SHRSP). External diameter, stress, and strain of pial arterioles were calculated from measurements of pial arteriolar pressure (servo null), diameter, and cross-sectional area of the arteriolar wall. During maximal dilatation produced with ethylenediaminetetraacetic acid, cross-sectional area of the arteriolar wall was greater in SHRSP than in WKY rats (2,038±57 vs. 1,456±61 μm², p<0.05). External, as well as internal, diameter was less in SHRSP than in WKY rats (101±3 and 88±3 μm in SHRSP vs. 111±3 and 102±3 μm in WKY rats for external and internal diameter, respectively, p<0.05). Reduction in external diameter accounted for 76% of encroachment on the lumen in SHRSP, and hypertrophy per se accounted for only 24%. Distensibility of deactivated pial arterioles was increased in SHRSP. These findings suggest that reduction in external diameter plays an important role in impairment of maximal dilatation of cerebral arterioles in SHRSP, and reduction in vascular diameter in SHRSP cannot be accounted for by altered distensibility. We propose that, during chronic hypertension, cerebral arterioles undergo structural remodeling that results in a smaller external diameter and encroachment on the vascular lumen. Reduction in external diameter appears to account for most of the impairment of cerebral vasodilatation that occurs in chronic hypertension. (Hypertension 1989;13:968–972)
shown previously that EDTA produces maximal dilatation of cerebral arterioles in WKY rats and SHRSP. Diameter of deactivated arterioles was measured at a pial arteriolar pressure of 70 mm Hg in 15 WKY rats and 15 SHRSP. Pial arteriolar pressure was adjusted to 70 mm Hg either by removal of arterial blood when pressure was greater than 70 mm Hg or by infusion of blood when pressure was less than 70 mm Hg.

In six of the WKY rats and six of the SHRSP, we obtained pressure–diameter relations in deactivated pial arterioles by reduction of pial arteriolar pressure in decrements of 10 mm Hg at pressures between 70 and 10 mm Hg. After the last pressure step, blood was reinfused to restore pial arteriolar pressure to control levels.

On completion of in vivo measurements, maximally diluted arterioles were fixed in situ by vascular perfusion of 200 ml glutaraldehyde fixative (2.25% glutaraldehyde in 0.10 M cacodylate buffer) via the ascending aorta. A pressure reservoir was used to maintain perfusion pressure at approximately 110 mm Hg in WKY rats and 180 mm Hg in SHRSP. The brain was removed and weighed; brains were not dried before they were weighed. The arteriolar segment used for pressure–diameter measurements was removed with a microsurgical knife. Fixed arterioles were postfixed in osmium tetroxide (1%), dehydrated, embedded in Spurr’s medium, and sectioned at 1 μm.

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

To determine whether pial arterioles in WKY rats and SHRSP were from similar levels in the vascular tree, we traced the branching order of the middle cerebral artery in six WKY rats and six SHRSP. In all rats, the arteriolar segment examined in vivo was immediately distal to the fourth-order branching point of the middle cerebral artery.

Calculation of Vascular Mechanics

Circumferential stress was calculated as

\[ \sigma = \frac{(PAP \times PAD_i)}{(2WT)} \]

where PAP is pial arteriolar pressure in dynes per centimeter squared, PAD_i is internal diameter of pial arterioles and WT is wall thickness. Wall thickness was calculated from cross-sectional area of the vessel wall (CSA) and internal diameter of pial arterioles:

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

External diameter of pial arterioles (PAD_i) was calculated as
TABLE 1. Baseline Measurements in Pial Arterioles

<table>
<thead>
<tr>
<th>Measurements</th>
<th>WKY</th>
<th>SHRSP</th>
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<tbody>
<tr>
<td><strong>Before maximal dilatation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>109±3</td>
<td>191±7*</td>
</tr>
<tr>
<td>Mean pial arteriolar pressure (mm Hg)</td>
<td>66±2</td>
<td>115±6*</td>
</tr>
<tr>
<td>Internal diameter of pial arterioles (μm)</td>
<td>59±3</td>
<td>48±3*</td>
</tr>
<tr>
<td>External diameter of pial arterioles (μm)</td>
<td>73±3</td>
<td>70±2</td>
</tr>
<tr>
<td>Arterial blood gases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pco₂ (mm Hg)</td>
<td>34±1</td>
<td>36±1</td>
</tr>
<tr>
<td>pH</td>
<td>7.36±0.02</td>
<td>7.35±0.01</td>
</tr>
<tr>
<td>Po₂ (mm Hg)</td>
<td>115±3</td>
<td>111±6</td>
</tr>
<tr>
<td><strong>During maximal dilatation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal diameter of pial arterioles (μm)</td>
<td>102±3</td>
<td>88±3*</td>
</tr>
<tr>
<td>External diameter of pial arterioles (μm)</td>
<td>111±3</td>
<td>101±3*</td>
</tr>
<tr>
<td>Cross-sectional area of arteriolar wall (μm²)</td>
<td>1,456±61</td>
<td>2,038±57*</td>
</tr>
<tr>
<td>Wall thickness (μm)</td>
<td>4.3±0.2</td>
<td>6.7±0.1*</td>
</tr>
</tbody>
</table>

Values are mean±SEM in pial arterioles of 15 Wistar-Kyoto (WKY) rats and 15 stroke-prone spontaneously hypertensive rats (SHRSP).

*p<0.05 vs. WKY rats.

PADₑ=PADᵢ+2WT

Circumferential strain (e) was calculated as

\[ e = \frac{(PADᵢ - PAD₀)}{PAD₀} \]

where PAD₀ is original diameter. Internal diameter measured at 10 mm Hg was used for original diameter in the calculation of circumferential strain, because reliable measurements of the internal diameter of pial arterioles could not be obtained at a pial arteriolar pressure of 0 mm Hg, as discussed previously.⁶

Statistical Analysis

Comparison of pressure–diameter curves and stress–strain curves were performed by multivariate analysis of variance. Sources of variance were groups (WKY and SHRSP), subjects within groups, and pressure or strain. Baseline measurements were compared with an unpaired \( t \) test.

Results

Baseline Measurements

Body weight was greater in WKY rats than SHRSP (430±6 vs. 363±8 g, \( p<0.05 \)). Brain weight, however, was not significantly different in the two groups of rats (2.42±0.05 vs. 2.38±0.03 g). Thus, brain weight is not decreased in SHRSP, despite a lower body weight.

Before deactivation of smooth muscle, pressure was greater and internal diameter was less in pial arterioles of SHRSP than in those of WKY rats (Table 1). During maximal dilatation produced by EDTA, both internal and external diameter were less in SHRSP than in WKY rats. Cross-sectional area of the arteriolar wall and wall thickness were greater in SHRSP than in WKY rats. Based on the mean values (Table 1) of internal and external diameter and cross-sectional area of the arteriolar wall in WKY rats (\( PADᵢ, PADₑ, \) and \( CSAᵪ, \) respectively) and SHRSP (\( PADᵢ, \) \( PADₑ, \) and \( CSAᵦ, \) respectively), we estimated that 76% of the decrease in internal diameter in pial arterioles of SHRSP resulted from a smaller external diameter, which was calculated as

\[ \frac{[PADᵢ_(W)-\frac{(PADₑ_i-4CSAᵦ_i)/\pi)^{1/2}}{PADᵢ-(PADₑ_i+2WT)}]}{PADᵢ} \times 10^{-2} \]

whereas only 24% resulted from hypertrophy of the arteriolar wall, which was calculated as

\[ \frac{[PADᵢ_(W)-\frac{(PADₑ_i-4CSAᵦ_i)/\pi)^{1/2}}{PADᵢ-(PADₑ_i+2WT)}]}{PADᵢ} \times 10^{-2} \]

These findings suggest that, not only does the smaller external diameter contribute to encroachment on the lumen of cerebral arterioles in SHRSP, its contribution is greater than that of hypertrophy per se.

Vascular Mechanics

During reductions in pressure, internal diameter of deactivated pial arterioles decreased passively in both WKY rats and SHRSP (Figure 1, left panel). Diameter was significantly less in SHRSP than in WKY rats at pressures between 10 and 70 mm Hg. The stress–strain curve of arterioles in SHRSP

\[ \text{FIGURE 1. Pressure–diameter (left panel) and stress–strain (right panel) relations in pial arterioles deactivated by EDTA in six Wistar-Kyoto (WKY) rats and six stroke-prone spontaneously hypertensive rats (SHRSP). Values are mean±SEM. *p<0.05 vs. WKY rats.} \]
demonstrated a pronounced rightward shift with respect to the curve in WKY rats (Figure 1, right panel). Stress–strain curves closely approximated an exponential curve in the two groups of rats ($r^2=0.99±0.01$ and $0.99±0.01$). These findings indicate that distensibility of arterioles is paradoxically increased in SHRSP.

**Discussion**

The major new finding in this study is that external, as well as internal, diameter of deactivated cerebral arterioles is reduced in SHRSP. Furthermore, the reduction in external diameter apparently makes a greater contribution than hypertrophy to the reduction in internal diameter. The implication of this finding is that the reduction in internal diameter of cerebral arterioles in SHRSP cannot be attributed primarily to encroachment on the lumen by arteriolar hypertrophy. In addition, confirmation of our previous finding that distensibility of cerebral arterioles is increased in SHRSP indicates that the reduction in diameter does not result from impairment of arteriolar distensibility.

**Consideration of Methods**

The methods that we used to determine dimensional and mechanical characteristics of pial arterioles take into account several factors that could compromise the validity of our findings. These factors, which include plasma skimming, effectiveness of smooth muscle deactivation, compressibility of the vessel wall, and definition of original diameter in the determination of strain, have been considered in detail previously.

We considered the possibility that size of pial arterioles of the same branching order might be different in SHRSP than in WKY rats because of differences in body weight. If vessel size is proportional to the mass of tissue that it supplies, and if brain weight is proportional to body weight, then pial arterioles would be expected to be smaller in SHRSP than in WKY rats because body weight is less in SHRSP. In contrast to body weight, however, brain weight is similar in SHRSP and WKY rats. It is unlikely, therefore, that differences in body weight can account for the smaller size of pial arterioles in SHRSP.

**Consideration of Previous Studies**

Previous studies have demonstrated that chronic hypertension impairs maximal dilatation of blood vessels in the brain. During maximal dilatation, internal diameter of the basilar artery and branches of the posterior cerebral artery is significantly less in SHR and SHRSP than in WKY rats. Furthermore, the finding in this study that internal diameter of deactivated pial arterioles is less in SHRSP than in WKY rats indicates that maximal dilatation of cerebral arterioles is reduced in SHRSP. Thus, chronic hypertension impairs maximal dilatation of both large arteries and arterioles in the brain.

In contrast to our findings in this study and a previous study, internal diameter of passive pial arterioles has been reported to be similar in WKY rats and SHR. There may be two reasons for the apparent discrepancy in findings. First, internal diameter of passive pial arterioles was measured at prevailing levels of systemic arterial pressure in both normotensive and hypertensive rats. In contrast, we measured internal diameter of passive arterioles at the same level of pial arteriolar pressure (70 mm Hg) in the two groups of rats. Second, rats were examined at a younger age (18–21 weeks old) in the previous study than in this study (10–12 months old). We have shown previously that internal diameter of pial arterioles during maximal dilatation is significantly less in SHRSP than in WKY rats at 6–8 months of age, but not at 3 months of age. Thus, prolonged periods of hypertension may be required to produce impairment of maximal dilatation in cerebral arterioles.

To examine the possibility that smaller external, as well as internal, diameter may be related to the duration of hypertension, we calculated external diameter of pial arterioles in 3-month-old WKY rats and SHRSP from values of internal diameter and cross-sectional area of the arteriolar wall that we obtained previously. External diameter was not significantly different in 3-month-old WKY rats and SHRSP ($117±3$ and $113±5 \mu m$, $p>0.1$). Furthermore, external diameter was significantly less in 10–12-month-old SHRSP than in 3-month-old SHRSP ($101±3$ [from Table 1] vs. $113±5 \mu m$, $p<0.05$). These findings suggest that the smaller external diameter of pial arterioles in 10–12-month-old SHRSP results from a reduction in diameter during the course of hypertension and may not be related to an inherent difference in caliber of pial arterioles in WKY rats and SHRSP.

Impairment of maximal dilatation by chronic hypertension has been attributed in part to reduction of distensibility of cerebral blood vessels. This concept is supported by findings in large cerebral arteries in vitro. Distensibility of the basilar artery and branches of the posterior cerebral artery is less in SHR and SHRSP than in WKY rats. In contrast to large cerebral arteries, however, we found in this and a previous study that distensibility of cerebral arterioles is paradoxically greater in SHRSP than in WKY rats. Thus, impairment of maximal dilatation of cerebral arterioles in SHRSP cannot be attributed to reduction in vascular distensibility.

A likely explanation for the different effects of chronic hypertension on distensibility of large cerebral arteries and cerebral arterioles is that the effect of hypertension on composition of the vessel wall may differ with vessel size. In branches of the posterior cerebral artery in SHR, reductions in distensibility are accompanied by an increase in the ratio of nondistensible-to-distensible components in the vessel wall. In contrast, we have shown previ-
ously that the ratio of nondistensible-to-distensible components is reduced in cerebral arterioles of SHRSP, with a corresponding increase in distensibility. During chronic hypertension, therefore, proportion of the vessel wall is altered in a direction that favors a reduction in distensibility of large arteries in SHR and an increase in distensibility of cerebral arterioles in SHRSP.

The primary mechanism that has been proposed to account for impairment of maximal dilatation by chronic hypertension is hypertrophy of the vessel wall with reduction of internal diameter by encroachment on the vascular lumen. Several studies have demonstrated hypertrophy of cerebral arterioles in SHR and SHRSP. If reductions in internal diameter resulted solely from encroachment by hypertrophy, however, external diameter of cerebral arterioles would not be expected to be less in SHRSP than in WKY rats. This study demonstrates that external, as well as internal, diameter of pial arterioles is significantly smaller in SHRSP than in WKY rats. Therefore, another mechanism, in addition to encroachment on the vascular lumen by hypertrophy, must be invoked to account for impairment of maximal dilatation of cerebral arterioles in chronic hypertension.

Hypothesis

We propose that cerebral arterioles undergo structural remodeling during chronic hypertension. The possibility of vascular remodeling in hypertension is supported by the observation that wall-to-lumen ratio of intestinal arterioles is increased in humans with chronic hypertension, even without evidence of hypertrophy of the arteriolar wall. Based on this finding, it was proposed that, during prolonged hypertension, smooth muscle cells may become shorter and are no longer able to extend to their original length during relaxation, thus resulting in a reduction in maximal dilatation. We are aware of no evidence to support the hypothesis that length of vascular smooth muscle decreases during chronic hypertension. Nevertheless, our findings suggest the possibility that chronic hypertension may produce remodeling of cellular or extracellular components in the vessel wall, which thereby reduces external diameter without reducing vascular distensibility. We propose that structural remodeling occurs in cerebral arterioles during chronic hypertension and results in a reduction of external diameter. Based on this concept, maximal dilatation of cerebral arterioles is impaired by reductions in external diameter, as well as by hypertrophy of the vessel wall, with encroachment on the lumen.

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References


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