Scanning Microscopy

Volume 7 | Number 1 Article 15

1-6-1993

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Scanning Microscopy, Vol. 7, No. 1, 1993 (Pages 137-143)
Scanning Microscopy International, Chicago (AMF O'Hare), IL 60666 USA

0891-7035/93$5.00+.00

VASCULAR REMODELING IN HYPERTENSION

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(Received for publication May 11, 1992, and in revised form January 6, 1993)

Abstract

Cerebral arterioles in stroke-prone spontaneously hypertensive rats (SHRSP) paradoxically become more distensible, despite hypertrophy of the vessel wall. Cerebral arterioles in SHRSP also undergo remodeling with a reduction in external diameter. Based on these findings, we have proposed the concept that remodeling of cerebral arterioles may be an important mechanism, in addition to hypertrophy, for encroachment on the vascular lumen in SHRSP. The purpose of this review is threefold. *First*, consequences of vascular hypertrophy that have been proposed previously are reviewed with an emphasis on the hypothesis that encroachment on the vascular lumen by hypertrophy is an important mechanism of altered vascular responses in chronic hypertension. *Second*, the concept of vascular remodeling is considered with an emphasis on the possibility that remodeling with a reduction in external diameter may contribute importantly to altered cerebral vascular responses in SHRSP. *Finally*, possible mechanisms of vascular remodeling are considered with an emphasis on the hypothesis that a reduction in external diameter may be related to a decrease in the length of individual smooth muscle cells without an increase in cell number, or an increase in the number of times each smooth muscle cell wraps around the arteriole.

Key Words: Remodeling, hypertrophy, minimal resistance, cerebral blood vessels, confocal microscopy

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Introduction

Cerebral vascular structure and function are profoundly altered by chronic hypertension. For example, chronic hypertension alters the pressure-flow relationship in the cerebral circulation with a shift of the autoregulatory 'plateau' to the right (Strandgaard et al., 1973). The shift in the autoregulatory plateau is beneficial to the brain, because cerebral blood flow is maintained relatively constant during large increases in arterial pressure. At the same time, however, the shift is detrimental because susceptibility to critical reductions in cerebral blood flow during acute hypotension is increased.

Cerebral vascular hypertrophy occurs during chronic hypertension (Harper and Bohlen, 1984; Baumbach et al., 1988) and probably contributes to the shift of the autoregulatory plateau. Folkow has proposed that hypertrophy is responsible for both enhanced vasoconstriction and impaired vasodilatation in chronic hypertension, by virtue of encroachment on the vascular lumen and increased wall-to-lumen ratio (Folkow, 1971). A logical extension of Folkow's hypothesis is that vascular hypertrophy might play a critical role in the shift of cerebral vascular autoregulation during chronic hypertension, by enhancing vasoconstriction during increases in arterial pressure and impairing vasodilatation during hypertension.

Thus, hypertrophy would appear to be an important adaptive response of the cerebral circulation to chronic hypertension. Some critical questions remain, however, regarding consequences of vascular hypertrophy. One of the aims of this review is to reexamine Folkow's hypothesis as it applies to altered responses of cerebral blood vessels during chronic hypertension. Another aim is to review some of our recent findings in cerebral arterioles of stroke-prone spontaneously hypertensive rats (SHRSP) (Baumbach and Heistad, 1989). Based on these findings, we have proposed as an alternative to Folkow's hypothesis that, during chronic hyperten-

sion, encroachment on the vascular lumen with increased wall-to-lumen ratio may result mainly from reductions in external diameter of the vessel, or "remodeling," with a lesser contribution from hypertrophy of the vessel wall (Baumbach and Heistad, 1991). The third aim of this review is to consider our recent efforts to determine the structural basis of remodeling of cerebral arterioles in SHRSP. We have described in particular the application of confocal laser microscopy to the examination of whole mounted arterioles as a promising method to accomplish this goal.

Consequences of Vascular Hypertrophy

A clearly recognized consequence of vascular hypertrophy is that wall stress is reduced in blood vessels because thickness of the vessel wall is increased. According to concepts first established by Folkow (1978), however, the consequences of vascular hypertrophy go beyond a simple reduction in wall stress. Folkow's concept rests on the premise that increases in peripheral vascular resistance which typically characterize chronic hypertension result primarily from vascular hypertrophy, rather than from increased levels of smooth muscle activity. Folkow et al. (1970) tested this concept experimentally by examining vascular responses to norepinephrine in isolated, perfused hindquarters of Wistar Kyoto rats (WKY) and spontaneously hypertensive rats (SHR). Minimal resistance of the hindquarter circulation was 35% greater in SHR than WKY. Norepinephrine produced significantly greater constriction in SHR than WKY, even though sensitivity of vascular smooth muscle, as determined by "threshold" sensitivity to a variety of vasoconstrictors was, if anything, reduced in SHR. Folkow's interpretation of these findings was that contractile mass is increased in hindquarter blood vessels of SHR which results in an increase in encroachment on the vascular lumen and vascular narrowing.

It is easy to imagine how encroachment could account for the increase in minimal vascular resistance. It is more difficult, however, to imagine how encroachment by hypertrophy might contribute to increased responsiveness to constrictor stimuli. Folkow resolved this dilemma by utilizing mathematical concepts to show that an increase in wall-to-lumen ratio by hypertrophy could reset the baseline from which smooth muscle exerts its dynamic control of vascular resistance to a higher level (Folkow et al., 1973; Folkow et al., 1958). Resetting of the baseline upward would be expected to result in a leftward shift of the relationship between smooth muscle shortening and vascular resistance.

Folkow's hypothesis derives its credibility from the striking similarity between the resistance curves that were obtained experimentally in WKY and SHR and those that were deduced from his mathematical model. The beauty of the hypothesis is that it provides a way by which structural adaptations, such as vascular hypertrophy, can account for two of the major alterations that occur in the cerebral vascular bed during chronic hypertension: increased responsiveness to constrictor stimuli, such as acute increases in pressure (Strandgaard et al., 1973), and increased minimal vascular resistance (Sadoshima et al., 1983; Johansson and Nilsson, 1979).

Vascular Remodeling

Given the far-reaching implications of Folkow's hypothesis, an important question needs to be asked. Is hypertrophy the only change in vascular structure which can lead to increased reactivity of vascular smooth muscle during chronic hypertension? Folkow

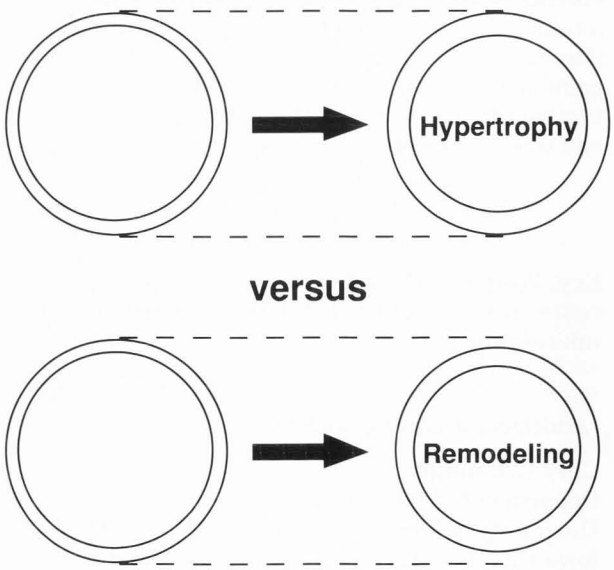

Figure 1. A basic tenet of Folkow's hypothesis is that, when a vessel undergoes hypertrophy during chronic hypertension, its wall grows inward and encroaches on the vascular lumen. The hypothesis does not assume a change in external diameter of the vessel. Our findings (Baumbach and Heistad, 1989) suggest that cerebral arterioles in SHRSP undergo remodeling of the vessel wall, with a reduction in external diameter, as well as hypertrophy. Our calculations suggest that most of the encroachment on the lumen which occurs in cerebral arterioles of SHRSP is a consequence of remodeling with a lesser contribution from hypertrophy.

addressed this question early in his considerations of this subject. The hypothesis required only that wall-to-lumen ratio increase with inward displacement of smooth muscle (Folkow et al., 1958). The mechanism by which increases in wall-to-lumen ratio occur was of secondary importance with respect to the predicted outcome of augmented responses of smooth muscle. Nonetheless, Folkow came to emphasize the concept that hypertrophy of the vessel wall is the primary mechanism for increases in wall-to-lumen ratio.

An alternative mechanism for increases in wall-to-lumen ratio that has received little attention is that external diameter of blood vessels decreases during chronic hypertension. Reductions in external diameter would be expected to have the same effect on vascular reactivity that Folkow predicted for hypertrophy: encroachment of the tunica media on the vascular lumen and increased wall-to-lumen ratio. Recently, we examined effects of chronic hypertension on cerebral arterioles in-vivo. In addition to pronounced hypertrophy of the vessel wall, we found that both external and internal diameter during maximal dilatation were reduced in cerebral arterioles of SHRSP (Baumbach and Heistad, 1989) (Fig. 1). It should be emphasized that reductions in maximal diameter could not be accounted for by a reduction in arteriolar distensibility. In contrast to large cerebral arteries which become less distensible during chronic hypertension (Brayden et al., 1983; Winquist and Bohr, 1983; Toda et al., 1982), distensibility of cerebral arterioles is paradoxically increased in SHRSP (Baumbach et al., 1988). An implication of the mechanical alterations of cerebral arterioles that accompany chronic hypertension is that increases in arteriolar distensibility may help to preserve dilator capacity of cerebral arterioles (Baumbach and Heistad, 1991).

Based on the finding that external diameter is reduced in SHRSP, we have proposed that, during chronic hypertension, structural changes may occur in cerebral arterioles which result in remodeling of the arteriolar wall with a reduction in external diameter. Reduction in external diameter accounts for three quarters of the decrease in internal diameter of cerebral arterioles in SHRSP, whereas hypertrophy accounts for only one quarter of the decrease (Baumbach and Heistad, 1989). Thus, not only does vascular remodeling with reduction in external diameter contribute to encroachment on the lumen and increased wall-to-lumen ratio of cerebral arterioles in SHRSP, the contribution of remodeling is greater than that of vascular hypertrophy per se. In addition, recent findings by Mulvany and his colleagues (Mulvany, 1991) suggest that remodeling may contribute to altered structure of peripheral resistance vessels in humans with essential hypertension and in spontaneously hypertensive rats (SHR).

We also have applied Folkow's mathematical model to values of diameter and cross-sectional area of the vessel wall that we obtained in WKY and SHRSP to estimate the contributions that vascular remodeling and hypertrophy might be expected to make to increases in vascular reactivity (Baumbach and Heistad, 1991). Both remodeling and hypertrophy shifted the relationship between degree of smooth muscle shortening and increases in vascular resistance, and their effects appear to be synergistic (Fig. 2). Thus, vascular remodeling with reduction in external diameter contributes importantly to increased vascular reactivity, as well as increased minimal resistance, in cerebral arterioles of SHRSP.

The implications of remodeling may be especially important with respect to the shift in cerebral vascular autoregulation with chronic hyperten-

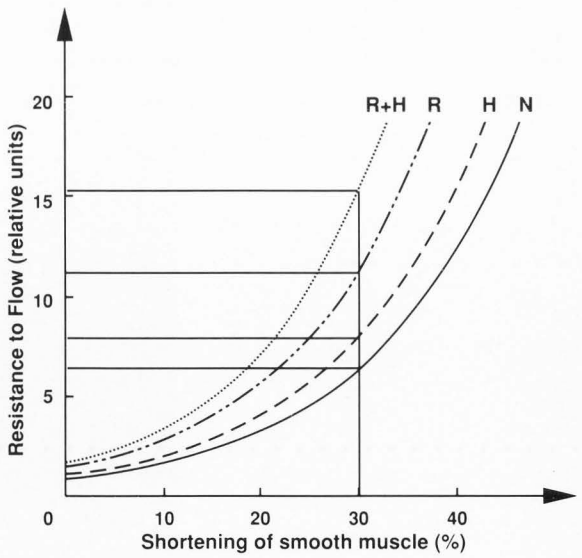

Figure 2. This figure illustrates the relationship between the degree of smooth muscle shortening and resistance in a normal vessel (N), a vessel that has undergone only hypertrophy (H), a vessel that has undergone only remodeling with a reduction in external diameter (R), and a vessel that has undergone both remodeling and hypertrophy (R+H). The relationships were determined using values of external diameter, internal diameter and cross-sectional area of the vessel wall that we obtained previously in WKY and SHRSP (Baumbach and Heistad, 1989).

sion. During chronic hypertension, the pressure-flow relationship in the cerebral circulation is shifted to the right. Thus, constriction of cerebral blood vessels is enhanced during acute increases in arterial pressure, and vasodilatation during hypotension is impaired. Previously, attention has focused on hypertrophy as the primary factor that contributes to the shift in cerebral vascular autoregulation. We propose that, in the cerebral circulation, vascular remodeling with encroachment on the lumen, and an increase in wall-to-lumen ratio plays a critical role in the rightward shift of the autoregulatory plateau.

Possible Mechanisms of Vascular Remodeling

Distinction between hypertrophy and remodeling may be important in relation to mechanisms of encroachment on the vascular lumen because determinants of hypertrophy and remodeling probably are different. We recently found that treatment of SHRSP with hydralazine is not as effective as an inhibitor of angiotensin converting enzyme in attenuation of remodeling of cerebral arterioles, even though both antihypertensives completely prevent hypertrophy of the arteriolar wall (Hajdu et al., 1991). We suggest, therefore, that remodeling can occur in cerebral arterioles independently of vascular hypertrophy. Thus, elimination of the consequences of hypertrophy through its prevention or reversal during treatment of chronic hypertension does not necessarily assure a return to normal cerebral vascular responses, because vascular remodeling may persist.

An important consideration in relation to the mechanism of vascular remodeling is to determine the alterations that take place within the vessel wall which lead to a reduction in vessel size. We have speculated previously that a reduction in total circumference of cerebral arterioles may be related to one of two possibilities: a decrease in the length of individual smooth muscle cells without an increase in cell number, or an increase in the number of times each smooth muscle cell wraps around the arteriole (Baumbach and Heistad, 1988). To determine whether either of these possibilities occurs, one must be able to measure not only length of individual muscle cells but also wrapping distance of the cells around the arteriolar lumen. An important first-step toward accomplishing this goal would be to identify an appropriate method for obtaining these measurements.

Scanning electron microscopy, as demonstrated by Evan et al. (1976), Miller et al. (1982) and Krizmanich and Lee (1987) would appear to be an ideal method for obtaining measurements of length and wrapping distance of smooth muscle cells in the arteriolar wall. We would assert, however, that there are at least two potential problems that are associated with using scanning electron microscopy for this purpose. *First*, techniques that are required to prepare tissues for scanning electron microscopy result in profound shrinkage of biological tissue. *Second*, adequate visualization of smooth muscle cells requires enzymatic digestion and mechanical manipulation of the tunica adventitia and extracellular matrix material that invest smooth muscle cells in the tunica media (Miller et al., 1982).

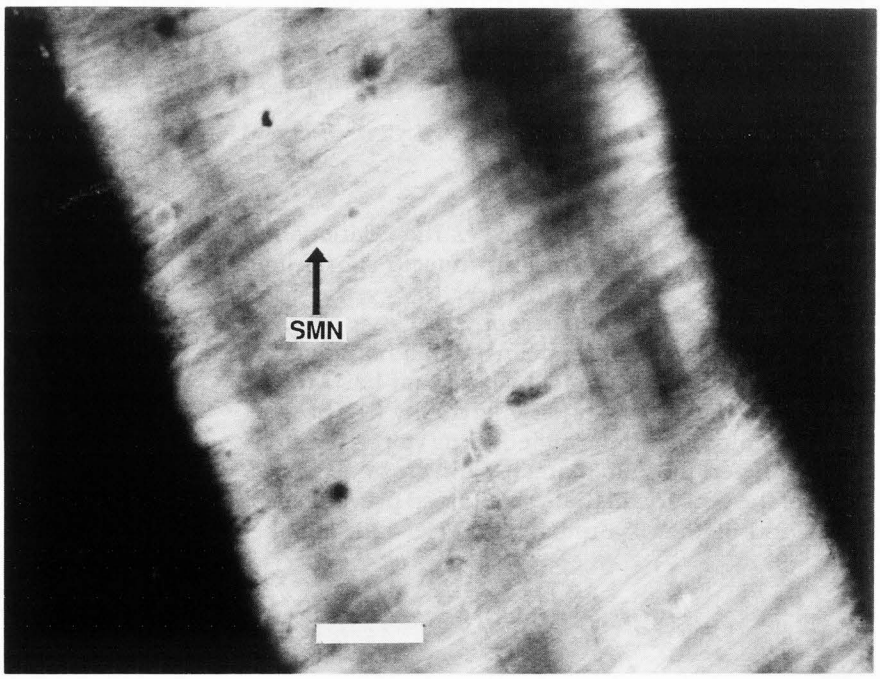

Figure 3. Confocal fluorescence image of cerebral arteriole. Note the nucleus (SMN) of a smooth muscle cell in vessel wall. The spindle-shaped, negatively-stained structures in the vessel wall are assumed to represent the nuclei of smooth muscle cells. The basis for this assumption is that the longitudinal axis of the nuclei are oriented at 90° relative to the longitudinal axis of the arteriole. Bar = 25 μm.

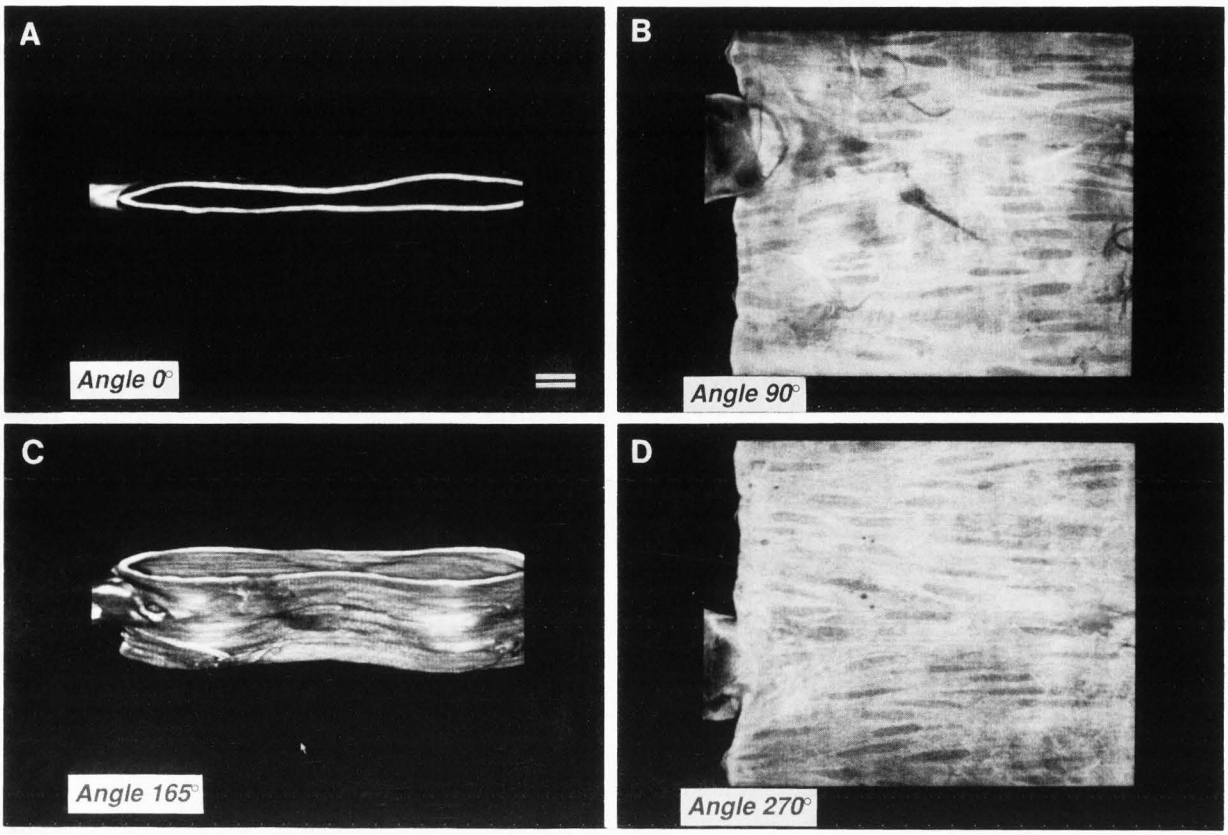

Figure 4. Rotation of pial arteriole about its longitudinal axis. A. Reconstruction at 0° angle. B. Reconstruction at 90° angle. C. Reconstruction at 165° angle. D. Reconstruction at 270° angle. B and D enable one to examine independently cells in opposite sides of vessel wall. Bar = 25 μm.

It would seem desirable, therefore, to develop an alternative method for quantitating morphological characteristics of vascular smooth muscle which retains the advantages of scanning electron microscopy and at the same time avoids the potential problems. Thus, our goal in this study was to determine whether confocal laser microscopy could be used to visualize individual smooth muscle cells in cerebral arterioles. The rationale for this approach was that preparations for confocal microscopy avoid critical point drying, and thus would be expected to produce significantly less tissue shrinkage than the preparations that are required for scanning electron microscopy. Furthermore, optical sectioning of the arteriolar wall with confocal microscopy obviates the need for tissue digestion and mechanical manipulation of the tunica adventitia.

We studied pial arterioles of adult SHRSP. Pial arterioles were perfuse fixed with 2.25% glutaraldehyde in 0.1M cacodylate buffer at levels of arterial pressure that are normally observed in WKY and SHRSP. Perfusion pressure was about 110 mmHg in WKY and 180 mmHg in SHRSP. Following excision and an additional 12 hours of fixation, selected vascular segments were rinsed in 0.1 M cacodylate buffer and distilled water, stained with Harris Hematoxylin, and whole mounted on glass slides. Whole mounted vessels were examined under oil immersion using a Biorad MRC-600 Confocal Imaging System in the epifluorescence mode. The resolution of the confocal system approached 100 nm. Serial optical sections of 0.9 μm thickness were obtained from each vessel. A Silicon Graphics Iris Work Station in combination with Voxel View (Vital Images) was used to reconstruct the sections at various angles of rotation ranging from 0° to 270°. Images of the reconstructed vessels were photographed directly from the computer monitor using a 35 mm camera and tripod.

Confocal microscopy demonstrated clear images of individual smooth muscle cells and their nuclei in the pial arteriolar wall (Fig. 3). Factors that likely contributed to the clarity of these images were 1) autofluorescence of the vascular tissue which probably resulted from glutaraldehyde fixation, and 2) hematoxylin staining of nuclear chromatin and basement membrane material which quenched autofluorescence of these structures and thus resulted in negative staining of nuclei and smooth

muscle basement membrane. Images of vascular cells were further enhanced by computer reconstruction of serial optical sections (Fig. 4). Rotation of the reconstructed images enabled us to visualize the arteriolar wall in cross-section (Fig. 4 A) and longitudinal section (Fig. 4 B-D). By rotating the vessel from 90° to 270°, it was possible to visualize independently smooth muscle cells from each side of the vessel wall (Fig. 4 B and D).

Based on these findings, we conclude that confocal laser microscopy in combination with glutaraldehyde fixation and hematoxylin staining is a simple, reproducible method for examining cellular morphology in the vessel wall. The ability to visualize smooth muscle cells without having to resort to enzymatic digestion techniques should allow us to pursue the hypothesis that changes in length or wrapping distance of smooth muscle contribute to remodeling of cerebral arterioles in SHRSP during chronic hypertension.

Acknowledgments

We thank Tom Moninger of the Central Electron Microscopy Research Facility, the University of Iowa for assistance with the operation of the Biorad Confocal Microscope and the Silicon Graphics Iris Work Station. Original studies described in this review were supported by funds from NIH Grants HL-22149 and NS-24621. Gary Baumbach is the recipient of an Established Investigatorship Award from the American Heart Association.

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Discussion with Reviewers

G. Pasquinelli: In relation to the possibility of improving the ability of confocal microscopy to image individual smooth muscle cells in the vessel wall, have you planned any special stains to enhance the boundaries of individual smooth muscle cells?
Authors: As of this writing, we have no specific plans in this regard. We have, however, given this matter considerable thought. One possibility might be to use a fluorescent-tagged membrane marker, such as a phospholipid probe, to investigate not only structural, but also dynamic characteristics of the cell surface. Another possibility might be to use a stain for a specific component in the basement membrane surrounding smooth muscle cells. A third possibility might be to stain the cytoskeleton of smooth muscle cells using a marker for alpha-actin, and then employ digital subtraction methods to enhance the non-staining extracellular region between individual cells.

J. S. Smeda: The term "remodeling" suggests that at one point in time the pial vasculature of WKY and SHRSP was identical in dimensional structure and that with time the vascular wall of SHRSP reorganizes to produce a smaller external diameter. Is there proof that this actually occurs?
Authors: Yes. We have found that, when compared with WKY, external diameter of pial arterioles is significantly smaller in 6-month old, but not 3-month old, SHRSP (Baumbach and Heistad, 1989).

J. S. Smeda: Within our colony, WKY typically have larger body weights than SHRSP. Is it possible that the smaller external diameters observed in the cerebrovasculature of SHRSP are the result of strain differences or differences in body weight? In this regard, have the authors carried out studies comparing WKY to non-stroke-prone SHR?
Authors: In relation to the possibility of differences in body weight, we have found that, whereas total body weight is larger in SHRSP than in WKY, brain weight is similar in the two groups (Baumbach and Heistad, 1989). Because vessel size is more likely to be proportional to the mass of tissue that it supplies rather than total body mass, it is unlikely that differences in total body weight can account for the smaller size of pial arterioles in SHRSP. In relation to comparing WKY to non-stroke-prone SHR, we recently examined mechanical and dimensional characteristics of pial arterioles in SHR. The findings are pending publication and thus cannot be detailed here, except to say that the changes observed in pial arterioles of SHR were similar to those that we have observed previously in SHRSP (Baumbach et al., 1988; Baumbach and Heistad, 1989).

J. S. Smeda: Using in-vivo microscopy techniques in combination with artificial methods of elevating blood pressure, it should be possible to determine the degree of blood pressure elevation that overcomes pressure-dependent constriction and produces forced-dilatation of the pial vasculature. This latter phenomenon might be expected to be shifted to a higher level of pressure by the presence of a higher contractile reactivity within remodeled blood vessels. Do the authors have any evidence indicating a relationship between the degree of vascular remodeling and the blood pressure required to produce to produce forced-dilatation of the pial vasculature?
Authors: We have speculated previously that remodeling of cerebral arterioles might be expected to contribute to increased vascular reactivity, and thus may contribute to alterations in the pressure-flow relationship that occur in the cerebral circulation during chronic hypertension with a shift of the autoregulatory 'plateau' to the right (Baumbach and Heistad, 1991). We have no hard data as of yet, however, to support this speculation.

J. S. Smeda: The occurrence of remodeling of the cerebrovasculature would suggest a dramatic reorganization of smooth muscle cell orientation within the blood vessel wall and/or a change in smooth muscle cell size (length). It would be of interest to know the speculative views of the authors as to the stimuli/mechanisms that might contribute to the above type of reorganization.
Authors: We would speculate that angiotensin II may be a stimulus of remodeling in cerebral arterioles of SHRSP. This possibility was suggested by our recent finding that treatment with an inhibitor of the angiotensin converting enzyme, but not hydralazine, prevents remodeling of pial arterioles in SHRSP (Hajdu et al., 1991). Furthermore, we have evidence from other studies that suggest increases in arterial pressure (Baumbach et al., 1991) and sympathetic nerve activity (Baumbach et al., 1989) are not mechanisms of cerebral vascular remodeling in SHRSP.

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