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Composition and Mechanics of Cerebral Arterioles in Hypertensive Rats

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It was demonstrated recently that, in contrast to large cerebral arteries, distensibility of cerebral arterioles is increased in stroke-prone spontaneously hypertensive rats (SHRSP). The goals of this study were to examine composition of normal cerebral arterioles, and to determine whether chronic hypertension alters relative composition of the arteriolar wall. Pial arterioles in normotensive Wistar Kyoto rats contain large amounts of smooth muscle, small amounts of elastin and basement membrane, and very little collagen. Hypertrophy of pial arterioles in SHRSP is characterized by increases in the elastic components, smooth muscle and elastin. The stiffer components, collagen and basement membrane either did not change or decreased. It is concluded that cerebral arterioles contain proportionately more smooth muscle and less collagen than large arteries, and that hypertrophy of cerebral arterioles in SHRSP is accompanied by a relative increase in the more elastic components of the arteriolar wall, which probably contributes to the increase in arteriolar distensibility. (Am J Pathol 1988, 133:464–471)

CHRONIC HYPERTENSION ALTERS mechanical characteristics of cerebral blood vessels. Distensibility is decreased in basilar artery of spontaneously hypertensive rats (SHR)[1] and stroke-prone spontaneously hypertensive rats (SHRSP),[2,3] and in posterior cerebral artery of SHR.[4] In contrast to effects of chronic hypertension on large arteries, the authors found recently that distensibility of cerebral arterioles is increased in SHRSP.[5]

Alterations in vascular mechanics of cerebral arterioles presumably are related to changes in wall structure. Distensibility of blood vessels is influenced by proportional composition of the vessel wall.[6] For example, the decrease in distensibility of posterior cerebral artery that occurs in SHR is accompanied by an increase in the content of collagen, but not elastin.[4] There are exceptions, however, to the relationship between distensibility and proportional composition. For example, distensibility is decreased in the internal carotid artery of SHR, even though the ratio of collagen to elastin is reduced.[7]

The composition of blood vessels varies with vessel size. The content of collagen is proportionately less in the aorta (15% in thoracic aorta[8]) than its major branches (45% in femoral artery and 51% in carotid artery[9]). The content of smooth muscle is proportionately greater in arterioles (49% in arterioles of hamster cheek pouch[10] and 86% in pial arterioles[11]) than in large arteries (31% in femoral artery and 29% in carotid artery[9]). Whereas composition of large vessels has received considerable attention, there have been only a few studies that have systematically characterized the composition of arterioles.[6,10,11]

The goals of this study were first, to determine the composition of normal cerebral arterioles using a morphometric approach and second, to determine whether alterations in distensibility of cerebral arterioles in SHRSP are accompanied by alterations in arteriolar composition. Based on the finding that distensibility of cerebral arterioles is increased in SHRSP,[5] the hypothesis was that the relative proportion of elastic components, such as elastin and smooth muscle, might increase in cerebral arterioles of SHRSP.

Materials and Methods

Six to eight-month-old, male WKY and SHRSP rats were studied. The animals were anesthetized with

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sodium pentobarbital (5 mg/100 g body weight intraperitoneally), intubated, and mechanically ventilated with room air and supplemental O_2. Paralysis of skeletal muscle was obtained with gallamine triethiodide (20 mg/kg intravenously). Because the animals were paralyzed, they were evaluated frequently for adequacy of anesthesia. Additional anesthesia 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.

Measurement of Pial Arteriolar Pressure and Diameter

Pressure and diameter of first order (1A) pial arterioles[12] was measured through an open skull preparation using a method that was described in detail previously.[5] A craniotomy was made over the left parietal cortex, and the dura was incised to expose cerebral vessels. The exposed brain was suffused continuously with artificial CSF, warmed to 37–38 C, and equilibrated with a gas mixture of 5% CO_2–95% N_2. The composition of the CSF was KCl, 3.0 mM; $MgCl_2$, 0.6 mM; $CaCl_2$, 1.5 mM; NaCl, 131.9 mM; $NaHCO_3$, 24.6 mM; urea, 6.7 mM; and dextrose, 3.7 mM. The CSF pH was 7.24 ± 0.02 (mean ± SE), pCO_2 47 ± 1 mmHg, and pO_2 61 ± 2 mmHg.

Pial arteriolar pressure was measured with a micropipette connected to a servonull pressure measuring device (model 4A, Instruments for Medicine and Physiology, Inc, San Diego, CA). Pipettes were sharpened to a beveled tip of 3–5 μ in diameter and inserted into the lumen of a 1A pial arteriole using a micromanipulator. The pipette tip had no discernible effect on most pial arterioles. When hemorrhage or persistent constriction or dilatation occurred at the insertion point, pial arteriolar pressure was measured in another 1A arteriole distant from the original site, or the experiment was terminated. Two of 22 experiments were terminated because of damage to the arteriole by the pipette.

Pial vessels were monitored through a Leitz microscope (NP1 ×10 objective) attached to a video system consisting of a television camera, a videotape recorder and a video monitor. Final magnification of the video image was ×354. Inner diameter of pial arterioles was measured from videotapes using a Bioquant image analyzing system (R & M Biometrics, Inc., Nashville, TN). To determine the precision of this system, lengths of 10, 50, and 100 μ were measured 5 times each from a stage micrometer. The precision of the Bioquant system ranged from 0.4–0.6 μ.

To determine whether 1A pial arterioles in WKY and SHRSP were from similar levels in the vascular tree, the branching order of the middle cerebral artery was traced in four WKY and four SHRSP. In all rats, the arteriolar segment examined *in vivo* was immediately distal to the fourth order branching point of the middle cerebral artery.

Experimental Protocol and Tissue Preparation

About 30 minutes after completion of surgery, pressure and diameter were measured in pial vessels under baseline conditions. Vascular smooth muscle then was deactivated by suffusion of pial vessels with artificial CSF containing ethylenediaminetetracetic acid (EDTA; 67 mM). We have shown previously[5] that: 1) the maximal effect of EDTA in WKY and SHRSP is obtained at a concentration of 67 mM (25 mg/ml); 2) suffusion of pial arterioles with EDTA produces greater dilatation than suffusion with adenosine; 3) dilatation of pial arterioles is no greater during suffusion of EDTA in combination with intravascular injection of EDTA or systemic hypercapnia than during suffusion of EDTA alone; and 4) EDTA prevents constriction of pial arterioles that is produced by suffusion with vasopressin. Thus, multiple lines of evidence indicate that EDTA produces maximal dilatation of cerebral arterioles.

Pressure-diameter relationships were obtained in deactivated pial arterioles by reducing pial arteriolar pressure in decrements of 10 mmHg at pressures between 70 and 10 mmHg. Pressure was reduced using controlled hemorrhage. 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.

Fixation of pial arterioles was obtained before killing the animal by suffusion of vessels with glutaraldehyde fixative (2.25% glutaraldehyde in 0.10 M cacodylate buffer) while maintaining pial arteriolar pressure at *in vivo* levels (60–80 mmHg). Arterioles were considered to be adequately fixed when blood flow through the arteriole had ceased. To determine whether the fixation process altered vessel diameter, external diameter of pial arterioles was monitored during fixation. External diameter before and after fixation was 109 ± 4 (mean ± SE) and 110 ± 4 μ in ten WKY and 104 ± 4 and 104 ± 4 μ in ten SHRSP ($P > 0.05$).

After the animal was killed, the arteriolar segment used for measurement of pressure and diameter *in vivo* was removed with a microsurgical knife. Fixed arterioles were postfixed in osmium tetroxide (1%), dehydrated, stained *en bloc* with uranyl acetate

(0.5%), and embedded in Spurr's media while maintaining cross-sectional orientation.

Calculation of Vascular Mechanics

Circumferential stress (σ) was calculated as $\sigma = (PAP \cdot PAD_i)/(2WT)$, where PAP is pial arteriolar pressure in dynes/sq cm, PAD_i is inner pial arteriolar diameter, and WT is wall thickness. Because volume of the vessel wall does not change with changes in intravascular pressure,[13,14] it was assumed that cross-sectional area of the vessel wall remains constant with changes in arteriolar diameter. Thus, wall thickness was calculated from cross-sectional area of the vessel wall (CSA) and inner pial arteriolar diameter: $WT = ([4CSA/\pi + PAD_i^2]^{1/2} - PAD_i)/2$. Histologic determinations of cross-sectional area were used in all calculations of wall thickness and circumferential stress.

Circumferential strain (ϵ) was calculated as $\epsilon = (PAD_i - PAD_o)/PAD_o$, where PAD_o is original diameter. Original diameter is defined as diameter at 0 mmHg or at very low pressure with the vessel extended to *in situ* length.[14,15] Because blood flow stops during reduction of pressure to 0 mmHg and because passive vascular collapse is likely at 0 mmHg, reliable measurements of inner diameter of pial arterioles could not be obtained at 0 mmHg. Blood flow through pial arterioles at 10 mmHg of pial arteriolar pressure was adequate to maintain an intact red cell column. Therefore, inner diameter measured at 10 mmHg was used for original diameter in the calculation of circumferential strain.

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: $\sigma = \sigma_o e^{\beta\epsilon}$, where σ_o is stress at original diameter and β is a constant that is related to the rate of increase of the stress-strain curve. Tangential elastic modulus (E_T) was calculated at several different values of stress from the derivative of the exponential curve: $E_T = d\sigma/d\epsilon = \beta\sigma_o e^{\beta\epsilon}$.

Determination of Wall Composition

Cross-sectional area of the vessel wall was measured histologically from 1-μ sections using 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 vessel wall. The inner and outer edges of the vessel wall were defined by the luminal surface of endothelium and the abluminal surface of the tunica media, respectively. Cross-sectional area of the arteriolar wall was calculated by subtracting luminal cross-sectional area from total cross-sectional area.

Volume density of smooth muscle, elastin, collagen, basement membrane, and endothelium was quantitated from electron micrographs of the vessel wall. Ultrathin sections of the arteriolar wall were cut on an LKB ultramicrotome and stained with phosphotungstic acid (0.25%). Sections from two different levels in each tissue block were examined with a Phillips 300 electron microscope. Electron micrographs were taken at a standard magnification of ×9000 and enlarged by a factor of 2.45 for a final magnification of ×22,050. To insure uniform sampling, the vessel wall was divided into 4 quadrants of equal size. One or two electron micrographs were taken randomly in each quadrant for a total of 7 or 8 electron micrographs per level.

A standard point counting grid (double square lattice test system D16)[16] was used to count the number of points contained within profiles of smooth muscle, elastin, collagen, basement membrane, and endothelium. Volume density (V_V) of each component was calculated from the number of points in each component (P_a) and the total number of points contained within the vessel wall (P_T): $V_V = P_a/P_T$. The total number of counts per electron micrograph was 395 ± 8 in WKY and 515 ± 9 in SHRSP, and the total number of counts per level was 3026 ± 125 in WKY and 3580 ± 132 in SHRSP. To determine the precision of counting, the relative standard error (SE_R) of mean volume density was calculated for each level. The relative standard errors for smooth muscle, elastin, basement membrane, and endothelium were less than 10%. The relative standard errors for collagen ranged from 6–15%. Thus, the number of points counted per level achieved a precision ($100 - SE_R$) of at least 90% for smooth muscle, elastin, basement membrane and endothelium. The precision obtained for collagen, which was the component with the smallest volume density, was between 85 and 94%. Cross-sectional area of individual wall components (CSA_C) was calculated from V_V of each component and total cross-sectional area (CSA_T) of the wall measured histologically: $CSA_C = CSA_T \times V_V$.

Statistical Analysis

Comparison of relationships of stress to strain and tangential elastic modulus to stress was performed using analysis of variance. The sources of variance were groups, subjects within groups, and strain or stress. Measurements of pressure, diameter, total cross-sectional area, wall thickness, volume density, and cross-sectional area of individual components were compared with an unpaired *t*-test. The standard error of the means are based on comparison between animals.

Results

Vascular Mechanics

Before deactivation of smooth muscle with EDTA, diameter of pial arterioles was significantly smaller in SHRSP than in WKY (Table 1). After deactivation of smooth muscle, diameter tended to be smaller in SHRSP than in WKY (Table 2), but the difference in diameter (6 ± 5 μ) was not statistically significant ($P < 0.25$). Cross-sectional area and thickness of the arteriolar wall were greater in SHRSP than in WKY during maximal dilatation (Table 2). Thus, cerebral arterioles develop significant hypertrophy in SHRSP, with minimal encroachment on the vascular lumen.

The stress–strain curve for SHRSP was shifted to the right of the curve in WKY (Figure 1, left panel). The shape of the stress–strain curves closely approximated an exponential curve in both SHRSP and WKY ($r^2 = 0.99 \pm 0.01$ and 0.98 ± 0.01). Tangential elastic modulus increased linearly with respect to stress in SHRSP and WKY (Figure 1, right panel). Furthermore, the slope of tangential elastic modulus *vs.* stress was significantly less in SHRSP than in WKY (5.1 ± 0.4 *vs.* 7.0 ± 0.6; $P < 0.05$). Because the slope of tangential elastic modulus *vs.* stress reflects stiffness of biologic tissue,[17,18] these findings indicate that circumferential stiffness of pial arterioles is reduced in SHRSP.

Composition

Morphology

The composition of pial arterioles was qualitatively similar in WKY and SHRSP (Figure 2), and consisted of five major components: endothelium, smooth muscle, elastin, basement membrane, and collagen. Smooth muscle was the predominant component in the arteriolar wall. The number of layers of smooth muscle, which varied between 1 and 2, appeared to be similar in WKY and SHRSP, but thickness of smooth muscle cells appeared to be greater in SHRSP. Elastin was confined primarily to the internal elastica, although small amounts of elastin were observed between smooth muscle cells occassionally in SHRSP and rarely in WKY. Other components in the arteriolar wall included basement membrane, which lined endothelial and smooth muscle cells, and collagen fibrils, which were found between smooth muscle cells. Collagen also was found in arachnoid tissue adjacent to pial arterioles. The distribution of arachnoid was irregular with respect to the arteriolar wall. There were many large gaps in the arachnoid layer which did not contain collagen fibrils.

Stereology

The arteriolar wall was composed primarily of smooth muscle in both WKY and SHRSP (Table 3).

Table 1—Baseline Values Before Deactivation of Pial Arterioles

	WKY	SHRSP
Systemic arterial pressure (mmHg)	100 ± 5	187 ± 4*
Pial arteriolar pressure (mmHg)	58 ± 3	113 ± 4*
Pial arteriolar diameter (μ)	54 ± 3	45 ± 2*

Values are mean ± SE in ten WKY and ten SHRSP.
* $P < 0.05$ *vs.* WKY.

The contributions of elastin, basement membrane, and endothelium to wall volume (Table 3) were much smaller than the fraction of smooth muscle. The volume density of collagen accounted for less than 1% of the total volume of pial arterioles in both normotensive and hypertensive rats (Table 3).

Most of the hypertrophy that occurred in pial arterioles of SHRSP resulted from increases in cross-sectional area of smooth muscle and elastin (Table 3). Cross-sectional area of collagen and basement membrane tended to increase in SHRSP, whereas cross-sectional area of endothelium tended to decrease (Table 3). Thus, hypertrophy of pial arterioles in SHRSP resulted primarily from increases in the more elastic components of the arteriolar wall, smooth muscle and elastin, whereas the stiffer components, collagen and basement membrane, contributed little to the increase in wall mass.

To relate alterations in structure of pial arterioles to alterations in distensibility, we calculated the ratio of nondistensible to distensible components in the arteriolar wall. Previously only collagen and elastin have been considered when calculating this ratio in large arteries.[7] The ratio of collagen to elastin was similar in pial arterioles of WKY and SHRSP (Figure 3, left panel). Pial arterioles, contain very little collagen however. Other components of the vessel wall, such as basement membrane and smooth muscle, constitute a major fraction of the arteriolar wall and may contribute importantly to distensibility of pial arterioles. When basement membrane was added to collagen, the ratio of nondistensible to distensible components in pial arterioles was less in SHRSP than in WKY (Figure 3, middle panel).

The elastic moduli of smooth muscle and elastin indicate that both components are relatively elastic.[19] When smooth muscle and elastin were added to-

Table 2—Baseline Values After Deactivation of Pial Arterioles

	WKY	SHRSP
Pial arteriolar diameter (μ)	99 ± 3	93 ± 4
Cross-sectional area of wall (sq μ)	1413 ± 87	1787 ± 67*
Wall thickness (μ)	4.4 ± 0.2	5.8 ± 0.3*
Wall-to-lumen ratio	0.06 ± 0.01	0.10 ± 0.01*

Values are mean ± SE in ten WKY and ten SHRSP.
* $P < 0.05$ *vs.* WKY.

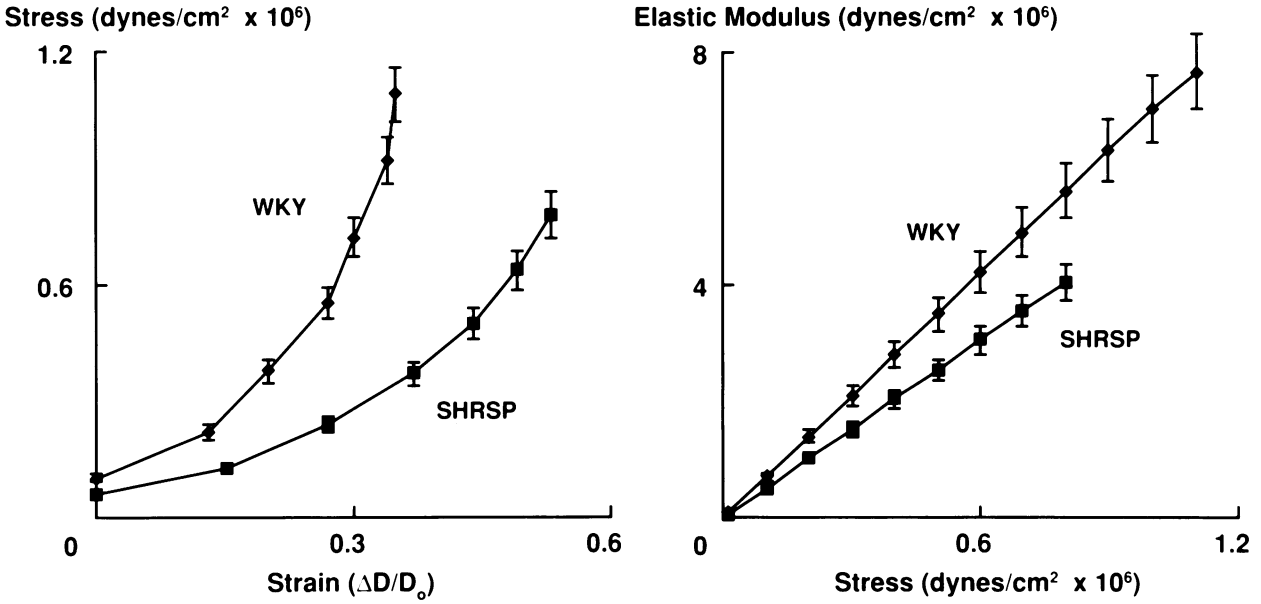

Figure 1—Stress–strain relationship and tangential elastic modulus *vs.* stress in deactivated pial arterioles of WKY and SHRSP. The slope of tangential elastic modulus *vs.* stress, which is an indicator of stiffness of the arteriolar wall, was significantly less in WKY than in SHRSP. A reduction in slope indicates a reduction in stiffness. Values are mean ± SE.

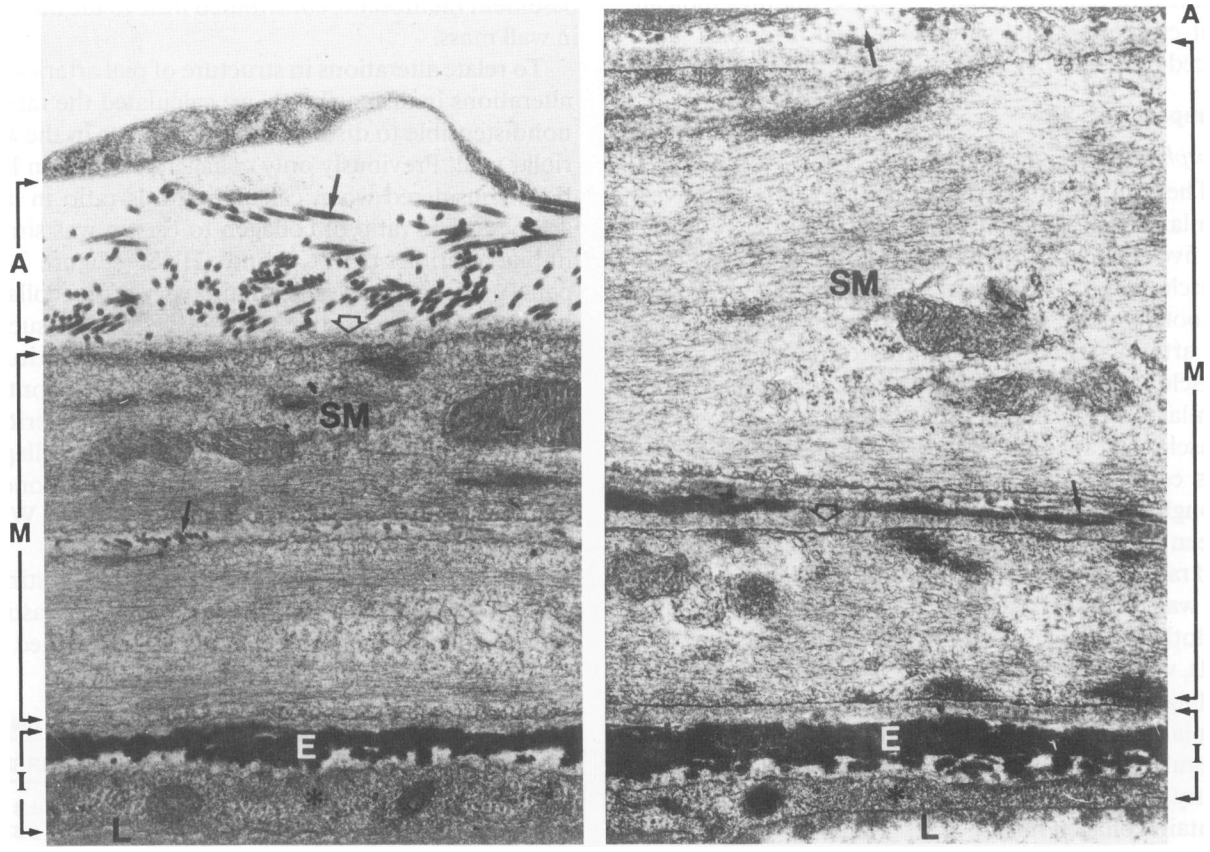

Figure 2—Electron micrographs of pial arterioles in WKY (left panel) and SHRSP (right panel). The vascular lumina (L) are oriented toward the bottom. Major divisions of the vessel wall are intima (I), media (M), and arachnoid (A). Components of the vessel wall include endothelium (*), elastin (E), smooth muscle (SM), collagen (closed arrows) and basement membrane (open arrows). Elastin is electron dense because of staining by phosphotungstic acid. (Phosphotungstic acid enhanced with uranyl acetate, ×12,350)

gether, the ratio of nondistensible to distensible components was less in SHRSP than in WKY (Figure 3, right panel). Thus, hypertrophy of pial arterioles in SHRSP is accompanied by a relative increase in the more elastic components of the arteriolar wall.

Discussion

This study indicates that increases in distensibility of cerebral arterioles during chronic hypertension are accompanied by increases in smooth muscle and elastin. Other components in the arteriolar wall, such as collagen and basement membrane, do not increase significantly. Because smooth muscle and elastin are relatively elastic, and collagen and basement membrane are stiffer, the proportion of distensible elements increases in cerebral arterioles of SHRSP. A consequence of these changes is that proportional composition of cerebral arterioles is shifted during chronic hypertension in a direction that favors an increase in distensibility of cerebral arterioles.

Consideration of Methods

The method 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.[5]

The application of point counting methods to cerebral arterioles presents some potential limitations. First, there is a large disparity in volume density of the various wall components. The arteriolar wall contains more than 70 times as much smooth muscle as collagen. Methods for determining optimal point density[16] predict that volume density of smooth muscle (V_V = ~70%) can be estimated with a precision of 90% using fewer than 100 counts per representative sample. Using the same criteria, it would take 10,000 counts per representative sample to estimate volume density of collagen (V_V = ~1%) with the same precision. We counted about 3000 points per representative sample, which would be expected to achieve a precision of at least 90% for any component with a volume density greater than 3%.[16] Based on the relative standard errors of mean volume density that were obtained in this study, the precision of point counting was greater than 90% for all components except collagen. The precision for collagen was between 85 and 94%. Thus, 3000 counts per representative sample were sufficient to achieve a reasonable level of precision for all components in cerebral arterioles.

Another potential limitation is that random sampling of the vessel wall may be impeded by heterogeneous orientation of the components within the vessel wall. Elastin is concentrated primarily in the internal elastic lamina, whereas smooth muscle, basement membrane, and collagen are concentrated primarily within the tunica media. The proper application of point counting methods requires that the tissue is sampled in a random manner.[16] To increase the randomness of our sampling process, we included the full-thickness of the arteriolar wall in all electron micrographs to insure that each component had an equal

Table 3—Components of Pial Arterioles

	WKY	SHRSP
Cross-sectional area (sq μ)		
Smooth muscle	978 ± 59	1339 ± 44*
Elastin	89 ± 8	117 ± 10*
Collagen	12 ± 2	15 ± 1
Basement membrane	161 ± 13	173 ± 12
Endothelium	174 ± 12	141 ± 11
Volume density (%)		
Smooth muscle	69.4 ± 1.3	75.0 ± 0.9*
Elastin	6.4 ± 0.3	6.6 ± 0.3
Collagen	0.8 ± 0.1	0.8 ± 0.1
Basement membrane	11.3 ± 0.4	9.7 ± 0.4*
Endothelium	12.1 ± 0.7	7.9 ± 0.5*

Composition was quantitated in the arteriolar segment used for *in vivo* determination of vascular mechanics in ten WKY and ten SHRSP (1 arteriole per rat). Values are mean ± SE.
* $P < 0.05$ *vs.* WKY.

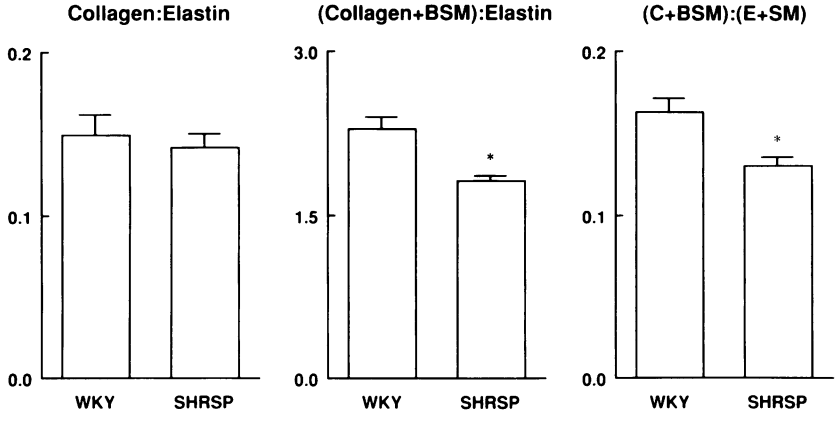

Figure 3—Ratio of collagen to elastin, collagen plus basement membrane to elastin ([Collagen + BSM]:Elastin), and collagen plus basement membrane to elastin plus smooth muscle ([C + BSM]:[E + SM]) in pial arterioles of WKY and SHRSP rats. *$P < 0.05$ *vs.* WKY.

chance of inclusion, randomized the orientation of the point counting grid with respect to the arteriolar wall, and sampled each quadrant of the arteriolar wall equally to improve the uniformity of individual samples.

The arachnoid that is adjacent to the outer surface of pial arterioles contains numerous collagen fibrils. One might assume that the collagen in arachnoid contributes to structural integrity of the arteriolar wall and, therefore, should be considered as part of the collagen component of pial arterioles. We did not include arachnoid collagen in our calculation of the volume density of collagen in pial arterioles for several reasons. First, there were many gaps in the arachnoid layer that contained no collagen. Thus, it is unlikely that arachnoid collagen could affect the arteriolar wall in a uniform manner. Second, it is unlikely that the tunica adventitia, which corresponds to the arachnoid tissue adjacent to pial arterioles, contributes to the circumferential mechanics of peripheral blood vessels.[6]

In considering the contribution of basement membrane to the composition of pial arterioles, we assumed that mechanical properties of basement membrane and collagen are similar. Because the elastic modulus of basement membrane has not been measured, we can only speculate about its mechanical characteristics. Our rationale for adding basement membrane to collagen, rather than to elastin, is that basement membrane contains significant amounts of type IV collagen.[20,21] Although the fibrillary structure of type IV collagen is not as highly organized as that of type III collagen, type IV collagen is organized into fibrils that form a netlike structure.[22,23] It seems reasonable, therefore, to include basement membrane with the relatively nondistensible elements of the vessel wall. Smooth muscle, on the other hand, was included with the relatively distensible elements because it has an elastic modulus that is similar to that of elastin.[19]

Consideration of Previous Studies

This study is the first, to our knowledge, to characterize the composition of cerebral arterioles with respect to the content of collagen. A surprising finding was that cerebral arterioles contain very little collagen. In the only other study in which collagen content was estimated in arterioles, Wiederhielm[6] found that collagen accounted for 22% of the wall of mesenteric arterioles in frog. The large difference in collagen content of arterioles in this study and Wiederhielm's study may reflect regional differences in composition of cerebral and peripheral arterioles, or species-dependent differences in composition of the arteriolar wall.

A fundamental hypothesis of vascular mechanics is that passive distensibility of blood vessels is dependent, at least in part, on proportional composition of the vessel wall.[6,7,24] This hypothesis is based on classical principles of vascular mechanics that consider the relationship between structure and mechanics of the vessel wall in terms of the elastic moduli of individual wall components. Because elastic modulus is normalized for wall thickness, the contribution of individual wall components is assumed to be proportional to the elastic modulus and volume of each component.[6,24] Thus, when considering the effects of chronic hypertension on structure and passive distensibility of cerebral arterioles, this hypothesis provides a way to separate the effects of alterations in wall composition from the effects of hypertrophy.

If the hypothesis, that passive distensibility is dependent on proportional composition, is valid, then changes in composition of blood vessels during chronic hypertension would be expected to influence mechanical characteristics of the vessel wall. In branches of the posterior cerebral artery, the amount of collagen is greater in SHR than WKY, and the amount of elastin is similar in the two groups.[4] Thus, there is an increase in the collagen to elastin ratio of SHR. Distensibility of these vessels is decreased.[4] In branches of posterior cerebral artery, therefore, an increase in the ratio of nondistensible to distensible components in SHR is associated with a reduction of vascular distensibility.

Our findings in this study and a previous study[5] also suggest an association between changes in proportional composition and mechanics in cerebral arterioles of SHRSP. In contrast to findings in posterior cerebral artery, we found that the ratio of nondistensible to distensible components is decreased, with a corresponding increase in distensibility. Thus, alterations in proportional composition of cerebral vessels during chronic hypertension may contribute to alterations in the mechanics of the vessel wall.

The association of compositional and mechanical changes in cerebral vessels, however, may be coincidental. The relationship of vascular structure and distensibility is complex and no doubt depends on factors other than proportional composition, including orientation of wall components with respect to vascular circumference and connections between elastin, collagen, and smooth muscle.[24] In some vessels, therefore, alterations in composition may not be predictive of alterations in vascular mechanics. For example, distensibility of internal carotid artery is decreased in SHR, despite a reduction in the ratio of collagen to elastin.[7]

Implications

This study has shown that cerebral arterioles are composed primarily of smooth muscle, with very little

collagen, and that hypertrophy of cerebral arterioles in SHRSP results from a disproportionate increase of smooth muscle and elastin, which probably are more distensible than the other components of the arteriolar wall. An implication of our findings is that collagen may contribute less to vascular mechanics in cerebral arterioles than in large arteries. In large arteries, collagen accounts for as much as 50% of the vessel wall.[9] Thus, it is reasonable to assume that collagen is a major determinant of stiffness in large arteries. In comparison to large arteries, the content of collagen in cerebral arterioles is very small. It seems likely, therefore, that other components of cerebral arterioles, such as smooth muscle, elastin, and basement membrane, may contribute importantly to stiffness of the arteriolar wall.

Another implication of our findings is that the disproportionate increase of smooth muscle and elastin in cerebral arterioles of SHRSP may contribute to our previous finding that distensibility is increased in cerebral arterioles of SHRSP.[5] This possibility depends on the assumption that stiffness of blood vessels is influenced by the proportional composition of the vessel wall. This study does not rule out the possibility, however, that other factors, such as qualitative changes in arteriolar elastin, smooth muscle and collagen, also contribute to the increase in distensibility of cerebral arterioles in SHRSP. Nevertheless, these findings may provide a structural basis for the surprising finding that cerebral vascular hypertrophy in SHRSP is accompanied by reductions in vascular stiffness.

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