Active and Passive Arteriolar Regulation in Spontaneously Hypertensive Rats

H. Glenn Bohlen, Julia M. Lash

Abstract This study determined to what extent active and passive wall tensions increase in vivo intestinal arterioles of 13- to 15-week-old and 25- to 27-week-old spontaneously hypertensive rats (SHR) to maintain normal or smaller arteriolar diameters during microvascular hypertension. Acetylcholine and nitroprusside were used to determine whether vascular muscle relaxation to endothelium-derived relaxing factor or cyclic GMP is impaired. Large arterioles of hypertensive rats have passive tension-circumference relations that are steeper and shifted to the left compared with those of age-matched controls; passive resistance to distension limits vasodilation in hypertensive rats except at their naturally elevated arteriolar pressure. Passive tension contributes approximately 30% of the total resting tension in arterioles of hypertensive and normotensive rats because a greater passive tension occurs at the 20% to 25% constricted resting diameter in hypertensive rats. Absolute and relative changes in the diameter of SHR arterioles during acetylcholine and nitroprusside application were equal to or greater than those in Wistar-Kyoto rats. However, reduction in active tension was suppressed in older SHR and remained approximately 50% higher than that found in older Wistar-Kyoto rats during drug application. Vasoconstriction and increased passive resistance to distension of the arteriolar wall diminish the active tension required to maintain normal or smaller resting diameters against microvascular hypertension. However, the elevated microvascular pressure in hypertensive rats is required to allow near-normal dilation to compensate for their increased passive resistance to stretch and decreased ability to relax active tension through cyclic GMP mechanisms. (Hypertension. 1994;23[part 1]:757-764.)

Key Words • endothelium-derived factors • hypertension • arterioles

Studies of intestinal arterioles in our laboratory indicate that in large arterioles of both normal and diabetic rats, 60% to 75% of the total vessel wall tension at rest is derived from active muscle tension, and therefore, active tension dominates the regulation of resting arteriolar diameter.1-2 A very different situation may occur in the arterioles of the spontaneously hypertensive rat (SHR). In a series of studies Baumbach and colleagues3-8 have shown that the passive distensibility of cerebral arterioles is increased in the stroke-prone SHR compared with normotensive animals when distensibility is defined as the percent change in diameter per millimeter of mercury. However, their data indicate that the inner diameters of passive arterioles in adult SHR (≥6 months) are much smaller than in normotensive rats at equivalent distending pressures. These data also suggest that at equivalent diameters passive tension will be much higher in the arterioles of hypertensive than normotensive rats because a greater arteriolar pressure is required to distend SHR arterioles. The possible effect is, that for any given vessel diameter in the presence of active vascular control, passive tension may contribute more to maintaining the resting diameter in hypertensive than normotensive rats. However, the relative contributions of active and passive wall tension to the regulation of resting arteriolar diameter depend on the complex interaction of the passive tension versus diameter (circumference) relation, the prevailing microvascular pressure, and the magnitude of active tension generation.1 At this time, the role of changes in passive distensibility in the generation and maintenance of increased vascular resistance during hypertension is not clear.

The purpose of this study was to determine to what extent active and passive wall tensions increase in intestinal arterioles of SHR to maintain normal or smaller arteriolar diameters in the presence of microvascular hypertension. We chose the large arterioles of the intestine for study because these vessels clearly demonstrate a 40% hypertrophy of the muscle layer cross-sectional area by age 17 to 19 weeks.9 Similar hypertrophy of the muscle layer has been documented for large cerebral arterioles6-10 and small arteries of the mesentery11-14 and is suggested for the largest arterioles of skeletal muscle.15 Furthermore, on theoretical grounds Borders and Granger16 have determined that the greatest power dissipation, which includes all forms of resistance, occurs in those microvessels with the greatest flow per vessel, that is, the large arterioles. For the current study, we studied normotensive and hypertensive rats at 13 to 15 and 25 to 27 weeks of age because the earlier ages coincide with the time at which the elevated arterial pressure begins to plateau in SHR, and arterial pressure remains relatively constant to the later ages. Evaluations at these particular times provide an opportunity for determining the active and passive vascular consequences of the rapid rise in pressure up to age 13 to 15 weeks and any additional vascular consequences or compensations that may occur over time at a relatively stable hypertensive pressure. We used direct application of acetylcholine and nitroprusside to determine the extent to which diameter regulation is altered by both active cellular processes and passive...
mechanical properties of the vessel wall during the two phases of hypertensive life studied.

Methods

Male Wistar-Kyoto (WKY) rats and SHR were purchased at age 12 to 13 weeks (Taconic Farms) and used for experiments at either age 13 to 15 or 25 to 27 weeks. The experimental protocol was approved by the Animal Resource Committee of the Indiana University Medical School. All animals were anesthetized with sodium thiopental (initial dose, 100 mg/kg IP) (Abbott Laboratories) and were usually given a supplemental dose equal to one fourth the initial dose after surgery was completed; additional doses were rarely needed. The trachea and right femoral artery were cannulated for measurement of arterial blood pressure and replacement of fluids and drugs. Body fluid replacement was performed to maintain a constant arterial pressure. Fluids (Normosol, Abbott) were administered by continuous infusion (0.5 mL/100 g per hour) through the arterial cannula. The maximum flow of approximately 0.04 mL/min through the arterial cannula had no discernible effect on arterial pressure measurements (model 23 Db Statham transducer, 0 to 200 mm Hg calibration, Gould Brush 2400 chart recorder).

The intestine was prepared for observation using an established technique modified to facilitate micropipette penetration studies. Intestinal motility was suppressed in all animals with a bathing medium concentration of less than or equal to 5 x 10^-3 mol/L isotroperenol, which is below the threshold concentration that causes blood flow to change. The tissues were bathed in a bicarbonate-based physiological solution equilibrated with 90% N2, 5% O2, and 5% CO2. The fluid was protected from the atmosphere en route to the tissue bath and heated to 37°C before entering the heated (37°C) tissue support device. The animal's core temperature was monitored by a thermistor in the esophagus, and the body received heat from both the tissue support device and a water jacket placed beneath the animal.

The tissue and vessels were observed with an Olympus BMHJ microscope using a Nikon x20 water immersion lens (numerical aperture, 0.33). The image was recorded with a Hamamatsu Charge Coupled Device camera (model XC-77) and digitized with an Image 1 image-analysis system (Universal Image Corp.). The image-analysis system magnification factors were calibrated in the horizontal and vertical planes using a stage micrometer marked in 10- and 100-μm units. Average vessel inner diameters were determined from measurements obtained from digitized images taken at 10-second intervals during the last 30 seconds of the control and drug release periods.

Microvascular pressures were measured with a servo-null system (model 4A, Instrumentation for Physiology & Medicine) using micropipettes filled with 2 mol/L NaCl and sharpened to an outer diameter of 4 to 6 μm. The system was calibrated at both 0 to 50 and 0 to 100 mm Hg. Drugs were applied to the wall of the selected vessel using an ionophoresis programmer (model 160, World Precision Instruments) (sodium nitroprusside, 10^-3 mol/L; acetylecholine chloride, 10^-3 mol/L; Sigma Chemical Co.). A retarding current of 20 to 25 nA was used to prevent inadvertent diffusion of drugs from the micropipette. Drugs were released at currents of 25, 50, 100, and 200 nA. Each drug was released for 2 minutes at each current, and the current was then increased to the next higher setting. In most cases, steady-state diameter responses were reached during the first minute of drug release, and diameter measurements were obtained from 90 to 120 seconds after a constant drug release at a given setting was initiated. In each experiment, the ionophoresis micropipette was placed as needed, and then the vessel was penetrated approximately 200 μm downstream with the servo-null micropipette. After dual micropipette placement, the vessel was allowed to stabilize for approximately 5 minutes. If clots formed on the tip of the servo-null micropipette, the micropipette was withdrawn and reinserted once clot formation at the vessel penetration site had stopped.

To obtain the passive pressure-inner diameter relation for each vessel, nitroprusside was locally released at a supramaximal dose of 500 nA. This nitroprusside dose made the vessel refractory to intentional micropipette irritation, which normally is capable of causing vessel constriction to closure. After data for resting conditions were obtained, the microvascular pressure was lowered with a bolus injection of 0.1 mL 1A of 10^-3 mol/L sodium nitroprusside. As the arterial pressure fell and then gradually recovered over a 5- to 7-minute period, diameter and microvascular pressure data were obtained at approximately 8 to 12 mm Hg steps in arterial pressure. During this period, the arteriolo was continuously exposed to the 500-nA current of nitroprusside to ensure that the vessel remained completely passive. Typically, the microvascular pressure fell to 10 to 15 mm Hg, which corresponds to an arterial pressure of 30 to 40 mm Hg in normotensive rats and 50 to 60 mm Hg in SHR. This manipulation does not injure the animal or vessel, as arterial pressure was virtually always restored to that before drug administration, and the resting vessel diameter was regained within approximately 8 to 10 minutes. The resting vessel diameter after the passive phase recovery was 98.4±1.37% (mean±SEM) of the initial control diameter in all WKY rats and 104.1±3.95% of the initial control diameter in all SHR. If topical sodium nitroprusside and local occlusion of the inflow artery are used to reduce microvascular pressure, as previously described, a similar recovery time is required. Also, there is the additional side effect of edema rapidly occurring in hypertensive rats because of the high microvascular pressures that occur when vascular tone is abolished. With the current approach, microvascular pressures in exchange vessels never exceed those observed when resting vascular tone is present. In a group of four normotensive rats, arterial pressure was lowered or raised from a low pressure by sustained infusion rates of sodium nitroprusside into the systemic vasculature, and 10^-4 mol/L sodium nitroprusside was simultaneously suffused over the tissue. The slope of the logP passive tension versus circumference relation was determined for one of the largest arterioles for the conditions in which arterial pressure was maintained at a specific pressure for 3 to 5 minutes and then for the same vessel using the standard passive-state conditions described above. With the use of sustained drug infusions, the slope of the passive tension versus circumference relation was 0.00973±0.00079 N/m² (mean±SEM) compared with 0.01027±0.001 N/m² when blood pressure was allowed to rever to resting conditions after intravenous bolus injection of sodium nitroprusside while nitroprusside was simultaneously applied to the vessel wall with a micropipette, illustrating the validity of the technique used to determine the vessel passive tension versus circumference relation.

The following terms and formulas were used to define the mechanical status of each vessel. Passive wall tension is the product of radius and microvascular pressure (newtons per meter), as defined by the Laplace relation, and refers to conditions in which vascular tone was fully abolished. Total wall tension is the product of microvascular pressure and radius (newtons per meter) and for our purposes is measured when the arteriolar wall is capable of generating active tension such that total tension is the sum of active plus passive tension. Active wall tension (newtons per meter) is calculated for specific vessel diameters by subtracting the passive tension at that diameter from the total wall tension; we assume that active and passive tensions are predominantly arranged in parallel.

The pressure and vessel inner radius data for passive conditions were used to calculate the passive tension in newtons per meter using the Laplace relation, assuming a near 0 mm Hg external pressure. The passive tension and circumference data were used to calculate a linear regression fit of the logP of passive tension versus circumference. We have
 Previously shown that a linear fit of the log-transformed data accurately represents the passive tension versus circumference relation ($r^2=0.9$) for arterioles of normal and diabetic rats. Equivalent results were obtained for all groups of SHR and WKY rats in that the minimum $r^2$ value for any animal was 0.89. The slope (M) and intercept (B) of the relation allowed us to calculate the passive tension ($T_p$) at any given circumference (C) as $T_p=10^{\frac{M}{10C-B}}$. This is essential for interpolation between passive data points because many different diameters were encountered during application of various amounts of both vasoconstrictor and dilator drugs, which altered active vessel wall tension generation directly and passive tension indirectly as the vessel changed diameter.

All calculations were performed with LOTUS 1-2-3 for Windows and CSS:STATISTICA (StatSoft, Inc) on a Gateway 486 33-mHz computer. Three-way ANOVA (strain, age, dose) was used to find significant effects, and a least significant difference analysis was used for individual group comparisons. A probability value less than or equal to .05 was considered to indicate a significant difference. All data are presented as mean and 1 SEM.

**Results**

The data in Table 1 indicate that the 13- to 15-week-old WKY rats and SHR (Y-WKY and Y-SHR) had equivalent body weights, but by age 25 to 27 weeks, adult WKY (A-WKY) rats were much larger than adult SHR (A-SHR). SHR were very hypertensive compared with WKY rats at each age; however, during the interval from 13 to 27 weeks, mean arterial pressure changed little. At rest, SHR arterioles were constricted compared with their normotensive age-matched counterparts, and arteriolar pressure was much higher than normal. In Y-SHR the arteriolar hypertension was sufficient to significantly ($P<.05$) increase total and active tensions were normal. Active tension is present. Coefficients for each passive curve are presented in Table 1. Overall data indicate that for a given age of young (13 to 15 weeks) or adult (25 to 27 weeks) spontaneously hypertensive rats (SHR) the passive curve shifts left such that a higher tension occurs at smaller-than-normal diameters. Normal hypertensive Wistar-Kyoto (WKY) rats show a slight tendency for the same type of shift with advancing age. Data were obtained from the following numbers of vessels with the number of animals in parentheses: young WKY, 11 (7); young SHR, 12 (7); adult WKY, 12 (11); and adult SHR, 10 (8).

**Table 1. Body and Cardiovascular Characteristics of Young and Adult Wistar-Kyoto and Spontaneously Hypertensive Rats**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Y-WKY</th>
<th>Y-SHR</th>
<th>A-WKY</th>
<th>A-SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, g</td>
<td>309.6±10.3</td>
<td>298±10.8</td>
<td>560±17</td>
<td>356±9*</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>102.2±3.5</td>
<td>167.6±4.3*</td>
<td>106.2±2.4</td>
<td>174.2±6.8*</td>
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<tr>
<td>Inner resting diameter, μm</td>
<td>71.7±3.0</td>
<td>59.2±3.0*</td>
<td>62±3.8</td>
<td>45.4±3.4*</td>
</tr>
<tr>
<td>Arteriolar pressure, mm Hg</td>
<td>60.4±3.4</td>
<td>93.9±6*</td>
<td>58.2±2.8</td>
<td>81.9±5.2*</td>
</tr>
<tr>
<td>Total wall tension, N/m</td>
<td>0.288±0.021</td>
<td>0.382±0.042*</td>
<td>0.243±0.02</td>
<td>0.224±0.038</td>
</tr>
<tr>
<td>Active wall tension, N/m</td>
<td>0.184±0.018</td>
<td>0.276±0.029*</td>
<td>0.174±0.021</td>
<td>0.195±0.019</td>
</tr>
<tr>
<td>Passive wall tension, N/m</td>
<td>0.105±0.023</td>
<td>0.104±0.024</td>
<td>0.079±0.019</td>
<td>0.057±0.014</td>
</tr>
<tr>
<td>Active/total tension, %</td>
<td>65.6±6.4</td>
<td>74.0±6.6</td>
<td>72.8±8.6</td>
<td>70.1±3.2</td>
</tr>
<tr>
<td>Passive slope tension/circumference, (N/m)μm</td>
<td>0.0072±0.0007</td>
<td>0.0084±0.0008*</td>
<td>0.0087±0.0008</td>
<td>0.0096±0.0012*</td>
</tr>
<tr>
<td>Intercept, N/m</td>
<td>-2.69±0.19</td>
<td>-2.66±0.15</td>
<td>-2.98±0.23</td>
<td>-2.63±0.15</td>
</tr>
</tbody>
</table>

Y indicates young (13 to 15 weeks); A, adult (25 to 27 weeks); WKY, Wistar-Kyoto rats; and SHR, spontaneously hypertensive rats. *$P<.05$, equal-aged WKY rats and SHR.

**Fig 1.** Plot shows total tension vs vessel inner circumference relations for passive conditions and resting values when active tension is present. Coefficients for each passive curve are presented in Table 1. Overall data indicate that for a given age of young (13 to 15 weeks) or adult (25 to 27 weeks) spontaneously hypertensive rats (SHR) the passive curve shifts left such that a higher tension occurs at smaller-than-normal diameters. Normal hypertensive Wistar-Kyoto (WKY) rats show a slight tendency for the same type of shift with advancing age. Data were obtained from the following numbers of vessels with the number of animals in parentheses: young WKY, 11 (7); young SHR, 12 (7); adult WKY, 12 (11); and adult SHR, 10 (8).
that arterioles of both normotensive and hypertensive rats have spontaneously hypertensive rats (SHR). Each curve represents the active status for a specific circumference at resting arteriolar pressure and microvascular pressure measurements was at or near the peak possible tension for the prevailing arteriolar pressure (Y-WKY, 93.3±2.1%; Y-SHR, 93.1±4.2%; A-WKY, 96.4±9.3%; A-WKY, 92±1.6%). The relatively flattened top of the parabolic active tension versus circumference relation allowed the active tension to be near maximal, but for SHR the resting diameter was substantially below the diameter at which maximum tension occurred. For Y-SHR the resting diameter (circumference) was 90.8±3.7% of that for maximal tension development compared with 104.4±5.3% (P<.03) for Y-WKY; values for A-SHR and A-WKY were 83.3±4.5% and 103.3±8.3% (P<.03), respectively.

The top panel of Fig 3 presents the actual diameters of arterioles in all groups as the dose (current) of acetylcholine was increased, and the bottom panel presents the percentage of control responses to acetylcholine. For a given age group during release of a given acetylcholine dose, there were no significant (P<.05) differences between arteriolar inner diameters of age-matched WKY rats and SHR. However, arterioles of Y-SHR and A-SHR were constricted significantly (P<.05) relative to those of WKY rats at rest. As a consequence, the relative dilation of SHR arterioles was greater than that of WKY arterioles at all doses, from threshold to maximal response. During these measurements, arteriolar pressure unchanged little because only a single vessel dilated. As an example, which is representative for all groups, the resting arteriolar pressure in A-SHR before application of acetylcholine was 87.8±6.7 mm Hg, and during release of the 25, 50, 100, and 200 nA nitroprusside doses it was 89.4±7.8, 89.7±7.8, 91.1±7.5, and 92.1±6.9 mm Hg, respectively. The overall data for Y-SHR and A-SHR during acetylcholine application indicate that endothelium-mediated dilation by acetylcholine is not impaired relative to that in WKY rats if judged on the basis of vessel enlargement.

The diameter responses during microiontophoretic application of nitroprusside, in terms of both absolute diameter and percentage of control diameter, are shown in Fig 4. On a relative basis, shown in the bottom panel of Fig 4, the data indicate that cyclic GMP-mediated relaxation allowed equivalent dilation of arterioles in age-matched normotensive and hypertensive rats. However, in absolute terms, as shown in the top panel of Fig 4, SHR arterioles were initially constricted relative to their normotensive counterparts, and vasodilation with nitroprusside did not fully overcome this constriction despite comparable absolute changes in diameter. As was found during acetylcholine application, microvascular pressure was essentially constant as the nitroprusside dose was increased for all groups. As an example, the resting arteriolar pressure in A-SHR before application of acetylcholine was 81.8±5.2 mm Hg, and during release of the 25, 50, 100, and 200 nA nitroprusside doses it was 81.3±5.4, 80.8±5.5, 83±5.9, and 84.3±6.2 mm Hg, respectively.

In a situation in which microvascular pressure is relatively constant as vasodilation is induced by acetylcholine and nitroprusside, the active tension will follow the active tension versus circumference curve, as shown.
vascular pressure decreased by small amounts in norconstrictions than occurred in Y-WKY (Fig 7). Microvascular pressure occurred in the hypertensive rats. A-SHR and A-WKY, but Y-SHR demonstrated greater absolute and relative increased, whereas an approximate 30% decrease in motensive rat arterioles as the norepinephrine dose was approximately 50% higher than normal in A-SHR. This was confirmed by the calculation of active tensions shown in Fig 6.

Fig 4. Bar graphs show actual diameters and percentage of control responses during iontophoresis of nitroprusside onto arterioles of young (Y) and adult (A) Wistar-Kyoto (WKY) rats and spontaneously hypertensive rats (SHR). On an absolute basis, SHR vessels change diameters as much as or more than normal but do not fully reach normal diameters for most nitroprusside doses. On a percentage of control basis, vessels of YSHR and ASHR demonstrate responses equivalent to normotensive age-matched WKY vessels. Numbers of vessels and animals are as in Fig 1.

Application of norepinephrine to the arteriolar wall caused equivalent constriction in A-SHR and A-WKY, but Y-SHR demonstrated greater absolute and relative constrictions than occurred in Y-WKY (Fig 7). Microvascular pressure decreased by small amounts in normotensive rat arterioles as the norepinephrine dose was increased, whereas an approximate 30% decrease in arteriolar pressure occurred in the hypertensive rats.

These data are shown in Table 2. We believe that the minimal change in arteriolar pressure despite a 70% or greater constriction in normotensive arterioles can occur because constriction is restricted to only several hundred microns on either side of the site of drug release. In comparison, arterioles of hypertensive rats constricted for at least 1 mm in both the upstream and downstream directions, and side branch vessels constricted as much or more than the parent vessel. As identical pipette and drug conditions were used in all groups, the longitudinally extended constriction in SHR probably reflects enhanced cell-to-cell communication in the vessel wall or unusually great drug diffusion, which is highly unlikely with the microiontophoresis technique used. The overall consequence is that constriction of SHR arterioles is enhanced by the decreased distending pressure secondary to the effects of vasoconstriction over an extended length of the vessel.

The specific large arterioles studied are known to have approximately a 40% hypertrophy of the cross-sectional area of the muscle cell layer by age 19 to 21 weeks in SHR, in the absence of hyperplasia and increased cell length. These arterioles did not exhibit hypertrophy of the muscle cells in SHR at age 4 to 6 weeks. For purposes of mathematical modeling of the effect of muscle layer hypertrophy on the wall stress versus circumference relation, the vascular smooth muscle area of the normal arterioles was assumed to be 500 μm² and 700 μm² for both groups of hypertensive animals, which represents a 40% increase in muscle layer area, as found in the earlier morphometric study. Active wall stress was calculated as the active tension for a specific circumference divided by the estimated muscular wall thickness at that circumference. The results of the mathematical model are shown in Fig 8 for the entire range of circumferences at the resting arteriolar pressure in each group. The active wall stress at rest for each individual vessel was determined, and the group averages are shown. The implications of the mathematical model will be considered below.
Discussion

The primary purpose of this study was to determine to what extent active and passive wall tensions increase in intestinal arterioles of SHR to maintain or constrict vessel diameters in the presence of microvascular hypertension. As shown in Fig 1, for any given circumference or diameter a greater passive tension resists vessel expansion in SHR than in WKY rats in both young and adult animals. Had we presented the data as the passive vessel diameter versus pressure relation, SHR arterioles would be significantly smaller in diameter than their normotensive counterparts at similar distending pressures just as Baumbach and colleagues38 have reported for SHR cerebral arterioles. The data in Fig 1 clearly indicate that both the developmental and sustained phases of hypertension in SHR are associated with structural changes in the vessel wall that result in higher-than-normal passive tension development at smaller diameters when compared with the arterioles of their normotensive counterparts. The same conclusion can be derived from the data published by Baumbach et al38 for SHR cerebral arterioles. This increase in passive wall tension minimizes the extent to which active tension must increase to maintain the vessel at any given diameter in the presence of an elevated microvascular pressure. The combined result of vasocostriction and increased passive tension allows the vascular smooth muscle of intestinal arterioles in adult SHR to have normal active tension development at rest (Fig 1) despite a 30% to 35% increase in microvascular pressure. Although in young SHR active tension development is higher than in WKY rats, an additional 25% increase in active tension would be required to maintain their constricted diameter if there were no increase in the passive resistance to distension. Therefore, the decreased ability for passive vascular expansion reduces the load that the active components of the vessel wall must bear, but simultaneously limits the ability of the vessel to dilate unless microvascular pressure is elevated. However, complete compensation by passive elements does not occur based on the fact that the vascular smooth muscle cells of these arterioles are known to hypertrophy by approximately 40%, as judged by an increased cross-sectional area of the total muscle layer and no evidence of cellular hyperplasia.

The preceding discussion leads to the issue of whether the microvasculature ultimately attempts to regain a normal active tension and stress by compensatory structural growth and regulatory events. Based on a mathematical model of vessel wall stress using mechanical data obtained in this study and morphological data from a previous study on similarly aged animals and identical types of arterioles,6 we have determined that the active wall stress is normal at rest in young SHR (Fig 8), but active tension is elevated (Figs 1 and 2, Table 1). However, although active tension appears to be fully normalized by age 25 to 27 weeks in adult SHR (Figs 1 and 2), the vessel wall appears to have overcompensated in terms of active stress, in that it is 65% to 70% of normal (Fig 8). In fact, if both wall hypertrophy and vasoconstriction occur, it is mathematically impossible for both active tension and stress to be within a normal range in arterioles of hypertensive animals. Our data indicate that SHR did not maintain either of these indexes of the active state within the normal range as both-young and adult animals. However, for any given age at least one of these indexes appeared to be in the normal range.

As previously noted, it is difficult to propose that any given mechanical index of the active state is actively maintained in a normal range in the presence of luminal hypertension and constriction. However, it is possible that SHR vessels attempt to regulate the active state as a constant fraction of some ideal status rather than maintain a specific tension or stress. Our data would support such regulation because active tension and stress are at about the same fraction of peak active status (80% to 90%) in both young and adult SHR and WKY rats (Figs 2 and 8). In view of the major differences in diameter, intravascular pressure, and wall thickness between normotensive and hypertensive rats, it seems beyond coincidence that normal fractions of maximum would exist for both indexes of the active status in all animal groups, especially when the absolute values can be substantially different between age-matched WKY rats and SHR as well as WKY rats and SHR at different ages. However, it may be that the
intestinal arterioles has also been found for rats with acute and chronic insulin-dependent diabetes, even though absolute active wall tensions and stresses were abnormal. Therefore, regulation of near-peak active state at rest appears to occur under a wide variety of pathological conditions in intestinal large arterioles and in a wide variety of differently aged normotensive animals. As we did not find evidence that the modifications of vessel behavior and structure maintained an absolute value of tension or stress, perhaps these modifications occur to resolve the even more complex requirement of maintaining near-maximal performance for the evolving changes in long-term resting physical conditions.

The consequence of an active regulatory system that strives to maintain near-peak performance is that when the vessel has a higher passive tension for any given diameter, the peak active tension and wall stress always will occur at a smaller-than-normal diameter for all microvascular pressures at and above normal. Notice in Figs 2 and 8 that for a given age group the isobar for active tension or stress and the circumference (diameter) at the peak of the curves for young and adult SHR are shifted to the left of the normal range. This occurs because increased passive tension limits the upper range of the diameter for any given pressure such that the active tension-length curve is restricted to a lower range of vessel circumferences and diameters, including the circumference at the peak active state.

We fully expected to find a decrease in the dilatory response to acetylcholine similar to that generally reported for in vitro studies of mesenteric arteries of SHR. On both an absolute and relative basis, the arterioles of young and adult SHR increased diameters as much as and in some cases more than the vessels of WKY rats at equal doses of both acetylcholine and nitroprusside (Figs 3 and 4). However, the absolute diameter of the arterioles in both SHR groups remained smaller than normal at each nitroprusside dose, which may simply reflect the vasoconstriction at rest and greater passive forces impeding vessel dilation (Fig 1, Table 1). Perhaps the best insight into endothelial cell- and cyclic GMP–mediated relaxation is provided by the decreases in active tension shown in Fig 6. Both acetylcholine and nitroprusside suppressed the active tension in young SHR as much as or more than normal, but neither mechanism was as potent in adult SHR. If the end point of relaxation is to reduce active tension, then adult SHR have decreased cyclic GMP relaxation in response to nitroprusside. However, if in vivo dilation is the frame of reference, the mechanisms function relatively normally to both acetylcholine and nitroprusside.

**TABLE 2. Microvascular Pressures at Rest Immediately Before and After 3 Minutes of Iontophoretic Application of Norepinephrine to Arteriolar Walls in Young and Old Wistar-Kyoto and Spontaneously Hypertensive Rats**

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>25 nA</th>
<th>50 nA</th>
<th>100 nA</th>
<th>200 nA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y-WKY (n=9)</td>
<td>56±4.4</td>
<td>52.4±5.7</td>
<td>53.9±6.4</td>
<td>51.2±7.3</td>
<td>54.5±6.8</td>
</tr>
<tr>
<td>Y-SHR (n=12)</td>
<td>81.0±6.1</td>
<td>74.4±6.3</td>
<td>60.3±8.4*</td>
<td>51.2±5.9*</td>
<td>48.5±9.9*</td>
</tr>
<tr>
<td>A-WKY (n=12)</td>
<td>53.9±3.3</td>
<td>51.7±3.9</td>
<td>46.6±3.2*</td>
<td>48.7±3.9</td>
<td>46.5±6.8</td>
</tr>
<tr>
<td>A-SHR (n=8)</td>
<td>79.5±9.5</td>
<td>80.4±9.6</td>
<td>54.9±6.8*</td>
<td>47.3±6.7*</td>
<td>49.7±8.8*</td>
</tr>
</tbody>
</table>

Y indicates young (13 to 15 weeks); A, adult (25 to 27 weeks); WKY, Wistar-Kyoto rats; and SHR, spontaneously hypertensive rats.

*P<.05, control vs response.
application in young and adult SHR (Figs 3 and 4). Therefore, in the sense of reducing arterial resistance and increasing blood flow in response to an endothelium-mediated vasodilator or direct agonist of muscle cyclic GMP, the vessels could function normally as long as the arterial pressure is elevated even though absolute decreases in active tension are reduced in adult SHR.

Beginning with the first demonstration by Folkow et al. of increased reactivity to norepinephrine in the hindlimb vasculature of SHR, there has been a general consensus that norepinephrine causes greater-than-normal vasoconstriction in SHR. The data from intestinal arterioles of young SHR shown in Fig 7 are certainly consistent with this consensus and demonstrate constriction comparable with that observed in arterioles of the cremasteric muscle of similarly aged SHR when exposed to identical norepinephrine release onto the vessel wall. In contrast, the same vessels in adult SHR do not demonstrate vasoconstriction, in absolute or relative terms, that is greater than normal (Fig 7). The microvascular responses in young and adult hypertensive rats were accompanied by a major decrease in microvascular pressure during point source application of norepinephrine. As shown in Table 2, the localized vasoconstriction during application of norepinephrine had a minor effect on microvascular pressure in normotensive rats, but as shown in Fig 7 the absolute changes in arteriolar diameters in equivalently aged WKY rats and SHR were similar. As explained in “Results,” the much more extensive distance over which vasoconstriction occurred in both young and adult SHR caused a major decrease in arteriolar pressure and hence the total active tension and stress that must be developed to maintain constriction. This raises the issue of whether exaggerated conduction of vasoconstriction along the arterioles is yet another means by which inappropriate increases in resistance occur in response to constrictor agents in hypertensive rats.

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