Reactivity of Small Blood Vessels in Hypertension: Relation with Structural Changes
State of the Art Lecture
Ernesto L. Schiffrin

Small blood vessels, particularly small arteries of 150–300 μm in lumen diameter and larger arterioles of 50–150 μm in lumen diameter, are the most important location of the arterial bed that undergoes changes resulting in the increased peripheral resistance that characterizes elevated blood pressure. This article reviews these morphological and functional alterations of small blood vessels. Study of mesenteric small arteries with a lumen diameter of 220–260 μm revealed consistently a reduced external and lumen diameter in renal and deoxycorticosterone acetate–salt hypertensive rats early in the evolution of hypertension. The media of the vessel wall was significantly thickened in the hypertensive rats, and the media/lumen ratio was increased. Although the tension that developed in response to different vasoconstrictors was not elevated or was even decreased in hypertensive rats, exaggerated transmural pressures resulted in the isolated blood vessels as a consequence of the law of Laplace because of the narrowed lumen. Similar findings were obtained in small resistance arteries from subcutaneous gluteal biopsies of hypertensive humans. In arterioles, on the other hand, decreases in the density of blood vessels (rarefaction) and in vasomotion amplitude may play a more important role than reductions in lumen diameter. As a consequence of the design of small resistance blood vessels and as a result of functional and structural alterations, which may be primary to or a consequence of high blood pressure, the pressor effect of vasoconstrictors is amplified and interacts with other factors to contribute to the maintenance of elevated blood pressure even if the intrinsic response of vascular smooth muscle to these agents is not exaggerated. (Hypertension 1992;19[suppl II]:II-1-II-9)

Increased resistance to blood flow in tissues is the hallmark of arterial hypertension and results in elevation of blood pressure, even in the face of reduced cardiac output. This hemodynamic profile is found in most forms of both human and experimental hypertension. Our understanding of the mechanisms underlying the increase in peripheral resistance has been enhanced over the past few years, as we have acquired new knowledge on the structure and function of different segments of the circulation. As our understanding of the circulation in hypertension has increased, it has become clear that important changes in large and small vessels occur in hypertension and that these structural alterations may ensure that tissues are not overperfused while at the same time contribute to the elevation of blood pressure. Whether the structural and functional changes of blood vessels precede hypertension, and are thus involved in its pathogenesis to some degree, or whether they result from the elevation of blood pressure is still a matter of debate. Furthermore, the study of different vascular beds and segments of the circulation has shown that morphological and physiological adaptation to hypertension may be different in macrovessels and in microvessels of different vascular beds, between the larger and smaller arteries, and even within microvessels of different caliber. These studies have allowed investigators to develop, support, or contradict the hypothesis put forward by Folkow and colleagues that cardiovascular adaptation, in the form of thickened media of blood vessels and encroachment on the lumen, contributes to the development or maintenance of elevated blood pressure.

For practical purposes, the arterial side of the circulation may be divided into large blood vessels (>300 μm i.d.) and small blood vessels (<300 μm i.d.). Large blood vessels undergo extensive changes in their morphology in hypertension. This affects

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the endothelium, subintimal layers, and the media and results in altered behavior regarding contractility, elasticity, and possibly resistance to flow. However, the precise contribution of larger blood vessels to blood pressure elevation is uncertain, although undoubtedly in humans severe extensive atherosclerosis of the aorta and its larger branches probably does play an important role in the elevation of systolic blood pressure due to decreased compliance and often may be associated with isolated systolic hypertension.

The main part of the energy dissipation generated by resistance to flow occurs, however, predominantly at the level of small blood vessels of less than 300 \( \mu \text{m} \) i.d.\(^8\) These smaller blood vessels include small arteries (150–300 \( \mu \text{m} \) i.d.) and arterioles (<150 \( \mu \text{m} \) i.d.). The relative contributions of these different small blood vessels to peripheral resistance and the profile of pressure drop along the arterial bed have been evaluated. Small arteries of 150–300 \( \mu \text{m} \) in lumen diameter probably contribute approximately 40% of the blood pressure drop before capillaries, whereas another 30% is probably the result of passage through 50–150-\( \mu \text{m} \) arterioles.\(^8\) The work of Borders and Granger\(^10\) has demonstrated, through calculations based on power dissipation depending on the length of blood vessels and velocity of flow as measured in microvessels in the cremaster muscle, that small arteries and larger arterioles have a greater effect than any other segment of the microcirculation on resistance to flow. More recently, Imig and Anderson\(^11\) have shown, using pressure measurements at a proximal and distal site of vessels in the cremaster circulation with a servonull micropipette system during the development of one-kidney, one clip (1K1C) renal hypertension, that the small arteries upstream from the microcirculation contribute to a very important degree to increases in vascular resistance, which do not develop uniformly through all vessel branches. Thus, we may probably safely state that these "resistance" blood vessels, small arteries and larger arterioles are the sites where most of the elevated peripheral resistance is generated in different forms of hypertension. In smaller blood vessels, particularly in arterioles of less than 100 \( \mu \text{m} \), different mechanisms than in small arteries may be operative, namely, a reduction in the number of blood vessels of some vascular beds or rarefaction.\(^12\)

**Morphology of Small Arteries in Hypertension**

The study of interactions of morphological and functional characteristics of small blood vessels has become possible, among other developments, by the creation of the "wire myograph" by Halpern and colleagues.\(^13\) More recently, video dimension analysis of pressurized microvessels mounted on a glass microcannula\(^14\) may offer a more physiological alternative for the study of functional and morphological interactions in hypertension, because blood vessels conserve their in vivo shape, contract isotonically, and are exposed to the action of agents administered intraluminally rather than adventitiously. However, the studies with the wire myograph have allowed a large component of the investigation to date of interactions of structure and function on the same blood vessel under highly controlled isometric conditions.\(^13,16-19\) With the myograph, it has been possible to study small blood vessels of 150–300 \( \mu \text{m} \) i.d. Blood vessels mounted on two wires are stretched with a micrometer to basal relaxed wall tensions equivalent to those they would be exposed to in vivo if the transmural pressure they had to contract against were 50–100 mm Hg or more. The wall thickness and distance between wires can be measured, and as a result, the external and the lumen diameters and circumference can be calculated, assuming these blood vessels have a cylindrical shape in vivo. Hypertensive rats present very early in the course of blood pressure elevation a reduction of blood vessel outer diameter and a thickening of the width of blood vessel walls (Table 1).\(^19\) The lumen diameter and consequently the inner circumference of the small arteries are reduced as a result of encroachment of the thickened media on the vessel lumen, as originally proposed by Folkow et al.\(^4\) Similar results have been reported recently in small arteries (approximately 150 \( \mu \text{m} \) in lumen diameter) in the developing 1K1C hypertensive rat.\(^11\) The feeding artery (external spermatic) of the cremaster muscle examined under videomicroscopy showed reduction of both outer and lumen diameters at 2 and 4 weeks of hypertension, as did A1 arterioles (approximately 100 \( \mu \text{m} \) in lumen diameter). The cross-sectional area of the wall (volume per unit length) may be increased (in 1K1C Goldblatt hypertensive rats after 4 weeks of hypertension\(^19\) or in deoxycorticosterone acetate [DOCA]–salt hypertensive rats after 2 weeks of hypertension\(^20\)) or not (in two-kidney, one clip [2K1C] Goldblatt hypertensive rats, there was a nonsignificant trend to increase\(^19\), thus indicating or not the presence of vascular hypertrophy (which may have in different experimental and genetic models a variable component of cell hypertrophy or hyperplasia or changes in deposition of intercellular material). The reduction of the outer diameter corresponds to the phenomenon termed remodeling.\(^22\) The mechanism underlying this reduced outer diameter of hypertensive blood vessels may be an increase in basal tone or a rearrangement of smooth muscle cells in the vessel wall. The morphological changes in small arteries have been studied extensively by Mulpavy et al.\(^16-18\) in the spontaneously hypertensive rat (SHR). In blood vessels obtained from subcutaneous gluteal biopsies of mild untreated essential hypertensive patients (Table 1), similar changes are also present,\(^21\) as was demonstrated previously by Aalkjaer et al.\(^23\)

**Function of Small Arteries in Hypertension**

The response of small arteries to stimuli is critically dependent on characteristics of the lumen and wall of the blood vessel.\(^16\) The tension developed per unit of length of a small artery (tension [mN/
TABLE 1. Morphological Characteristics of Small Arteries From the Mesentery of Experimental Hypertensive Rats and From Human Gluteal Subcutaneous Biopsies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypertensive</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-kidney, one clip Goldblatt rats (n=12–13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External diameter (µm)</td>
<td>254±4</td>
<td>281±6</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Lumen diameter (µm)</td>
<td>216±4</td>
<td>249±5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Media thickness (µm)</td>
<td>14.5±0.6</td>
<td>11.1±0.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Media/lumen (%)</td>
<td>6.9±0.3</td>
<td>4.4±0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Wall cross-sectional area (µm²)</td>
<td>14,968±748</td>
<td>13,299±639</td>
<td>NS</td>
</tr>
<tr>
<td>One-kidney, one clip Goldblatt rats (n=10–12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External diameter (µm)</td>
<td>250±4</td>
<td>288±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lumen diameter (µm)</td>
<td>205±4</td>
<td>257±8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Media thickness (µm)</td>
<td>15.7±0.7</td>
<td>10.8±0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Media/lumen (%)</td>
<td>7.7±0.4</td>
<td>4.2±0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Wall cross-sectional area (µm²)</td>
<td>16,050±899</td>
<td>13,205±626</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>DOCA-salt hypertensive rats (n=10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External diameter (µm)</td>
<td>275±6</td>
<td>293±3</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Lumen diameter (µm)</td>
<td>238±5</td>
<td>264±5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Media thickness (µm)</td>
<td>13.8±0.3</td>
<td>10.0±0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Media/lumen (%)</td>
<td>5.5±0.1</td>
<td>3.8±0.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Wall cross-sectional area (µm²)</td>
<td>15,242±780</td>
<td>12,464±376</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Human (n=13–19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External diameter (µm)</td>
<td>374±32</td>
<td>459±42</td>
<td>NS</td>
</tr>
<tr>
<td>Lumen diameter (µm)</td>
<td>304±26</td>
<td>401±39</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Media thickness (µm)</td>
<td>24.8±2.2</td>
<td>20.2±1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Media/lumen (%)</td>
<td>8.1±0.2</td>
<td>5.2±0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Wall cross-sectional area (µm²)</td>
<td>42,811±7,577</td>
<td>41,192±5,933</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data from References 19–21. DOCA, deoxycorticosterone acetate.
contribute to the maintenance of elevated blood pressure once vascular hypertrophy is initiated because of the amplifier effect of encroachment on the lumen by the hypertrophied media or as a result of vascular remodeling. This interpretation of vascular responses in isolated small resistance arteries on the myograph is valid and shown by the fact that, although tension responses to vasopressin are reduced or normal in renal or DOCA-salt hypertensive rats and only calculated transmural pressure responses to vasopressin are exaggerated in mesenteric small arteries mounted on the wire myograph,pressor responses of the perfused mesenteric vascular bed preparation to vasopressin are also exaggerated in renal and DOCA-salt hypertensive rats. The latter preparation contains all the resistance vessels of the mesenteric circulation as well as the larger vessels. This confirms the need to take into account the design of blood vessels to understand the contribution to peripheral resistance of tension responses of isolated blood vessels. It should be clarified at this point that increased media width is found in some experimental hypertensive models in the absence of increased cross-sectional area (Table 1), indicating the absence of true vascular hypertrophy. This may be due to rearrangement of media components within a smaller outer diameter as part of remodeling, resulting necessarily in increased media width for the same wall volume per unit length (cross-sectional area) within a reduced outer circumference. The mechanism of hypertrophy leading to either increased cell number or cell volume and media thickening is unknown but may implicate different vasoactive peptides, such as angiotensin II, vasopressin, endothelin, or growth factors (epidermal growth factor). The possibility that some of these substances may initiate the hypertensive process by increasing cell volume or number, followed by amplification of vasoconstrictor responses due to the amplifier role of the reduced lumen diameter of small blood vessels, is certainly an attractive hypothesis and is currently under investigation.

**Figure 1.** Line graphs show calculated active tension (force/2 length) and pressure (tension/radius) responses to arginine vasopressin (AVP) of small arteries from uninephrectomized (UNI-Nx) or one-kidney, one clip (1K,1C) Goldblatt hypertensive rats. Results are mean±SEM of 10–12 rats per group. Data from Reference 19 with permission.

**Figure 2.** Line graphs show calculated active tension (force/2 length) and pressure (tension/radius) responses to norepinephrine (NE) of small arteries from uninephrectomized (UNI-Nx) and one-kidney, one clip (1K,1C) hypertensive rats. Results are mean±SEM of 10–12 rats per group. Data from Reference 19 with permission.
In most of these studies of small arteries with the wire myograph,16–19,23 hypertensive and normotensive blood vessels have been stretched to a similar degree, corresponding to a transmural pressure between 50 and 60 mm Hg.19 A recent study in pressurized dog renal small arteries suggests that if blood vessels are stretched to different degrees by exposing them to increasing perfusion pressure, sensitivity to norepinephrine is progressively exaggerated.33 However, in rat mesenteric small arteries, the maximum responsiveness to depolarizing concentrations of potassium or to norepinephrine is, if anything, decreased,19 whereas the sensitivity to norepinephrine is unchanged and that to vasopressin or endothelin is reduced.34 Thus, transmural pressure of relaxed blood vessels may exert different effects in different vascular beds and in different species. The differential response to increased pressure in renal and mesenteric microvessels may relate to differences in the functional requirements in each vascular bed in the face of increasing blood pressure (such as autoregulation in the kidney). These data also suggest that the results obtained with small hypertensive and normotensive arteries from the mesenteric bed exposed to similar transmural pressures may be extrapolated to the in vivo situation of the hypertensive versus the normotensive state.

Another functional phenomenon that may contribute to vascular resistance to flow is the existence of spontaneous phasic contractile activity of blood vessels (vasomotion). Oscillatory contractions of tail arteries can be observed in the stroke-prone SHR in response to several agonists, such as norepinephrine, serotonin, or histamine.35 These oscillatory contractions are associated with bursts of calcium-dependent action potentials36 and activation of potassium conductance.36,37 The degree to which this type of vasomotion contributes to rises in peripheral resistance remains to be established, but these oscillatory decreases in vessel diameter result in significant increments in resistance to flow because of the nonlinear characteristics of Poiseuille’s equation.

A structural alteration of another kind may have important functional consequences. In the SHR it has been reported that mesenteric arteries are hyperinnervated in the prehypertensive period.38 A functional abnormality that may be related to this is the displacement to the left of the concentration–response curve to norepinephrine in the presence of cocaine, found in both SHR17 and in essential hypertensive humans.23 This finding may be related to exaggerated reuptake of catecholamines in SHR and essential hypertensive patients, which may be selectively blocked by cocaine. This could thus be a functional consequence of a structural or developmental abnormality that produces vascular hyperinnervation.

Morphological and Functional Alterations in Arterioles and Venules in Hypertension

Larger arterioles, together with small arteries, are a prime site of generation of resistance to blood flow.9,10 Microvessels smaller than 100 μm in lumen diameter have been studied with different techniques to determine their morphological and functional characteristics and possible contribution to elevation of blood pressure. When intestinal microvascular pressures were measured in SHR at 18–21 weeks, it was shown that, although the pressure profile shows a fall of 40–50% of arterial pressure in small arteries preceding arterioles, pressures in the smaller arterioles of SHR were higher than those of the larger arterioles of normotensive rats29; similar results have been observed in other vascular beds. Elevated pressures extend to terminal arterioles, capillaries, and initial venules, although to a reduced degree in comparison to the elevation of mean arterial pressure. This may play a protective role on the exchange vasculature these vessels represent and results from the structural and functional alterations of true resistance vessels (small arteries and larger arterioles) and the increased resistance to flow at the level of the latter. In spite of these elevated pressures, the walls of arterioles have not been found to be thickened nor lumen diameters altered at maximal dilatation,40 in contrast to the changes found in small arteries. In some vascular beds, however, such as the cerebral circulation, morphological changes similar to those of small arteries do occur. In studies of pressurized pial arterioles, of approximately 50–100 μm in diameter, it has been reported that outer and lumen diameters are reduced, whereas cross-sectional area is not increased in stroke-prone SHR, a phenomenon that has been termed remodeling.22 Similar results have been reported recently in proximal and distal A1 arterioles (approximately 100 μm lumen diameter) of the cremaster muscle examined by videomicroscopy in the 1K1C hypertensive rat at 2 and 4 weeks of hypertension, with reduced inner and outer diameters.11

A mechanism that may play a role in the resistance generated by the microcirculation, resulting in the steep fall in pressures in hypertension, is a reduced density of arterioles, a phenomenon also called rarefaction.12 Rarefaction may be initiated by a partial vessel closure secondary to arteriolar constriction, followed by anatomic rarefaction.41 The causes that initiate this phenomenon, its actual importance, and the distribution of microvascular rarefaction remain to be clarified.42 It has been suggested that increased sensitivity or responsiveness to norepinephrine43 or other agents or myogenic vasoconstriction in response to elevated blood pressure44 may contribute to temporary closure of small vessels, eventually leading to permanent closure or rarefaction. Using a mathematical model applied to the hamster cheek pouch microcirculation, Greene et al42 have proposed that rarefaction may contribute approximately 20% to elevation of resistance in arterioles, whereas more than 70% was attributed to vasoconstriction. Rarefaction has been noted not only in genetic hypertension in skeletal muscle and other vascular beds10,43,45,46 but also in the cremaster muscle of experimental models such as renal hypertensive
Recent studies using in vivo videomicroscopy have shown that in 2K1C hypertensive rats, lumen diameters of arterioles of 100 μm were significantly smaller than controls after 2 weeks of hypertension and that wall/lumen ratios were increased but wall cross-sectional area was reduced. Mild rarefaction was functional at 2 weeks but structural at 8 weeks of hypertension. Vasoconstriction and functional rarefaction of small arterioles may reduce blood flow and result in the reduced diameter of blood vessels without development of hypertrophy. An additional type of microvascular alteration involving vasomotion has been recognized recently. Using the dorsal skin flap to study skeletal muscle microcirculation in conscious 12-week-old SHR by videomicroscopy, Le Noble et al showed resting diameters of first- and second-order arterioles to be reduced in hypertensive rats relative to Wistar-Kyoto control rats, whereas in third- and fourth-order arterioles, diameters were similar, and those of postcapillary small venules were larger in SHR. Third- and fourth-order arterioles presented vasomotion whose amplitude was greater in SHR. The exact functional significance of the increased amplitude of vasomotion is unknown. It may represent enhanced myogenic tone and result in either increased resistance to flow or partial closure of arterioles leading to rarefaction, thus participating in either blood flow distribution or blood pressure elevation. Oscillatory reductions in diameter may increase resistance considerably as a consequence of the nonlinear characteristics of Poiseuille's equation, as mentioned above.

Biochemical Events in Smooth Muscle Cells of Blood Vessels Associated With Hypertrophy

The hypertrophic response is not only manifested by increased reactivity to circulating and locally acting vasoactive agents through the amplifier function of the reduced vascular lumen. As expected, hypertrophied smooth muscle may present changes in its intrinsic response to different agents. In SHR, vasopressin elicits in part increased pressor responses of mesenteric resistance blood vessels because of exaggerated responses of phospholipase C coupled to the V₁ vasopressin receptor. Exaggerated inositol phosphate responses tonorepinephrine in SHR have also been reported.

In experimental hypertensive rats, such as the DOCA-salt rat, initially decreased responses to endothelin due to receptor downregulation or prior receptor occupancy may be replaced by exaggerated responses, in part because of increased phosphoinositide turnover occurring a few weeks later or in the chronic phase of

![Figure 3](http://hyper.ahajournals.org/)

**FIGURE 3.** Panel A: Scatterplot shows correlation of media width and active tension developed by mesenteric resistance microvessels in response to 124 mmol/l KCl in renal hypertensive rats. Correlation coefficient was −0.47 for n=58 (y=2.29−0.09x). Data are in part from Reference 19 with permission. Panel B: Scatter plot shows correlation of blood pressure and active tension in response to KCl in the same rats as in panel A. Correlation coefficient was −0.65 for n=58 (y=2.49−0.009x). Correlation for media width and blood pressure in the same rats was 0.78. 2-K, two-kidney; 1C, one clip; 1-K, one-kidney.
DOCA-salt hypertension. Other aspects of the intracellular signal transduction mechanisms may be altered in hypertensive smooth muscle cells, including resting or stimulated cytosolic levels of calcium, calcium binding and release, protein kinase C activity, and numerous other biochemical steps leading to contraction and involving also the role of the contractile apparatus itself. Evidence of the alterations occurring in association with cardiovascular adaptation in some biophysical or biochemical events involved in vascular contractility includes the inverse correlation between tension responses of mesenteric resistance microvessels from renal hypertensive rats to a depolarizing concentration of potassium chloride (124 mmol/l), which should produce massive opening of voltage-dependent calcium channels in vascular smooth muscle cells, and the width of the media of the vascular wall in these small blood vessels or the level of blood pressure (Figures 3A and 3B), indicating a depression of excitation–contraction coupling.

Endothelial Function in Hypertensive Blood Vessels

Work by many investigators has documented that structural (and functional) abnormalities in blood vessels are not limited to smooth muscle cells. Over the past few years, there has been increasing evidence that the endothelium produces a variety of agents, some of which are vasoconstrictors (such as endothelin and thromboxanes) and others of which are vasorelaxants (such as endothelium-derived relaxing factor, endothelium-derived hyperpolarizing factor, and prostacyclin). These agents may be released by the endothelium and act locally on vascular smooth muscle cells to modulate vascular tone in different ways in health and disease. Structural abnormalities of endothelium and the subintimal layer have been demonstrated in larger blood vessels but possibly occur as well in the smaller resistance blood vessels exposed to raised blood pressures. Indeed, there is increasing evidence of malfunction of endothelium of larger and smaller arteries in experimental hypertension. Indomethacin, by inhibiting the generation of a prostanoid that may be a putative endothelium-derived contracting factor whose production is enhanced in hypertension, restores endothelium-dependent relaxation in small mesenteric arteries of SHR. An abnormal endothelium-dependent vascular relaxation has also been reported in patients with essential hypertension. A reduced capacity for relaxation of smaller blood vessels would result in an increased vascular tone (and may be in part responsible for the phenomenon of remodeling) and decreased relaxation in response to phenomena normally associated with a vasodilator response. This could produce elevated blood pressure either in basal conditions or in response to certain stressors that in health are associated with an increased tissue perfusion.

Conclusion

Increases in peripheral resistance in different forms of hypertension both in experimental animals and in humans result from a complex array of interactions occurring mainly at the level of small arteries and larger arterioles (“resistance vessels”). There is increasing evidence of the critical role these changes play in the maintenance of elevated blood pressure through increases in resistance to blood flow. There is no agreement, however, whether these alterations are only a consequence of hypertension or whether some may actually be involved in its pathogenesis. There are, on the one hand, structural alterations (reduced outer and vessel lumen diameter; thickened wall width; and increased, at least in some hypertensive models, wall cross-sectional area of small arterioles).
ies and arterioles, and rarefaction of the latter) and, on the other hand, functional alterations (increased circulating and local vasoconstrictors, perhaps reduced circulating and locally produced vasorelaxants; increased contractility or vasomotion of vascular smooth muscle cells; changes in the barrier role as well as other functions of endothelium; exaggerated biochemical responses of the calcium–phosphoinositide–protein kinase C system and other biochemical steps involved in signal transduction or contraction). The interaction of structural and functional changes appears to play a critical role, because even in the absence of exaggerated intrinsic functional responses, blood vessels will produce an increased pressor response to normal or even reduced stimuli because of the amplifier role of the structural alterations, namely, the reduced lumen of blood vessels, as a result of the law of Laplace. These geometric considerations should be taken into account when the behavior of blood vessels is examined, because tension changes in isolated arteries or arterioles do not provide an indication of their actual effect in vivo. In themselves, these abnormalities in the design or structure of small arteries produced by encroachment on the lumen will contribute to produce an increased resistance to flow in vivo, independent of all other factors involved. These considerations have critical importance for treatment, because hypertension therapy should strive to develop drugs that not only relax blood vessels or lower blood pressure by other means (such as natriuresis) but also contribute to produce regression of the reduced blood vessel lumen to as close to normal diameter as possible (Figure 4). If, in contrast, remodeling and a reduced lumen diameter persist or if remodeling occurs under treatment, even if the wall thickness is normalized, the resistance to flow will remain elevated in resistance vessels, and blood pressure will be more difficult to control. On the other hand, true regression might even result in prolonged periods of blood pressure control to within normal limits even in the absence of medication if lumen diameter is normalized. It is disappointing to note that, at present, available data do not indicate an important effect of relatively short periods of antihypertensive treatment on structure or function of small arteries in essential hypertension in humans.67

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