Enhanced Cerebral Vascular Regulation Occurs by Age 4 to 5 Weeks in Spontaneously Hypertensive Rats

H. Glenn Bohlen

SUMMARY Although the primary emphasis of research on spontaneously hypertensive rats (SHR) tends to be on adult animals, the young SHR can have a mean arterial pressure that is elevated above normal almost proportionately as much as in adult SHR. This study attempted to determine whether the cerebral vasculature of 4- to 5-week-old SHR used existing normal mechanisms to tolerate hypertension or had microvascular characteristics uniquely suited for hypertensive life. At mean arterial pressures above about 60 mm Hg, the arterioles of SHR were constricted compared with similar branch order vessels of normal Wistar-Kyoto rats (WKY). At arterial pressures below 60 mm Hg, however, the inner diameters of arterioles in normal and hypertensive rats can be similar. At arterial pressures of 40 to 120 mm Hg, normal WKY maintained blood flow within ± 10 of that at the resting arterial pressure of 90 mm Hg; SHR with a mean arterial pressure of 120 mm Hg regulated blood flow over a pressure range of 60 to 160 mm Hg. Normal WKY had petechial hemorrhages from venules and sustained loss of arteriolar tone at arterial pressures above 120 mm Hg, which is the resting arterial pressure of 4- to 5-week-old SHR. Microvascular pressure measurements indicated that the resistance of cerebral arteries was increased, because they dissipated about 50% of the arterial pressure in SHR compared with about 40% in WKY. Pressures in the smallest venules of WKY and SHR (12.7 ± 1 vs 10.6 ± 1 mm Hg) were similar, and presumably, capillary pressures were protected from hypertension in SHR. The overall data indicated that at as early as 4 to 5 weeks of age normal cerebral vascular regulatory mechanisms are incapable of protecting the microvasculature from hypertension and mechanisms to enhance vasoconstriction are an essential requirement in the developmental stage of hypertension. (Hypertension 9: 325-331, 1987)

KEY WORDS • hypertension • spontaneously hypertensive rats • brain • microcirculation • juvenile rats

The cerebral vasculature of adult spontaneously hypertensive rats (SHR) has been shown to be very well adapted to hypertensive arterial pressures. The cerebral blood flow and microvascular pressures in exchange vessels are within normal limits because of vasoconstriction caused partly by hypertrophy of the arterial and arteriolar walls. There is a general consensus that the autoregulatory pressure range is shifted upward such that adult SHR can tolerate mean arterial pressures in excess of 200 mm Hg compared with about 160 mm Hg in normal rats. Sadoshima et al. and Werber and Heistad have demonstrated that an intact sympathetic nervous system to the brain vasculature during maturation was necessary for full compensation to develop. The variety of compensatory changes is constantly increasing as more studies are completed and currently include vessel wall hypertrophy, enhanced myogenic depolarization, and increased ability of cerebral arteries and arterioles to sustain vasoconstriction at arterial pressures that damage normal vessels. Whether these anatomical and physiological changes needed to ensure protection of the cerebral vasculature during hypertension evolve gradually from normal mechanisms or are present to some extent early in the hypertensive process is unknown.

Little is known about cerebral vascular regulation in the young SHR during the early phases of mild hypertension. For example, DeLano and Zweifach reported

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that the mean arterial pressure of unanesthetized 1-month-old SHR was about 120 mm Hg. Sadoshima et al. found that this pressure was the upper limit for cerebral autoregulation in young SHR; the upper limit for normal rats was not evaluated. However, the important point is that young SHR may live at a mean arterial pressure very close to their maximum ability to effectively regulate cerebral blood flow. If this proposal is correct, young SHR may be constantly at risk for microvascular damage.

The current study evaluated the ability of 35- to 45-day-old Wistar-Kyoto rats (WKY) and SHR to regulate the cerebral cortical vasculature at hypotensive and hypertensive arterial pressures. At this age, both the general physiological state of the animal and cerebral vasculature were very easily altered. However, in stable animals, it was possible to determine to what extent the early phases of hypertension place the cerebral vasculature at risk and to define some of the early microvascular adaptations to hypertensive life.

Materials and Methods

Male WKY and SHR (Taconic Farms, Germantown, NY, USA) were studied at age 35 to 45 days and will be referred to as 4- to 5-week-old animals. All animals were anesthetized with sodium thiopental (Abbott Laboratories, North Chicago, IL, USA) 100 mg/kg i.p., and the anesthesia was supplemented with one fifth the original dose after about 3 to 4 hours. Although Delano and Zweifach have recommended that tracheal cannulation be avoided in SHR, the arterial blood oxygen tension (PaO₂) in the current study would not consistently remain above 90 mm Hg unless the trachea was cannulated. Therefore, all rats, other than those used in preliminary studies, had their trachea cannulated with polyethylene tubing that did not stretch the trachea. The left femoral artery and vein were cannulated to measure the arterial pressure and to change the blood volume, respectively. To evaluate the arterial pressure, norepinephrine solution (25 mg/kg i.p., and the anesthesia was supplemented with one fifth the original dose after about 3 to 4 hours. Although DeLano and Zweifach have recommended that tracheal cannulation be avoided in SHR, the arterial blood oxygen tension (PaO₂) in the current study would not consistently remain above 90 mm Hg unless the trachea was cannulated. Therefore, all rats, other than those used in preliminary studies, had their trachea cannulated with polyethylene tubing that did not stretch the trachea. The left femoral artery and vein were cannulated to measure the arterial pressure and to change the blood volume, respectively. To evaluate the arterial pressure, norepinephrine solution (25 μg/ml, 0.01–0.05 ml/min) was administered intravenously.

The left parietal cortex was exposed by a midline incision and removal of the parietal bone. Bleeding from the skin, muscle, tissue and bone was stopped by compression or by placing a few thrombin crystals (Parke-Davis, Morris Plains, NJ, USA), on the site of bleeding. Removal of the dura with minimal bleeding from the meningeal blood vessels can be accomplished by drying the dura until the flow in the visible microvessels ceases. Before the dura was removed, a heated (38°C) physiological solution was constantly suffused (3–5 ml/min) over the brain’s surface. The oxygen and carbon dioxide tension of fluid aspirated from the brain’s surface was 35 to 45 mm Hg throughout the experiment, and the temperature was 37 to 38°C.

After the operation was completed, the animal was allowed to recover for 20 to 30 minutes. Vascular tone at resting arterial pressure was not assessed because even brief (3–5 minutes) vasodilation with adenosine (10⁻⁴ M) or isoproterenol (10⁻⁵ g/ml) caused noticeable brain swelling. However, the arterioles did dilate at least 40 to 50% in response to a 20-second period of breathing 5% O₂ and 5% CO₂ (balance, N₂) or lowering arterial pressure by a brief hemorrhage (2–3 minutes). The animal was discarded or data collection was stopped if the vessels failed to dilate, the arterial pressure was slowly decreasing, any petechial hemorrhages in the brain were present, or the PaO₂ was below 90 mm Hg and PacO₂ was above 45 mm Hg. Stable animals maintained a virtually constant (± 5 mm Hg) mean arterial pressure and exhibited no signs of cerebral swelling for at least 4 to 5 hours after operation. The success rate was about 50%, based on the criteria mentioned previously. A total of 23 SHR and 22 WKY were evaluated successfully.

Preliminary studies indicated that young rats had to be heated as soon as the anesthetic agent took effect or the arterial pressure decreased. Furthermore, the temperature of the heating mat had to be 35 to 36°C to avoid overheating or underheating the animal. If the rectal temperature fell below 37°C, the animal was covered with insulation, because if the heating mat temperature was raised above 37°C, the mean arterial pressure decreased, particularly in SHR.

The microvasculature was observed with Nikon (Garden City, NY, USA) water immersion lenses (10 × , numerical aperture = 0.22; 20 × , numerical aperture = 0.33) mounted on an Olympus metallurgical microscope (Model BMJ; New Hyde Park, NY, USA). Vessel dimensions were measured with a clear, flexible ruler mounted on the center third of a video monitor screen at a magnification of 800 or 1550 × . Illumination was provided by a 100-W quartz-iodine lamp powered by a precision DC voltage source (Model 62012G; Hewlett-Packard, Palo Alto, CA, USA) and delivered through an 18-in. long, ½-in. diameter fiberoptic bundle positioned at a 25- to 30-degree angle to the brain’s surface. Infrared and ultraviolet filters were placed between the light source and fiberoptic bundle.

Microvascular pressures were measured with a servonull pressure measurement system (Instrumentation for Physiology and Medicine, San Diego, CA, USA), which used micropipettes sharpened to an outer tip diameter of 1 to 3 μm. The angle of beveling for micropipette tips was about 20 degrees, which seemed to minimize arteriolar constriction as the pipette entered the vessel wall. In all experiments, microvascular pressures were measured in series-coupled arterioles and their venules such that a red blood cell could have passed through all vessels studied in a given rat.

Red blood cell velocity in the first order arterioles (1A) was measured with a velocity tracking correlator (Instrumentation for Physiology and Medicine). Blood flow was calculated from the inner cross-sectional area of the vessel and the red blood cell velocity. Although a slight amount of vasomotion could be detected for the small arterioles, the diameter of the large arterioles was constant at a given stable arterial pressure. All
blood flow measurements are presented as a percentage of control, and a constant correction factor for measured versus mean center line red blood cell velocity was assumed. The latter assumption is based on the observation of Proctor et al.\(^\text{14}\) that the correction factor is relatively constant so long as substantial vasoconstriction does not occur. In addition, Proctor and Busija\(^\text{15}\) have reported that the relative change in blood flow predicted with velocity-diameter measurements corresponds to whole tissue flow changes measured with the microsphere technique.

Because of the fragility of the cerebral vasculature and overall animal, the protocol duration was kept to about 3 hours. After the microvascular pressure measurements, which required about 1 hour to complete, the alterations of arterial pressure were attempted. Elevation of arterial pressure of more than 40 mm Hg in young rats had a very high (>90%) risk of permanent microvascular damage. Therefore, in all instances, arterial blood pressure was first lowered by hemorrhage and then restored before the arterial pressure was elevated. There was virtually no risk with hemorrhage, and the animal's arterial pressure returned to within ± 5 mm Hg of its resting pressure when the shed blood was infused.

Statistical analysis of paired values between WKY and SHR was done with a t test for unequal numbers of observations.\(^\text{15}\) Multiple comparisons between or within animal groups were evaluated with Duncan's new multiple-range test.\(^\text{13}\)

**Results**

The microvascular pressure distribution in series-coupled vessels in 4- to 5-week-old WKY and SHR is presented in the left panel of Figure 1. Note that the pressures in all arterioles, from largest (1A) to smallest (fourth order arterioles, 4A), are elevated 7 to 15 mm Hg in the young SHR as compared with age-matched WKY. A major dissipation of pressure occurred at some point in the 4A or at the capillary region, because pressures in the smallest venules, the third order venules (3V), in SHR were normal. Capillaries near the brain's surface were seen to empty into the 3V, and presumably, capillaries of the deeper cortex drained into the 3V before it reached the brain's surface. Therefore, it is likely that the capillary pressures, as indirectly accessed from pressures in 3V, were nearly normal in SHR.

The microvascular pressure divided by the mean arterial pressure for the various vessels is presented in the right panel of Figure 1. These data revealed two important characteristics of SHR. First, the fraction of the arterial pressure that reached the largest arterioles was about 8 to 10% lower than normal. This finding indicates that arterial vessels of SHR dissipated arterial pressure more effectively than those of WKY. The second point of interest was that pressures in second order arterioles (2A) through 4A were the same fraction of the arterial pressure in normal and hypertensive rats. Therefore, the pressure dissipation by arteries and the largest arterioles of SHR did not fully protect the downstream vessels, and the smaller arterioles dissipated a normal fraction of the mean arterial pressure.

The inner diameters and vessel wall characteristics of the 1A through 3A are presented in Table 1. The vessel wall characteristics are based on in vivo observations and therefore represent a summation of all components of the vessel wall. In vivo microscopy did not provide adequate resolution to independently measure the muscle, basement membrane, and endothelial layers of the arterioles.

**Figure 1.** Microvascular pressures and microvascular pressures as a fraction of the mean arterial pressure throughout the cerebral microvasculature of 4- to 5-week-old WKY and SHR. The number above or below each data point represents the number of vessels studied and closely reflects the number of animals studied. Capillary pressures could not be measured but would be bracketed between the pressures in fourth order arterioles (4A) and third order venules (3V). Error bars represent the SEM. \(P_{\text{sys}}\) = mean systemic arterial pressure; A = arteriole; V = venule.
Table 1. Inner Diameter, Vessel Wall Characteristics, Microvascular Pressure, and Wall Tension for Cerebral Cortical Arterioles of 4- to 5-Week-Old WKY and SHR

<table>
<thead>
<tr>
<th>Type of vessel</th>
<th>Inner diameter (μm)</th>
<th>Wall thickness (μm)</th>
<th>Wall/lumen ratio</th>
<th>Wall area (μm²)</th>
<th>Arteriolar pressure (mm Hg)</th>
<th>Vessel wall tension (dyn/mm)</th>
<th>Number of vessels</th>
<th>Number of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A WKY</td>
<td>53.7±8.7</td>
<td>8.0±0.5</td>
<td>0.15±0.01</td>
<td>1549±193</td>
<td>50.9±1.6</td>
<td>1822±198</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>1A SHR</td>
<td>43.6±8.7*</td>
<td>6.9±0.2*</td>
<td>0.16±0.01</td>
<td>1049±57*</td>
<td>61.3±4</td>
<td>1781±116</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>2A WKY</td>
<td>31.8±5</td>
<td>6.9±0.3</td>
<td>0.23±0.02</td>
<td>838±86</td>
<td>38.0±1.2</td>
<td>805±108</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>2A SHR</td>
<td>26.9±5*</td>
<td>6.3±0.3*</td>
<td>0.24±0.01</td>
<td>656±43</td>
<td>53.9±2.2</td>
<td>966±80</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>3A WKY</td>
<td>17.3±3.1</td>
<td>5.8±0.4</td>
<td>0.34±0.03</td>
<td>420±55</td>
<td>30.3±1.4</td>
<td>349±39</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>3A SHR</td>
<td>15.4±1.1*</td>
<td>5.5±0.3</td>
<td>0.36±0.02</td>
<td>361±24</td>
<td>44.5±1.5</td>
<td>456±21*</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

Vessel wall dimensions are based on in vivo observations, and all components of the vessel wall are considered, including the connective tissue sheath around the vessel. Inner diameters are means ± SD; all other data are means ± SEM. 1A, 2A, 3A = first, second, and third order arterioles, respectively.

*p < 0.05, compared with values in WKY (based on number of vessels studied).

All of the cortical arterioles in SHR were constricted at rest compared with comparable branch order vessels in age-matched WKY (see Table 1). However, the arterioles of SHR were capable of dilating to about the same diameter as normal vessels during hypotension, as shown in Figure 2 at mean arterial pressures of 35 to 60 mm Hg. Measurements of maximally dilated arterioles were avoided at control arterial pressures because brain swelling occurred and vasodilation persisted in both WKY and SHR after tissue trauma.

At mean arterial pressures greater than about 65 mm Hg, as shown in Figure 2 for the 1A, the arterioles in SHR were constricted compared with their normal counterparts. At pressures above about 120 mm Hg, the arterioles of WKY consistently were dilated whereas arterioles of SHR continued to constrict progressively until the mean arterial pressure exceeded 160 mm Hg; the vessels then dilated. The dilation at the maximum pressures mentioned did not occur abruptly as soon as the arterial pressure reached a given pressure. In all instances, the arteriole constricted or almost maintained its diameter at pressure until the mean arterial pressure exceeded 160 mm Hg; the vessels then dilated. The dilation coincided with petechial hemorrhages from nearby small venules, even though blood from the damaged venules did not reach the arterioles before the dilation occurred. Therefore, the blood itself was not the cause of the dilation. At rest, a blood clot could be allowed to form on the intact brain surface, and yet the arterioles would perform normally after the clot was removed. Furthermore, when blood was accidentally or intentionally introduced between the pial membrane and arterioles, the arterioles did not dilate. Arteriolar dilation only occurred if blood was present as a result of vascular damage during induced acute hypertension.

Figure 2. Inner arteriolar diameters for WKY and SHR at mean arterial pressures from about 40 mm Hg up to arterial pressures that caused irreversible dilatation of the arterioles. At arterial pressures of 65 to 90 mm Hg and 110 to 165 mm Hg, the arterioles of SHR were significantly (p<0.05) smaller than normal. At arterial pressures higher than those shown for each animal strain, the arterioles were dilated. Error bars represent the SEM. Psys = mean systolic pressure; Nv = number of venules; Na = number of arterioles.
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The percentage of control blood flow measured as the arterial pressure was raised and lowered is presented in Figure 3 for WKY and SHR. Blood flow was measured in 1A as they entered the field of tissue exposed by the craniotomy. The WKY maintained blood flow within less than ±10% of control at mean arterial pressures from 45 to 115 mm Hg as compared with 65 to 155 mm Hg in SHR. Once the arterial pressure exceeded the upper pressure limit for ±10% flow regulation, the blood flow remained high because of the vascular damage, even when the blood pressure was restored to the control pressure for the two strains of rats.

Discussion

One of the major goals of this study was to determine if the cerebral vasculature of young SHR would use the inherent control mechanisms found in normal young rats to adjust to a mild increase in arterial pressure. The overall data indicate that the normal regulatory mechanisms of young rats are inadequate to support the early stages of hypertension. This conclusion was reached because the resting arterial pressure of young, 5-week-old SHR caused extensive damage to the cerebral microvasculature of young normal rats. Furthermore, at hypertensive pressures, the arterioles of normal rats were incapable of sustaining the vasoconstriction typical of young SHR at their resting arterial pressure.

As shown in Figure 1, arteriolar microvascular pressures were elevated 8 to 10 mm Hg in young SHR, which was about a 20 to 35% increase in distending pressure. The influence of this increased pressure on vessel wall tension was offset by the 15 to 20% constriction of arterioles in SHR, such that the larger arterioles, the 1A and 2A, had a normal wall tension and the wall tension for smaller vessels was increased by, at most, 10 to 20% (see Table 1). A contributing factor to minimizing increased microvascular pressure was a proportionately greater pressure dissipation by cerebral arteries preceding the 1A of SHR than those of WKY. About 40% of the mean arterial pressure was dissipated by arterial vessels in WKY compared with about 50% in SHR (right panel of Figure 1). Had this not occurred, the input pressure to the cerebral microvasculature at the level of the 1A would have been about 10 to 12 mm Hg higher than was measured in SHR. Werber and Heistad2 and Harper and Bohlen3 have shown that the cerebral arterial vasculature in adult SHR is an important contributor to increased cerebral vascular resistance and actively participates in cerebral blood flow autoregulation, as initially demonstrated by Kontos et al.4 However, in both studies, the fraction of arterial pressure dissipated by the arterial vessels in adult SHR was about 10% less than normal whereas the reverse was true for young WKY and SHR (see Figure 1). In effect, the arteries of young SHR dissipated 20% more of the mean arterial pressure than those of adult SHR. Therefore, the increased resistance of the cerebral arterial vasculature was better developed to dissipate pressure in the young than in the mature SHR.

The vasoconstriction that could only be inferred for the cerebral arterial vasculature could be observed directly for the cerebral arterioles. As presented in both Table 1 and Figure 2, the arterioles of SHR were constricted compared with comparable branch order vessels at arterial pressures from 60 to 160 mm Hg. While it was obvious that vasoconstriction in SHR at hypertensive arterial pressures would be beneficial to protect the vasculature from overdistention and hyperemia, the vasoconstriction at hypotensive pressures of 60 to 90 mm Hg may be self-defeating. The finding that diameters of the same branch order vessels in normal and hypertensive rats were equivalent at arterial pressures of about 40 to 60 mm Hg indicated that during severe hypotension, vessels of young hypertensive rats were capable of dilation to diameters comparable to those in young normotensive rats. The constriction of arterioles of the young SHR must be due predominant-

![Figure 3. Percentage of control blood flow in cortical arterioles of WKY and SHR at mean arterial pressures from about 40 mm Hg up to pressures that damaged the microvasculature. Asterisks indicate blood flows that are significantly different (p<0.05) from those at the resting arterial pressure of the animal group. At arterial pressures higher than those shown, blood flow continued to increase. Error bars represent the SEM. See Figure 2 for key to abbreviations.](http://hyper.ahajournals.org/)

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ly to actions of the vascular smooth muscle. The smaller diameter of arterioles in young SHR than in WKY when vascular tone was present must be due to active smooth muscle contraction, because the maximum diameters of the vessels were similar and resting microvascular pressures in SHR exceeded those in WKY (see Table 1 and Figures 1 and 2). When vascular tone was present, the vessel wall tensions of the large (1A) and intermediate (2A) diameter arterioles of young WKY and SHR were not different (p > 0.05; see Table 1), because the vasoconstriction offset the increased microvascular pressures in SHR (see Figure 1). The vessel wall stress would be elevated because the wall thickness to lumen ratio in SHR was normal and microvascular pressure was increased (see Table 1 and Figure 1). The physical conditions for the arterioles of adult SHR previously studied were opposite to those of young SHR: wall stress was normal and wall tension was elevated.

The various differences in vessel wall characteristics can be partially related to the substantial vessel wall hypertrophy that existed in adult SHR compared with the absence of hypertrophy in young SHR (see Table 1); the arterioles were constricted compared to normal arterioles by about equal proportions at both ages (15-20%). In this context, both young and adult SHR require vasoconstriction as a means of adapting to hypertension. However, young SHR lack the substantial vessel wall hypertrophy of adult SHR and must depend on actively induced vasoconstriction to protect the microvasculature.

The net effect of greater constriction of both arterioles and the arterial vasculature in young SHR than in WKY was the ability of SHR to maintain a nearly constant blood flow at arterial pressures up to 40 mm Hg higher (155 mm Hg) than was possible in WKY (115 mm Hg; see Figure 3). A consequence of this enhanced autoregulatory ability was that the cerebral vasculature of SHR existed at a control arterial pressure of about 120 mm Hg, yet this same arterial pressure caused devastating damage to the vasculature of WKY. Qualitatively similar damage of venular hemorrhage and sustained arteriolar dilatation occurred in young SHR at arterial pressures above 160 mm Hg. Although the venular hemorrhage has a deleterious effect on the appearance of the vasculature, the blood itself was not the cause of the sustained arteriolar dilatation. The majority of arterioles dilated when the venules ruptured, but the response occurred before the blood reached the arterioles. Furthermore, intentional or accidental formation of a blood clot on the brain's surface had no sustained effect on arteriolar behavior. Therefore, it is possible that oxygen radicals formed during induced acute hypertension damaged the vessels and caused sustained vasodilation, as has been demonstrated by Kontos. However, whatever the cause of the damage, the primary reason that the cerebral vessels of young SHR survived during the developmental stage of hypertension was their ability to maintain arterial and arteriolar vasoconstriction at hypertensive arterial pressures.

The protection afforded the cerebral microvasculature by arterial and arteriolar constriction did not prevent a hypertensive pressure from existing in the smallest arterioles, the 4A (34 ± 1.6 mm Hg in SHR vs 27.2 ± 1 mm Hg in WKY). However, pressures in the smallest venules, the 3V, were equivalent in young normotensive and hypertensive rats (12.7 ± 1 vs 10.6 ± 1 mm Hg). If blood flow per mass of tissue is assumed to be similar in young WKY and SHR, as several studies have indicated, greater than normal resistance (> 50%) existed between the smallest arterioles and venules in SHR as compared with WKY. A comparable or even greater increase in resistance was previously reported for the smallest arteriole to venule region in adult SHR. A high resistance in the immediate precapillary region of the skeletal muscle and small intestine vasculatures has been observed in adult SHR. Therefore, the cerebral vasculature of young SHR is not unique in the sense of an unusually high resistance in the capillary region. What is of interest is that pressures in the smallest arterioles of the young and adult SHR, while higher than normal, were identical; of equal interest is the fact that these pressures were also equivalent in young and adult WKY. While these circumstances could occur by coincidence, it is also possible that some form of long-term regulation is responsible. For example, maturation increased the mean arterial pressure by at least 30 mm Hg in WKY and by over 50 mm Hg in SHR. The brain was obviously larger in adult than in 4- to 5-week-old rats, and blood vessels must have changed their resistance as they grew to suit this tissue enlargement. Finally, the venular pressures increased with age, possibly as a result of increased venular resistance as the venules elongated. If pressures in the capillary region are constant during maturation as a result of coincidence, a variety of presumably independent changes must passively interact such that no net effect occurs. Since blood flow per mass of tissue is known to be equal in WKY and SHR as well as in young and adult animals, long-term flow regulation may contribute to microvascular pressure maintenance in the vicinity of the capillaries. The equivalent pressures in the smallest arterioles of young and adult WKY or SHR may simply occur because the closer a vessel is to the terminal area of the high resistance vessels that regulate blood flow, the less likely it is that the vessel’s pressure will be disturbed during both maturation and the development of hypertension.

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