Effects of Chronic Hypertension and Its Reversal on Arteries and Arterioles

D. Lowell Stacy and Russell L. Prewitt

The reversibility of functional and structural microvascular alterations in chronic renal hypertension has not been established. Twelve weeks after surgery to induce hypertension, in vivo arteriolar and venular dimensions were measured in the cremaster muscle of rats with one-kidney, one-clip hypertension (1K1C), rats in which the clip was removed after 8 weeks (1KNT), and controls. Systolic blood pressure was significantly elevated after 3 days in 1K1C rats and reached a plateau by 6 weeks. In 1KNT rats, systolic blood pressures were similar to 1K1C rats but were normalized 1 day after unclipping. A marked medial-intimal hypertrophy was found by histological techniques in the thoracic and abdominal aortae (45% and 69%, respectively) but not in cremaster feeding arteries of 1K1C rats. These arterial changes were reversed after unclipping. In 1K1C rats, medial-intimal area decreased in first- through fourth-order (1A, 2A, 3A, and 4A) arterioles along with a decline in relaxed diameter (41%, 30%, 20%, and 21%, respectively), which was only partially restored after unclipping. Heart weight was increased by 67% in 1K1C rats, but it did not differ between 1KNT and controls. Therefore, the reversal of chronic renal hypertension can normalize gross structural alterations in the heart and large vessels, but more time may be required to normalize completely the arteriolar changes. These data indicate that long-term structural adaptations in renal hypertension are different in arterioles and arteries, and they may be related to chronic changes in blood flow and/or pressure. (Circulation Research 1989;65:869–879)
were hypertensive for 3–6 months. Therefore, there is increasing evidence that arteriolar alterations with chronic renal hypertension, when they occur, are qualitatively different from those observed in arteries.

There is much interest clinically in describing not only the mechanisms causing vascular alterations with hypertension but also in reversing or preventing these changes. It is generally believed that elevated blood pressure and wall stress stimulate myocardial and vascular smooth muscle growth, and thus, antihypertensive agents that are the most effective in lowering arterial blood pressure should be the most effective in reversing these structural changes. However, some agents such as captopril are thought to have effects that are beyond those associated with blood pressure reduction. Other factors are known to be involved in myocardial hypertrophy. Although a number of studies have examined the role of elevated transmural pressure or wall stress on vascular or cardiac structure, no known studies have examined the role of hypertension reversal on structural arteriolar alterations after chronic hypertension. The purpose of this study was to examine the changes in large and small arteries versus arterioles after chronic renal hypertension and to determine if these changes can be reversed after chronic normalization of arterial pressure.

Materials and Methods

Induction and Reversal of Hypertension

Male Wistar rats at 6–7 weeks of age were anesthetized with intraperitoneal injections of ketamine hydrochloride (80 mg/kg) and xylazine (12 mg/kg). After an abdominal incision, the right kidney was removed, and a silver clip (0.229-mm gap) was placed on the left renal artery, as close as possible to its branch point from the abdominal aorta (the 1K1C group). In control rats, the same procedure was used except the silver clip was removed before closing the abdomen. Penicillin G (25,000 units/100 g body wt) was injected intramuscularly after surgery, and after recovery the rats were given food and water ad libitum.

Eight weeks after surgery, rats were anesthetized with ketamine hydrochloride (80 mg/kg) and xylazine (12 mg/kg) to remove the renal artery clip from some of the hypertensive rats (the 1KNT group). After a flank incision, the silver clip on the left renal artery was cut and removed. Sham unclipping was performed on the control and remaining 1K1C rats. Penicillin G (25,000 units/100 g body wt) was injected intramuscularly after surgery. Four weeks after unclipping or sham unclipping, rats were prepared for microvascular studies. Thus, in all three groups, the microvascularture was observed 12 weeks after the initial induction of hypertension or sham surgery.

Systolic Blood Pressure Measurements

Indirect systolic blood pressure was measured by the tail-cuff technique once per week, including the day after unclipping or sham unclipping of the renal artery, for 12 weeks after the induction of hypertension. From 7:00–9:00 AM, conscious rats were placed for 5 minutes in a metal box warmed to 35°C and then restrained in a Plexiglas housing. The mean of five–seven consecutive measurements was obtained from each rat. Systolic blood pressure for the 12-week period was calculated and used as an index of the combined effects of pressure and time.

Microvascular Preparation

Twelve weeks after surgery to induce hypertension, rats were anesthetized with an intraperitoneal injection of urethane (480 mg/kg) and α-chloralose (96 mg/kg) to study the cremaster muscle in vivo. The trachea was intubated (PE-240), and the left carotid artery was cannulated (PE-90) for the measurement of mean arterial pressure. The mean arterial pressure was averaged during the microvascular experiment after pressure had stabilized. The right cremaster muscle was surgically exposed and continuously bathed with a warmed Tis-U-Sol solution (Travenol, Deerfield, Illinois) with added CaCl₂, 2.5 mM. A ventral incision in the cremaster muscle was made with a thermocautery, and care was taken to avoid cutting the large arterioles. The cremaster muscle was spread over the top of a Plexiglas pedestal with moderate tension and covered with Saran Wrap. The entire preparation was moved to a microscope stage (Laborlux II, E. Leitz Inc, Rockleigh, New Jersey); the pedestal was heated to 34°C, and the rat esophageal temperature was maintained at 37°C.

Arteriolar Dimensions

The preparation was allowed to regain tone, which usually required at least 30–90 minutes, and during this time the arteriolar architecture was characterized and drawn. The main feeding arteriole and venule were classified as the first-order arteriole (1A) and venule (1V). There were one to three feeding arterioles, but one was usually much larger than the others and was used for diameter measurements (Figure 1 and Reference 27). Most of the branches of the feeding vessels were arcading; they were classified as second-order arterioles (2A) and venules (2V). There are two subclasses of 2A arterioles; the most proximal are over 100 μm and the most distal about 60 μm. All of the proximal 2A arterioles were measured except those at the tip of the cremaster muscle. A representative sample of transverse arterioles (third-order or 3A) and terminal arterioles (fourth-order or 4A) were measured in consecutive branching segments in the thick portion of the cremaster muscle. All vessel dimensions were measured just distal from their parent branch point but before any daughter branches. In a preliminary study, it was found that a random selection of four 3A or 4A arterioles, as described above, gave mean resting or relaxed diameters that were not significantly different from those of the total
population of arterioles and, thus, were representative. Therefore, one 1A and 1V, five to nine 2A and 2V, and about four 3A and 4A measurements were averaged for each rat to give one value per vessel category.

Vessel dimensions were measured by transillumination from a 150 W halogen lamp, a model WV-5470 Panasonic video monitor, and an image splitter (model 308, Vista, Ramona, California). Magnification on the video monitor was ×1,060 and ×2,120 with Leitz UM20 and UM50 objectives, respectively. Arteriolar internal and external diameters were measured in the resting state and after topical application of adenosine (10^{-4} M) and were used to calculate the relaxed medial-intimal/cross-sectional area, medial-intimal thickness, and the medial-intimal/lumen (M/L) ratio. Venular internal diameters were measured in the relaxed state. The resting diameters of arterioles undergoing vasomotion were measured from freeze-framed videotape for several cycles. The maximum and minimum diameters were averaged; their waveform was assumed to be sinusoidal. Arteriolar tone was calculated as the change from resting to relaxed diameter, divided by the relaxed diameter, times 100.

**Arteriolar Density**

After the microvascular observations, the abdomen of the rat was opened, and heparin (1 unit/g body wt) was injected through the carotid catheter. The technique for perfusion-fixation of the cremaster muscle and measuring arteriolar density by stereological techniques has been described previously.\(^\text{16,24}\) The abdominal aorta was cannulated below the renal arteries, the left iliac artery was ligated, and an incision was made in the inferior vena cava. The inferior mesenteric artery or colon was clamped with hemostatic forceps to prevent backflow into the intestines and upper body. The right hindquarter and cremaster muscle were then perfused with 0.9% saline with adenosine, verapamil, and sodium nitroprusside at 10^{-4} M each and 58.7 g/l polyvinylpyrrolidone until the cremaster muscle microcirculation was cleared of blood. Then the cremaster was perfused with 10% buffered formalin for 5–10 minutes at the mean carotid artery blood pressure of the rat, followed by Microfil MV 122 (Canton, Boulder, Colorado). The microfil was allowed to polymerize, and the cremaster was cleared in glycerin and mounted between microscope slides. The density of arterioles was determined by counting their intersections with a 10×10 grid in the eyepiece of a dissecting microscope. Length density (mm/mm\(^2\)) of either small or large arterioles was calculated from the formula: \(\pi N/2L\), where \(N\) is the number of intersections, and \(L\) is the length of the grid system.

**Ventricular and Arterial Measurements**

The thoracic and abdominal aortas were dilated and perfusion-fixed at the mean arterial pressure of the rat. The entire aorta from the heart to just below the renal arteries was removed intact and placed in a vial of 10% formalin for analysis later. A section of thoracic aorta was taken about 5 mm distal to the apex of the aortic arch, and the descending or abdominal aorta was sectioned between branches of the renal and superior mesenteric arteries. Two small arteries, the pudic-epigastric and the superior pudendal, branch from the common iliac, and one or both feed the cremaster muscle (Figure 1 and Reference 27). These arteries were sectioned about 5 mm from the common iliac, and their dimensions were averaged.

Arteries were sectioned on a cryostat at \(-26°\) C and stained with toluidine blue. The image of these arterial sections was projected on a video monitor,
TABLE 1. Weights and Blood Pressures of Rats 12 Weeks After Surgery

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight (g)</th>
<th>SBP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>Ventricular weight (mg/100 g body wt)</th>
<th>Kidney weight (mg/100 g body wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=16)</td>
<td>482±7</td>
<td>126±2</td>
<td>143±2</td>
<td>131±2</td>
<td>104±3</td>
<td>419±11</td>
</tr>
<tr>
<td>1K1C (n=14)</td>
<td>442±17</td>
<td>194±5*</td>
<td>232±5*</td>
<td>211±5*</td>
<td>163±4*</td>
<td>387±10</td>
</tr>
<tr>
<td>1KNT (n=14)</td>
<td>474±12</td>
<td>209±4*</td>
<td>140±3†</td>
<td>184±4*†</td>
<td>97±4†</td>
<td>392±16</td>
</tr>
</tbody>
</table>

Values are mean±SEM. SBP, average tail systolic blood pressure; A, SBP 1-8 weeks after the surgery to induce hypertension; B, SBP 8-12 weeks after unclipping or sham unclipping; C, SBP for the entire 1-12 weeks after surgery to induce hypertension; MAP, mean arterial pressure; HR, heart rate; 1K1C, one-kidney, one-clip hypertensive rats; 1KNT, one-kidney, unclipped hypertensive rats. MAP and HR were measured in the femoral artery in anesthetized rats. Ventricular weight and kidney weight are dry weight values.

*p<0.01 vs. the control group.
†p<0.01 vs. the 1K1C group.

and the cross-section of the media-intima was traced on acetate. A ×1 objective was used to view the large artery sections, and a ×20 objective was used for the small arteries; the result was a magnification on the screen of ×126 and ×750, respectively. The medial-intimal area was measured with an Apple graphics tablet. The inner circumference/π was taken as the luminal diameter; the vessel was assumed to be round. If the internal elastic lamina and media showed any indication of crenation or compression, the vessel was not used. In addition, if the section was elliptical and the media-intima was thicker on the long axis by more than about 20% versus the short axis, the section was not used. Microfil in the cremaster feeding arteries helped align the vessel with the microtome blade; this alignment decreased the chance of obtaining oblique sections, and the microfil usually washed out during staining. Pilot studies were done to determine if the storage of aortas in 10% formalin altered medial-intimal area. Aortas from rats were sectioned; one end was placed in formalin, and the other end was immediately placed in the cryostat without fixation (−26°C). No significant difference was found in luminal diameter or medial-intimal area.

The large vessels and atria were dissected from the heart. The heart was blotted with paper, and the ventricles were placed in an oven at 80°C for 24 hours to obtain dry weight.

**Statistical Analysis**

Comparisons between the three groups were made using analysis of variance (ANOVA) and Duncan's multiple-range test. Statistical significance was set at *p*<0.05. Data are presented as mean±SEM.

**Results**

**Body Weight, Blood Pressure, and Heart Weight**

The body weights of the rats were not different initially or after 12 weeks (Table 1). The hypertensive rats (1K1IC) appeared to lose weight for 2 weeks after the sham unclipping surgery, but the difference was not statistically significant by ANOVA (Figure 2). After unclipping, the rats of the 1KNT group gained weight rapidly.

**FIGURE 2.** Top panel: Graph showing body weight for 12 weeks after the surgery to induce hypertension for the control (n=16), hypertensive (1K1C, n=14), and unclipped (1KNT, n=14) rats. Bottom panel: Graph showing tail systolic pressure. Values are mean±SEM.
Systolic blood pressure was elevated significantly in both groups of hypertensive rats (1K1C and 1KNT) beginning 3-4 days after surgery, reached a plateau at about 6-8 weeks, and for the 1K1C rats remained high for 12 weeks (Table 1 and Figure 2). In 1KNT rats the blood pressure was reduced to normotensive levels the day after surgery and, thereafter, did not differ from that of the control group.

Ventricular dry weight increased 67% in hypertensive rats, but there was no significant difference in heart weights between 1KNT and control rats (Table 1).

Arterial Dimensions

Internal diameters of the thoracic aorta, abdominal aorta, and feeding arteries did not differ among the three groups of rats (Table 2). Medial-intimal area of the thoracic aorta increased 45% in 1K1C rats, and this was reduced to an insignificant 13% in 1KNT rats. Medial-intimal area of the abdominal aorta increased by 69% in 1K1C rats and 28% in 1KNT rats, but this latter value was not statistically significant (Figure 3). Thus, there was a greater increase in medial-intimal mass in the more distal aorta and less of a normalization after the reversal of hypertension. The increases in aortic medial-intimal area with hypertension were also reflected in the increased medial-intimal thickness and M/L ratio, since lumen diameter was similar. However, the M/L ratio and media-intimal thickness were not completely normalized in the 1KNT rats. There were no significant changes in the feeding arteries to the cremaster muscle among the three groups (Table 2 and Figure 3).

In Vivo Microvascular Dimensions and Tone

There were marked decreases in the resting diameters of large arterioles (1A and 2A) of hypertensive rats versus control rats, along with reductions in the relaxed internal diameters (Figure 4). 1A and 2A relaxed internal diameters of the hypertensive rats were reduced by 41% and 30%, respectively, but after unclipping they were reduced by only 11% and 16%, respectively, which was still significantly different from control values. Diameters of small arterioles (3A and 4A) were not altered in the resting state, but their relaxed diameters were structurally reduced by 20% and 21%, respectively, in 1K1C rats and by a statistically insignificant 9% and 11% in 1KNT rats. Therefore, in cremaster arterioles of rats with surgical correction of chronic hypertension, a 9-16% structural decrease in diameter...
remains, but it was statistically significant only in the 1A and 2A vessels. There was little tone in large arterioles versus small arterioles, and the tone of small arterioles was not significantly altered with hypertension or unclipping compared with controls. No significant difference in relaxed venular diameters occurred among the three groups. Internal diameters of feeding venules were 262±16, 240±11, and 242±15 μm for the control, 1K1C, and 1KNT groups, respectively. Second-order venular diameters were 165±14, 141±10, and 155±12 μm for the control, 1K1C, and 1KNT groups, respectively.

Density of Cremaster Arterioles

Density was measured by stereological techniques. Large arteriolar density (1A and 2A) was similar in control and 1K1C rats at 0.29±0.01 and 0.29±0.02 mm/mm², respectively; small arteriolar density (3A and 4A) was also similar in control and 1K1C rats at 3.2±0.1 and 3.2±0.1 mm/mm², respectively.

Arteriolar Dimensions

Since there were large changes in arteriolar diameter with hypertension, the medial-intimal area was plotted as a function of relaxed internal diameter in Figure 5 for the four orders of arterioles in the three groups. The best fit for the data was a second-order polynomial equation \( r>0.99 \), which was plotted on a log-log graph. There were no significant differences among the regression curves for the three groups, that is, when all arteriolar orders were considered together. When each arteriolar order was analyzed separately (Table 3), there were significant decreases in medial-intimal area in the hypertensive rats versus controls for all four arteriolar orders, but this was related to their smaller diameters. Medial-intimal areas in 1A and 2A arterioles of 1KNT rats were smaller than in control but larger than in 1K1C arterioles, but there were no differences in medial-intimal areas of 3A and 4A arterioles versus the other groups. Basically the same pattern seen with medial-intimal area was seen with medial-intimal thickness, which was used to calculate M/L ratio. The M/L ratio is indicative of the relative change in medial thickness since it is normalized to the relaxed internal diameter; this ratio increased significantly in 1A arterioles of the hypertensive rats (Table 3). This tendency for a relative increase in medial-intimal area at a given diameter is also seen in Figure 5 where the curve shifts upward and to the left for larger arterioles of the hypertensive group.

Discussion

Arteriolar Alterations

The most important microvascular change found with chronic renal hypertension, in terms of its effect on vascular resistance, is the structural reduction in arteriolar diameter, especially in the larger arterioles. The marked decrease in relaxed diameter of 1A and 2A arterioles in the hypertensive rats
partially contributed to the smaller resting diameters of 1A and 2A arterioles. Relaxed diameters of 3A and 4A arterioles were also reduced in the hypertensive rats versus controls, but this did not result in smaller diameters under resting conditions.

The structural reductions in diameter of hypertensive rats, which have been shown to begin in the 1A arteriole of the cremaster muscle at 2 weeks,16,22 move downstream and include 3A arterioles at 4–5 weeks,15,16 and 4A arterioles at 12 weeks (Figure 4). Also, a structural reduction in diameter occurs in small intestinal arteries and arterioles in human hypertension28 and was recently demonstrated in mesenteric arteries and arterioles of spontaneously hypertensive rats.6 In Figure 6, the reduction in relaxed arteriolar diameters as a percent of the control group is shown for hypertensive rats of 8 and 12 weeks duration and for 1KNT rats. The 8-week microvascular data are from a study by Hashimoto et al.16 and were included because the 1KNT group were hypertensive for 8 weeks and it is possible that their vascular alterations were not as severe as those of the 12-week 1KIC group. The largest arterioles of the 12-week hypertensive group demonstrated the greatest relative reduction in relaxed diameter versus controls (41%) but also showed the greatest reversal after unclipping, although the remaining 11% reduction was still

![Graph showing the relation between relaxed internal diameter and medial-intimal cross-sectional area for four orders of arterioles in hypertensive (1KIC), control, and unclipped (1KNT) rats. The individual values are the average for each arteriolar order for each rat, with the number of rats given in Table 1. The regression lines for each group are second-order polynomial equations.](image_url)
Arteriolar density was unchanged in hypertensive rats. This density, determined in dilated, fixed preparations, is an index of structural rarefaction. In renal hypertensive rats, functional and structural rarefaction has been shown in arterioles of the cremaster muscle after 4–5 weeks and 8–9 weeks of hypertension and in the gracilis muscle after 8–10 weeks. It is unclear why rarefaction was found after 8–9 weeks of hypertension but not at 12 weeks. One possibility is that changes in small arteriolar density follow changes in arteriolar tone. The elevated tone found in the acute and developing stages of 1K1C hypertension is reduced after 12 weeks (Figure 4 and Reference 16). This implies that arteriolar rarefaction is an autoregulatory process.

Arteriolar Medial Area

In general, medial-intimal hypertrophy of small arterioles is not commonly found in either human or renal models of hypertension. With chronic hypertension, a structural reduction in both arteriolar diameter and medial-intimal area is a common observation in the cremaster muscle, hamster cheek pouch, human small intestine, and coronary arteries. When 2K1C hypertension in dogs was reversed by unilateral nephrectomy, increased passive stiffness of the great vessels was partially reversed. However, coronary arteries showed the greatest changes with hypertension and the least reversal after nephrectomy, indicating that the effects...
of hypertension and its reversal are not uniform, even in large arteries.

In this study, unclipping of male rats with 8 weeks of hypertension completely normalized medial-intimal hypertrophy in both the thoracic and abdominal aortas (Table 2). Internal diameters were not reduced in the aortas or feeding arteries of hypertensive rats. The M/L ratio was not completely reversed in either thoracic or abdominal aortas, nor was medial-intimal thickness reversed in abdominal aortas. One interesting finding was the relatively larger increase in medial-intimal area in abdominal versus thoracic aorta (69% vs. 45%, Figure 3) of 1K1C rats. The thoracic aorta has a higher relative content of elastin versus collagen than the abdominal aorta, and pulsatile pressure is increased in the distal versus proximal aorta.33 It is not known, however, if any of these factors, in addition to the elevated static pressure, contribute to medial-intimal hypertrophy.

In rats with 4 weeks of 1K1C hypertension, pressure was increased above control values in one of the proximal feeding arteries to the cremaster muscle by 63%.29 These and other data on elevated arteriolar pressures with chronic renal hypertension suggest that the medial-intimal area of feeding arteries should be increased. However, it is not known if pressure remains elevated in the proximal feeding arteries for up to 12 weeks of hypertension. In this study, medial-intimal hypertrophy was not observed in vessels smaller than 230 μm; however, in spontaneously hypertensive rats medial-intimal hypertrophy occurs in resistance arteries down to 150 μm.14,23 as well as in arterioles.18-20

**Mechanisms of Chronic Vascular Restructuring**

Cross-sections of the thoracic aorta, 1A arterioles, and 3A arterioles are shown in Figure 7 for the control, 1K1C, and 1KNT groups, to compare their relative structural alterations. After 12 weeks of hypertension, there was a 45% increase in the medial-intimal area of the thoracic aorta with no change in diameter, whereas in 1A arterioles there was a 56% decrease in media-intimal area and a 41% decrease in diameter. Similar changes, though not as great, were still statistically significant in the 3A arterioles, with a 26% decrease in medial-intimal area and a 20% decrease in diameter. Because the changes in arteries and arterioles in chronic renal hypertension are different, they must be due to different mechanisms.

**Mechanisms in Arterioles**

With acute changes in transmural pressure, arterioles can partially regulate flow by both myogenic and metabolic autoregulatory mechanisms.34 When transmural pressure is increased in small arterioles, wall tension and stress are increased, but after autoregulatory constriction, the wall/lumen ratio is increased, and the wall stress is reduced toward normal. Small arterioles are more reactive to pressure stimuli and, thus, are better able to adjust acutely to changes in wall stress,14,35,36 which include the early stages in renal hypertension.14,16,24,35-37 Thus, increased wall stress, thought to be the stimulus for medial hypertrophy,1 is not present.

With chronic renal hypertension, these functional arteriolar alterations are replaced by structural changes, including a structural reduction in diameter,14-17,24 rarefaction,16,24 and sometimes medial-intimal hypertrophy.14,20 Structural reductions in arteriolar diameter are related to local microvascular hemodynamics since they are greatly attenuated in coarctation hypertension, in which the cremaster is normotensive,30 compared with those found in 1K1C16 or 2K1C17 hypertension. Because chronic reductions in flow in large arteries result in a reduction in vessel size that is dependent on an intact endothelium,38 one possibility that should be investigated is a reduction in blood flow.

**Mechanisms in Arteries**

Unlike small arterioles, the aorta does not demonstrate short-term autoregulatory responses, and thus, the increase in pressure after the initiation of renal hypertension will increase wall stress proportionally. In this study, after 12 weeks of hypertension, passive medial stress was normalized in the thoracic and abdominal aorta of hypertensive rats by medial hypertrophy to 1.05 and 1.01 times that of control rats, respectively, despite a 57% increase in mean arterial pressure. Wolinsky3 found that wall stress was increased in some groups of two-kidney, two-clip hypertensive rats but not others. Therefore, the evidence is not conclusive that wall or
medial stress is tightly regulated in arteries or arterioles, but it remains an attractive hypothesis.

**Conclusion**

With chronic renal hypertension, there is an increase in aortic medial-intimal area with no change in diameter, but arterioles are structurally reduced in diameter with medial-intimal atrophy. Four weeks after unclipping, ventricular hypertrophy and aortic medial-intimal area were normalized, but arteriolar changes were only partially reversed. The long-term responses of arteries and arterioles to chronic renal hypertension and its reversal were vastly different and probably represent different mechanisms of adaptation. Chronic changes in intravascular pressure or wall stress may alter medial-intimal mass while chronic changes related to blood flow or shear stress may alter vessel diameter.

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**KEY WORDS** • renal hypertension • medial area • arteriolar diameter • arteriolar tone • arteriolar structural adaptations
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