Effect of Hydralazine on the Mesenteric Vasculature of Hypertensive Rats

John S. Smeda and Robert M.K.W. Lee

To test whether structural alterations observed in the mesenteric vasculature of Wistar-Kyoto spontaneously hypertensive rats (SHR) were dependent on the presence of hypertension, male SHR and Wistar-Kyoto normotensive (WKY) rats were treated in utero and postnatally with hydralazine up to 28 weeks of age. Treated SHR, WKY, and untreated WKY rats had comparable blood pressures that were less than those of untreated SHR. Treatment altered the dimensions of the superior mesenteric, intermediate-sized, and small arteries of the mesenteric vasculature. In the case of the superior mesenteric artery and intermediate vessels, hydralazine treatment increased the lumen and medial cross-sectional areas of the arteries in WKY rats and slightly decreased both parameters in SHR. Within the small arteries, treatment significantly increased the lumen size in SHR but not WKY rats and had no significant effect on the media of the vessels. Despite the above alterations, the media-to-lumen cross-sectional area ratios remained significantly elevated in SHR over WKY rats in both the treated and control groups of animals within all classes of arteries. The results indicate that there is an inherent increase in the quantity of media surrounding the arteries of SHR when compared with WKY rats that cannot be abolished by normalizing the blood pressure in utero and postnatally with hydralazine treatment. In SHR, such changes persist not only in arteries that exhibit an increase in the media-to-lumen ratio before hypertension but also in the superior mesenteric artery in which an increase in the ratio occurs after hypertension development. (Hypertension 1991;17:526–533)

The specific mechanisms involved in producing a thickened vascular wall and the role that wall thickening plays in the initiation of hypertension in Wistar-Kyoto spontaneously hypertensive rats (SHR) are not fully understood. Owens and coworkers observed that wall thickening in the aorta of SHR was produced primarily by smooth muscle cell (SMC) hypertrophy, and the number of SMCs was not altered when the aortas of SHR and Wistar-Kyoto normotensive (WKY) rats were compared. SMC hypertrophy in the aorta was reversed by antihypertensive therapy with hydralazine, suggesting that such changes were produced by an elevated blood pressure. Mulvany and his colleagues, however, observed that wall thickening in SHR was produced by an increase in the number of SMC layers (i.e., hyperplasia) in the media of small mesenteric arteries. Such alterations were present in prehypertensive SHR, and persisted under conditions where the blood pressure had been normalized. This suggested that SMC hyperplasia was not a secondary alteration resulting from the presence of hypertension.

Studies we have performed are consistent with the types of observations made by Owens et al and Mulvany et al. The superior mesenteric artery, an elastic artery with a stratified SMC elastic laminar structure similar to that present in the aorta, exhibited a thickened intimal medial portion of the vascular wall in 28-week-old SHR when compared with WKY rats. In this artery, wall thickening occurred after hypertension development in SHR without an alteration in the numbers of SMC layers within the media, suggesting that the size of the SMCs was increased. Conversely, smaller mesenteric arteries of SHR exhibited a thickened vascular wall in SHR when compared with WKY rats that was produced primarily by an increase in the numbers of SMCs within the media without a change in SMC size. Such alterations occurred in prehypertensive SHR, indicating that SMC hyperplasia developed in a manner that did not depend on the presence of an elevated blood pressure.

To further test if the structural changes observed in the superior mesenteric artery were dependent on...
the presence of an elevated blood pressure and to determine if the occurrence of SMC hyperplasia in SHR occurred in a manner not dependent on an elevated blood pressure, male SHR and WKY rats were treated in utero and postnatally up to 28 weeks of age with the antihypertensive drug hydralazine. Such treatment has been shown to normalize the blood pressure of SHR for the duration of the treatment. At 28 weeks of age, the blood vessel wall of the mesenteric vasculature of SHR was morphometrically analyzed and compared with similarly treated WKY rats and control SHR and WKY rats that had received no treatment.

Methods

SHR and WKY rats used within the study were obtained from a colony maintained at McMaster University, Hamilton, Ontario. These rats originated from Charles River Breeding Farms (Wilmington, Mass.). The hydralazine treatment protocol used to treat SHR and WKY rats has been outlined in detail by Smeda et al. Female SHR were treated by placing 100 mg hydralazine/l into the drinking water. Such treatment normalized the blood pressure (measured using a tail-cuff compression method, Narco Bio-Systems Inc., Houston, Tex.) within 1 week of treatment. Subsequently, a male SHR was introduced into the cage to inseminate the female. Hydralazine treatment (100 mg/l drinking water) was then continued throughout pregnancy. Newborn male SHR were fed hydralazine by gavage until they were weaned with doses (16.9 mg/kg body wt/day) of hydralazine equal to the amount required to produce normal blood pressure in adult SHR. Because hydralazine crosses the placental barrier and is present in the maternal and fetal circulation at similar levels, there is reason to believe that the hypotensive effects of hydralazine exerted on the mother were also experienced by the fetus in utero. After weaning, hydralazine (100 mg/l) was placed in the drinking water, and the SHR were treated in this manner up to 28 weeks of age. Such treatment normalized the blood pressure of SHR for the duration the animals were treated.

At 28 weeks of age, treated SHR were sampled and the blood vessels of the mesenteric vasculature supplying the jejunum were morphometrically analyzed and compared with corresponding blood vessels obtained from WKY rats treated with hydralazine in an identical manner as the SHR. In addition, the mesenteric vasculatures of age-matched SHR and WKY rats that had received no hydralazine treatment were also sampled. The perfusion fixation techniques and the morphometric protocol used to study the mesenteric vasculature were identical to those previously described. The mesenteric vasculatures of SHR and WKY rats were perfusion fixed under maximally relaxed conditions using a protocol that produces minimal alteration in the vascular smooth muscle volume. The vascular wall components and the lumen cross-sectional areas (CSAs) of the arteries were morphometrically measured and compensated for skewness in sectioning angle. After such compensation, the CSA of the components represents the area that would be present if the artery had been sectioned perfectly perpendicular to the direction of blood flow. Segments of the superior mesenteric artery, the long branching arteries emanating as an arcade from the superior mesenteric artery (L vessels), and the jejunal arteries (S vessels) were measured. Figure 1 of Lee et al diagrammatically outlines the specific sample sites from which these arteries were obtained. One or two segments of the superior mesenteric artery, four to six separate L vessels, and four to six separate S vessels were sampled from each rat. The CSA measurements of each vessel were performed in quadruplicate and averaged for each vessel. Subsequently, all the vessels per each category of artery were averaged so as to produce one mean value for the superior mesenteric artery, L, and S vessels per rat. The n values within the tables represent the number of rats sampled.

A two-way analysis of variance was used to statistically assess 1) differences between SHR and WKY rats, 2) the general effect of hydralazine treatment on SHR and WKY rats, and 3) the differential effect of treatment on SHR and WKY rats; (1, 2, and 3, respectively, p < SHR-WKY, p < treat, and p < interact in Tables 1 and 2). In addition to such an analysis, an unpaired Student’s t test was used to compare SHR and WKY rats in the treated and control groups of animals and to assess the individual effect of treatment on SHR and WKY rats. In the above analysis, results were considered significantly different at p < 0.05. In the case of analysis involving the relation of the media to the lumen in hydralazine-treated and nontreated blood vessels (i.e., Figure 1), a least-squares fit method was used to obtain the best fitting straight line of each plot and the Pearson product moment correlation coefficient in relation to the degrees of freedom of the plot (n-1) were used to assess the degree of fit of the plot.

Results

Table 1 outlines the physical characteristics of the hydralazine-treated and control SHR and WKY rats used in the study. Hydralazine-treated SHR and WKY rats exhibited lower mean body weights than nontreated control rats; this difference was significant (p < 0.05) in SHR but not in WKY rats. In the control group, the systolic blood pressure of SHR was significantly elevated over that of WKY rats. Hydralazine treatment markedly reduced the blood pressure of SHR but did not significantly affect the blood pressure of WKY rats. At 28 weeks of age, the blood pressures of treated SHR and WKY rats and nontreated WKY rats were not significantly different from each other.

At the time of sampling, the heart rate was significantly elevated in SHR over WKY rats in both the treated and nontreated groups of animals. Hydral-
azine treatment of SHR but not WKY rats produced a further elevation in the heart rate. The mesenteric/portal vascular resistance to flow observed when these vascular beds were perfused at a constant flow of 3.5 ml/min was not significantly different when SHR and WKY rats were compared within the hydralazine-treated and control groups. Hydralazine treatment produced a significant decrease in vascular resistance in both SHR and WKY rats.

Morphometric Analysis of the Superior Mesenteric Arteries

Table 2A outlines the structural parameters pertaining to the superior mesenteric artery that was measured in the hydralazine-treated and control (nontreated) SHR and WKY rats.

A comparison of hydralazine-treated SHR and control SHR and WKY rats indicated that the lumen CSAs of the superior mesenteric artery of these groups of animals was similar, whereas the CSAs of the lumen of superior mesenteric arteries from hydralazine-treated WKY rats was larger than those present in the above groups of animals.

At the magnification at which the measurements of the superior mesenteric arteries were performed, the CSA of the intimal layer was quite small and barely distinguishable from the media. Thus, the intima and media were measured as one unit. The CSA of the intima+media of the superior mesenteric arteries was significantly increased in SHR when compared with WKY rats. This difference was particularly pronounced when the superior mesenteric arteries of
TABLE 1. Physical Characteristics of Hydralazine-Treated and Nontreated Spontaneously Hypertensive Rats and Wistar-Kyoto Rats at 28 Weeks of Age

<table>
<thead>
<tr>
<th>Physical parameters</th>
<th>SHR</th>
<th>WKY</th>
<th>SHR</th>
<th>WKY</th>
<th>SHR</th>
<th>WKY</th>
<th>SHR</th>
<th>WKY</th>
<th>SHR</th>
<th>WKY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td>314±8 (6)</td>
<td>317±15 (6)</td>
<td>355±11 (6)</td>
<td>356±7 (6)</td>
<td>0.05</td>
<td>NS</td>
<td>0.05</td>
<td>NS</td>
<td></td>
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<tr>
<td>Blood pressure (mm Hg)</td>
<td>SHR</td>
<td>111±7 (6)</td>
<td>212±5 (6)</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
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</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>SHR</td>
<td>495±22 (6)</td>
<td>376±5 (6)</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
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</tr>
<tr>
<td>Mesenteric portal vascular resistance (mm Hg [ml/min]⁻¹)</td>
<td>SHR</td>
<td>4.24±0.68 (5)</td>
<td>7.58±0.28 (6)</td>
<td>0.05</td>
<td>NS</td>
<td>0.05</td>
<td>NS</td>
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<tr>
<td></td>
<td>WKY</td>
<td>3.13±0.38 (6)</td>
<td>6.51±0.86 (6)</td>
<td>0.05</td>
<td>NS</td>
<td>0.05</td>
<td>NS</td>
<td></td>
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</tr>
</tbody>
</table>

Values are mean±1 SEM shown in the table. Numbers in parentheses are the number of rats. SHR, Wistar-Kyoto spontaneously hypertensive rats; WKY, Wistar-Kyoto normotensive rats.

*p values obtained using an unpaired t test.

†p values obtained from a two-way analysis of variance.

nontreated SHR and WKY rats were compared. The difference between hydralazine-treated SHR and WKY rats was smaller than that observed in the control SHR and WKY rats and was not significantly different. This was due to the fact that the arteries sampled from treated WKY rats were physically larger (having a greater lumen diameter and concomitantly greater CSA quantities of intima+media) than those of control WKY rats; whereas the superior mesenteric arteries of treated SHR were slightly smaller than those of control SHR. In treated animals, the above changes decreased the absolute differences in intimal+medial CSAs observed in control SHR and WKY rats. Hydralazine treatment altered the wall and lumen of the superior mesenteric arteries in a proportionally similar manner in both SHR and WKY rats, and measurements of the intima+media/lumen CSA ratios (which compensate for differences in lumen size) remained greater in SHR than WKY rats in both the treated and control groups of animals.

No significant differences in the numbers of SMC layers in the media were observed in the superior mesenteric artery of SHR and WKY rats in either the hydralazine-treated or nontreated groups of animals. Hydralazine treatment did, however, significantly reduce the numbers of SMC layers present in the media of the superior mesenteric arteries of both SHR and WKY rats.

Morphometric Analysis of the Intermediate-Sized Mesenteric Arteries (L Vessels)

Table 2B summarizes the structural parameters morphometrically measured in the intermediate-sized L vessels of hydralazine-treated and control (nontreated) SHR and WKY rats. L vessels from control SHR and WKY rats exhibited comparable lumen CSAs, whereas the lumen CSAs of the L vessels from hydralazine-treated WKY rats were larger than those present in treated SHR or control WKY rats.

Control SHR were found to have increased CSA quantities of intima and media when compared with untreated WKY rats. Hydralazine treatment did not alter the CSA of intima but significantly decreased the CSA of media present in SHR. Hydralazine-treated WKY rats on the other hand, had L vessels with increased intimal and medial CSA when compared with control WKY rats. The net effect of the above changes was to create a situation where the significant differences in intimal and medial CSAs previously observed between control SHR and WKY rats were absent when hydralazine-treated SHR and WKY rats were compared. Hydralazine treatment increased and decreased both the media and lumen of the L vessels of WKY rats and SHR, respectively, in proportionally similar degrees. This resulted in a situation where the media-to-lumen CSAs were not changed by treatment and remained elevated in SHR over WKY rats in both treated and control groups of animals.

The number of SMC layers present in the media of L vessels was also increased in SHR over WKY rats in both the hydralazine-treated and control groups of animals. In this instance, however, the L vessels of hydralazine-treated SHR and WKY rats had significantly fewer SMC layers within the media than, respectively, control SHR and WKY rats.
<table>
<thead>
<tr>
<th>Vascular wall measurements</th>
<th>Hydralazine-treated</th>
<th>Nontreated controls</th>
<th>p&lt;*</th>
<th>p&lt;SHR-WKY†</th>
<th>p&lt;treat†</th>
<th>p&lt;interact†</th>
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</thead>
<tbody>
<tr>
<td><strong>A. Superior mesenteric arteries</strong></td>
<td></td>
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<tr>
<td>Lumen ($10^3 \mu m^2$)</td>
<td>SHR 4.22±0.41 (5)</td>
<td>4.41±0.22 (5)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>WKY 4.74±0.35 (6)</td>
<td>3.71±0.26 (6)</td>
<td>0.05</td>
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<tr>
<td>Intima+media ($10^3 \mu m^2$)</td>
<td>SHR 1.68±0.12 (5)</td>
<td>1.85±0.10 (5)</td>
<td>NS</td>
<td>0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>WKY 1.40±0.08 (6)</td>
<td>1.15±0.06 (5)</td>
<td>0.05</td>
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<tr>
<td>Intima+media/lumen CSA ratio</td>
<td>SHR 0.407±0.031 (5)</td>
<td>0.420±0.024 (5)</td>
<td>NS</td>
<td>0.05</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>WKY 0.299±0.018 (6)</td>
<td>0.313±0.014 (5)</td>
<td>NS</td>
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<tr>
<td>SMC layers</td>
<td>SHR 5.18±0.33 (5)</td>
<td>6.08±0.06 (5)</td>
<td>0.05</td>
<td>NS</td>
<td>0.05</td>
<td>NS</td>
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<tr>
<td>WKY 5.50±0.14 (6)</td>
<td>5.98±0.08 (5)</td>
<td>0.05</td>
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<td><strong>B. Intermediate-sized mesenteric arteries (L vessels)</strong></td>
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<tr>
<td>Lumen ($10^2 \mu m^2$)</td>
<td>SHR 3.56±0.20 (6)</td>
<td>4.00±0.25 (5)</td>
<td>NS</td>
<td>0.05</td>
<td>NS</td>
<td>0.05</td>
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<tr>
<td>WKY 5.15±0.32 (4)</td>
<td>3.71±0.27 (6)</td>
<td>0.05</td>
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<tr>
<td>Intima ($10^2 \mu m^2$)</td>
<td>SHR 2.00±0.13 (6)</td>
<td>1.86±0.13 (5)</td>
<td>NS</td>
<td>NS</td>
<td>0.05</td>
<td>0.05</td>
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<tr>
<td>WKY 2.11±0.15 (4)</td>
<td>1.16±0.06 (6)</td>
<td>0.05</td>
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<tr>
<td>Media ($10^2 \mu m^2$)</td>
<td>SHR 1.44±0.11 (6)</td>
<td>1.83±0.08 (5)</td>
<td>NS</td>
<td>0.05</td>
<td>NS</td>
<td>0.05</td>
</tr>
<tr>
<td>WKY 1.25±0.04 (4)</td>
<td>0.97±0.04 (6)</td>
<td>0.05</td>
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<tr>
<td>Media/lumen CSA ratio</td>
<td>SHR 0.403±0.015 (4)</td>
<td>0.463±0.027 (5)</td>
<td>NS</td>
<td>0.05</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>WKY 0.244±0.010 (4)</td>
<td>0.267±0.019 (6)</td>
<td>NS</td>
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<tr>
<td>SMC layers</td>
<td>SHR 4.90±0.15 (6)</td>
<td>5.54±0.04 (5)</td>
<td>NS</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
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<tr>
<td>WKY 3.76±0.09 (4)</td>
<td>4.76±0.11 (6)</td>
<td>NS</td>
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<td><strong>C. Small jejunal mesenteric arteries (S vessels)</strong></td>
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<tr>
<td>Lumen ($10^2 \mu m^2$)</td>
<td>SHR 6.86±0.40 (6)</td>
<td>5.15±0.18 (5)</td>
<td>0.05</td>
<td>0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>WKY 8.65±1.21 (4)</td>
<td>7.46±0.62 (6)</td>
<td>NS</td>
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<td></td>
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<tr>
<td>Intima ($10^2 \mu m^2$)</td>
<td>SHR 6.34±0.33 (6)</td>
<td>4.81±0.31 (5)</td>
<td>0.05</td>
<td>NS</td>
<td>0.05</td>
<td>NS</td>
</tr>
<tr>
<td>WKY 6.63±0.86 (4)</td>
<td>4.55±0.26 (6)</td>
<td>NS</td>
<td></td>
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<td></td>
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<tr>
<td>Media ($10^2 \mu m^2$)</td>
<td>SHR 2.26±0.12 (6)</td>
<td>2.08±0.08 (5)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>WKY 1.88±0.28 (4)</td>
<td>1.81±0.11 (6)</td>
<td>NS</td>
<td></td>
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<tr>
<td>Media/lumen CSA ratio</td>
<td>SHR 0.322±0.018 (6)</td>
<td>0.405±0.018 (5)</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>NS</td>
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<tr>
<td>WKY 0.217±0.007 (4)</td>
<td>0.250±0.022 (6)</td>
<td>NS</td>
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<tr>
<td>SMC layers</td>
<td>SHR 2.05±0.04 (6)</td>
<td>2.16±0.08 (5)</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>NS</td>
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<tr>
<td>WKY 1.70±0.13 (4)</td>
<td>2.07±0.06 (5)</td>
<td>NS</td>
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</table>

Values are mean±1 SEM. Numbers in parentheses are the number of rats. SHR, Wistar-Kyoto spontaneously hypertensive rats; WKY, Wistar-Kyoto normotensive rats; SMC, smooth muscle cell; CSA, cross-sectional area.

* p values obtained using an unpaired t test.
† p values obtained from a two-way analysis of variance.
**Morphometric Analysis of the Small Prejejunal Mesenteric Arteries (S Vessels)**

Table 2C summarizes the structural parameters morphometrically measured in the S vessels of hydralazine-treated and control (nontreated) SHR and WKY rats.

S vessels from hydralazine-treated SHR and WKY rats as well as those from control WKY rats were observed to have lumens of comparable CSA. The lumen CSA of the S vessels from control SHR were smaller than those present in treated SHR, treated WKY, or control WKY rats.

The CSA of the intima was similar in S vessels from SHR and WKY rats in hydralazine-treated and control groups, whereas the CSA of the intima was increased in hydralazine-treated SHR over control SHR. In the case of WKY rats, the mean CSA of intima was also larger in hydralazine-treated animals when compared with controls, but this difference was not significant at \( p < 0.05 \).

There was no significant difference in the CSA of the media in S vessels from SHR and WKY rats in both the treated and nontreated groups of animals. Hydralazine treatment of SHR or WKY rats did not affect the CSA of the media of the S vessels. The media-to-lumen CSA ratio was higher in S vessels from SHR over those of WKY rats in both the treated and nontreated groups of animals. Hydralazine treatment reduced this ratio in S vessels from SHR (by significantly increasing the lumen size of the arteries) but did not significantly alter the ratio in vessels from WKY rats.

The mean numbers of SMC layers were significantly greater in the S vessels of SHR when compared with those of WKY rats in the hydralazine-treated but not the control group of animals. Hydralazine treatment significantly reduced the number of SMC layers in S vessels from SHR but not WKY rats.

**Discussion**

Our study has shown that, although in utero and postnatal hydralazine treatment produces structural alterations in the mesenteric vasculature of SHR and WKY rats, such alterations do not appear to be related to the antihypertensive effects of hydralazine. There is an inherent difference in the size of the media surrounding the arteries of SHR when compared with WKY rats that cannot be abolished by normalizing the prenatal and postnatal blood pressure of SHR. This can be demonstrated by plots of the media versus the lumen CSA. As shown in Figure 1, the medial CSAs for any given lumen diameter are greater in SHR than those in WKY rats regardless as to whether SHR or WKY rats are or are not treated with hydralazine. Hydralazine treatment did produce a remodeling of the mesenteric vasculature. In this regard, treatment decreased the numbers of SMC layers in the superior mesenteric artery and the L and S vessels of both SHR and WKY rats. The above alterations were more pronounced in treated WKY rats than SHR and occurred despite the fact that hydralazine treatment did not alter the blood pressure of WKY rats. It would therefore appear that the above changes are not related to the hypotensive effects of hydralazine treatment and represent either a direct effect of hydralazine on the mesenteric vasculature or the result of some other secondary effect associated with long-term hydralazine treatment.

The results of the present study are in part consistent with previous observations made on the renal vasculature of in utero and postnatal hydralazine-treated and non-treated SHR and WKY rats. As in the present study, the media-to-lumen CSA ratio of renal arteries having lumen diameters less than 175 \( \mu \)m remained elevated in SHR over WKY rats in both treated and nontreated groups. However, unlike the situation present in the mesenteric vasculature, the luminal dimensions of the renal interlobar, arcuate, and interlobular arteries in SHR or WKY rats were not changed with treatment, and the absolute CSA remained comparable in treated and nontreated SHR, which in turn were greater than those present in treated and nontreated WKY rats. Unlike the situation in the present study, hydralazine treatment did not decrease the number of SMC layers in the renal vasculature of SHR; however, such treatment of WKY rats did significantly decrease the number of medial SMC layers in the main renal, interlobar, and certain classes of interlobular arteries when this group was compared with controls.

In other studies, Jespersen et al.\(^{12}\) treated 4-week-old SHR and WKY rats with hydralazine and studied the mesenteric vessels of a size range that would correspond to vessels slightly larger than the S vessels examined in the present study. In this instance, hydralazine treatment (up to 27 weeks of age) slightly increased the wall thickness in WKY rats and decreased this parameter in SHR; however, consistent with the observations made in the present study, the wall thickness-to-lumen diameter ratios of the vessels remained higher in SHR than WKY rats in both the hydralazine-treated and nontreated groups of animals. In this regard, some,\(^{13-15}\) but not all,\(^{16}\) studies have shown that the mesenteric and other arteries\(^{14,15}\) of SHR exhibit either a thickened vascular wall or an increased vascular wall-to-lumen ratio within the fetus and at birth. In view of the above observation and the fact that blood pressure may be elevated in SHR from birth, it could be argued that in the above study, where treatment was started at 4 weeks of age, antihypertensive therapy was unable to reverse structural changes already present in SHR. The observations made in the present study suggest that in SHR, such structural alterations are likely not produced by an elevated maternal blood pressure or by elevations in blood pressure during in utero and postnatal phases of life.

The observations of the present study are consistent with a number of hypotheses. Developmental differ-
ences between SHR and WKY rats could exist in that the mesenteric vascular wall could thicken within the SHR in a manner that is not dependent on the presence of an elevated blood pressure. An alternative hypothesis proposed by Folkow and his colleagues was that the blood vessels of SHR differed from those of WKY rats in that even at normal blood pressures, the vasculature of SHR hyperresponded to produce a thickened vascular wall. If this latter hypothesis is correct, then within the present study, normalizing the blood pressure of SHR to that of WKY rats would still promote wall thickening in the arteries of SHR, and in SHR, below normal blood pressures would be required to prevent such an occurrence. A third possibility is that in the SHR, vascular wall thickening may be a secondary alteration resulting from the trophic influence of an overactive sympathetic nervous system. In this regard, sympathectomy of normal blood vessels has been shown to produce a thinning of the vascular wall associated with a decrease in DNA synthesis. Various studies have demonstrated an increase in sympathetic nerve activity in young and adult SHR when compared with age-matched WKY rats. Studies involving adult SHR and WKY rats subjected to sympathectomy from indicated that the differences in medial CSA observed between SHR and WKY rats are decreased but not totally eliminated by sympathectomy. This would suggest that the sympathetic nervous system might be partially responsible in promoting vascular wall thickening in SHR.

Although the above and other studies have shown that lowering the blood pressure does not alter vascular wall thickening in SHR within the renal and mesenteric vasculatures, such observations cannot be extrapolated to all the vascular beds of SHR. Various researchers have demonstrated a regression of the structural changes that contribute to blood vessel wall thickening, and these studies cannot be discounted. It is very likely that in SHR, the capacity of the blood vessel wall to thicken in a pressure-dependent or independent manner differs between various types of blood vessels. Studies performed by Owens indicated that when compared with WKY rats, the aorta of SHR contained comparable numbers of hypertrophied SMCs during early established hypertension (5 months of age), whereas during later stages of hypertension (7 months of age) both SMC hypertrophy and hyperplasia were observed. It was also observed that SMC hypertrophy was associated with polyploidy of the SMC DNA. Antihypertensive treatment (hydralazine, reserpine, chlorothiazide) for a 2-month period during established hypertension promoted SMC atrophy, arrested the further development of SMC polyploidy but did not prevent SMC hyperplasia from occurring. In other studies involving the SMCs from small diameter segments of the mesenteric vasculatures of SHR and WKY rats, observed an increase in SMC mass associated with an absence of SMC hypertrophy and a low incidence of hyperplasty. It appeared that within the mesenteric vascular bed, SMC hyperplasia was primarily responsible for promoting blood vessel wall thickening in SHR. The above studies suggest that two mechanisms operating at the SMC level may be involved in promoting blood vessel wall thickening in the SHR. Large conduit vessels such as the aorta may have SMCs of a type that have a greater capacity to hypertrophy in response to elevated blood pressure. In these instances, DNA hyperplody of the SMCs may either contribute to or be associated with the SMC hypertrophy. The SMCs of small blood vessels of SHR may lack the above capacity but might, via an altered genetic programming, replicate to a greater degree, thus producing SMC hyperplasia. Alternatively, it could be possible that the SMCs of large and small arteries are comparable but that the input of growth factors differs between the two regions. In this regard, the degree of sympathetic innervation per unit of cross-sectional wall area is larger in smaller versus larger mesenteric arteries and is virtually absent in the aorta. Such differing degrees of trophic input might facilitate the occurrence of hyperplasia in the smaller as opposed to larger arteries.

In relation to the above discussion, previous studies performed in our laboratory indicated that thickening of the vascular wall in the superior mesenteric artery of SHR over that of WKY rats was not associated with an increase in SMC layers and occurred after hypertension had developed (between 12 and 28 weeks of age). Results of the present study indicate that the above structural changes in the superior mesenteric artery are not reversed by the normalization of blood pressure via hydralazine treatment. If in this instance wall thickening in SHR was produced by an increase in SMC size (as opposed to an increase in medial extracellular space), it would suggest that an increase in SMC size may occur in the superior mesenteric arteries under conditions where the elevation in blood pressure is prevented.

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