Cardiac Mass and Peripheral Vascular Structure in Hydralazine-Treated Spontaneously Hypertensive Rats

LENNARD T. JESPERSEN, NIELS C. B. NYBORG, OLE LEDERBAFFE PEDERSEN, ERICH O. MIKKELSEN, AND MICHAEL J. MULVANY

SUMMARY We have examined the effect of antihypertensive treatment on heart weight and on structural and functional characteristics of isolated mesenteric resistance vessels (internal diameter 170–220 μm) in spontaneously hypertensive rats (SHR) and in Wistar-Kyoto rats (WKY). The SHR and WKY were treated with hydralazine from the age of 4 weeks and were examined at ages 12 to 14 weeks and 23 to 27 weeks. Treated SHR had a mean blood pressure as much as 29% below that of control WKY, which in turn was 25 to 40% less than that of control SHR. In 12- to 14-week-old rats the heart to body weight ratio (which in control SHR was 13% greater than that of WKY) was unaffected by treatment. Thereafter, the heart to body weight ratio of treated SHR did not increase as much as usual. At both ages, the media thickness and contractile response of the resistance vessels of the SHR (which were, respectively, 37% and 30% greater than those of vessels of WKY) were unaffected by treatment. However, because treatment caused a small (8%) increase in the lumen diameter of the vessels of the SHR, treatment did cause small, but possibly physiologically important, decreases both in the media to lumen ratio (11%) and in the pressure against which these vessels would have been able to contract (10%). Treatment had little effect on the pharmacological characteristics of vessels of either SHR or WKY. The results suggest that the increased heart weight, media thickness, and contractile response in mesenteric resistance vessels of SHR up to ages 23 to 27 weeks are due primarily to factors other than increased pressure. (Hypertension 7: 734-741, 1985)

KEY WORDS • smooth muscle • cardiovascular structure • calcium, norepinephrine • resistance vessel • human essential hypertension, spontaneously hypertensive rats (SHR) • The aim was to determine whether preventing the development of high blood pressure in SHR, by antihypertensive treatment from an early age, would inhibit the development of the structural abnormalities that we have previously observed in these animals: increased heart to body weight ratio, increased resistance vessel media to lumen ratio, and increased resistance vessel contractility. Hydralazine was chosen as the antihypertensive drug since it has previously been shown to reduce blood pressure, primarily through its ability to decrease peripheral resistance. The animals were treated from the age of 4 weeks, at which age there is only a small elevation of blood pressure, and the parameters were measured in young adult animals aged 12 to 14 weeks, when the hypertension normally has fully developed, and then again in mature animals aged 23 to 27 weeks, to determine if long-term treatment could maintain (or cause) regression of abnormalities. To determine whether the hydralazine treatment was affecting parameters through mechanisms not associated with blood pressure control, the effects of hydralazine treatment on age-matched normotensive Wistar-Kyoto rats (WKY) also were investigated.

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T is well established that the hypertensive state is associated with structural abnormalities in the cardiovascular system. These abnormalities include cardiac enlargement, increased wall to lumen ratio in arteries and resistance vessels, increased relaxed peripheral resistance, and decreased venous compliance. Furthermore, these changes are seen at an early stage of hypertension, which suggests that they may play a role in the pathogenesis of the disease and are not just an adaptive change to the increased pressure.

One way of assessing the possible contribution of cardiovascular abnormalities to the development of hypertension is to determine the effect of antihypertensive therapy on the abnormalities. The present study was initiated to investigate this question in a model of human essential hypertension, spontaneously hypertensive rats (SHR). The aim was to determine whether preventing the development of high blood pressure in SHR, by antihypertensive treatment from an early age, would inhibit the development of the structural abnormalities that we have previously observed in these animals: increased heart to body weight ratio, increased resistance vessel media to lumen ratio, and increased resistance vessel contractility. Hydralazine was chosen as the antihypertensive drug since it has previously been shown to reduce blood pressure, primarily through its ability to decrease peripheral resistance. The animals were treated from the age of 4 weeks, at which age there is only a small elevation of blood pressure, and the parameters were measured in young adult animals aged 12 to 14 weeks, when the hypertension normally has fully developed, and then again in mature animals aged 23 to 27 weeks, to determine if long-term treatment could maintain (or cause) regression of abnormalities. To determine whether the hydralazine treatment was affecting parameters through mechanisms not associated with blood pressure control, the effects of hydralazine treatment on age-matched normotensive Wistar-Kyoto rats (WKY) also were investigated.

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In addition to these structural parameters, we have also determined the effect of hydralazine treatment on the pharmacological properties of the resistance vessels, for we have shown previously that the sensitivity of the resistance vessels of the SHR to norepinephrine and to calcium is increased compared with those from WKY. 13,17

Methods
Four-week-old male SHR and WKY were obtained from Møllegaard's Breeding Center, Lille Skensved, Denmark, and kept in an air-conditioned animal room (temperature, 20–21°C, lighting, 0700–1900 hr). Animals were housed three to a cage in macrocon cages (0.15 × 0.25 × 0.4 m) with sawdust bedding.

Medication
From the age of 4 weeks, half of the rats of each strain were given antihypertensive treatment consisting of the addition of hydralazine monohydrochloride (Apresolin) to their drinking water (160 mg/L tap water = 815 μM). Control animals were given tap water to drink. All rats were allowed to drink ad libitum; the water intake was 150 ml/kg/day in treated and untreated 4-week-old rats and fell to 100 to 110 ml/kg/day in the treated rats and to 50 to 75 ml/kg/day in the untreated rats at age 12 to 27 weeks. The treatment thus had a diuretic effect. Fresh solutions of the drug were prepared twice a week. Gas chromatographic analysis of the solutions showed that the hydralazine concentration decreased with a half-life of about 4 days. 18 From these findings the actual dosage received by the rats was about 20 mg/kg/day initially and about 15 mg/kg/day at the time of the experiment (when they were 12–14 or 23–27 wk old).

Blood Pressure Measurement
Rats were exposed to diethylether in an open system to induce the best possible standardization of physical and mental activity before measurements. The animals were closely observed during the procedure and were found to display the characteristic stages of ether anesthesia outlined by Guedel. 19 Exposure to the anesthetic was terminated at a point corresponding to Guedel's stage III, identified by a slowing of the respiratory rate. Duration of the ether exposure never exceeded 2 minutes. This short period of anesthesia was sufficient to calm the animals but did not induce the hypotension seen with longer periods of anesthesia. 20 The rat subsequently was transferred to the animal holder where pulsation in the tail artery was detected using a photo-plethysmographic device (8000 series, Simonsen and Weel, Albertslund, Denmark). With the use of a non-invasive tail cuff method as described by Jespersen et al., 21 both systolic and diastolic blood pressures were determined repeatedly over 5 to 10 minutes until stable recordings were obtained, at which time the rat was fully awake, although to some degree atactic. The records obtained at this stage were taken as our estimate of blood pressure. Mean blood pressure was calculated as the sum of diastolic blood pressure plus the difference in systolic and diastolic blood pressure divided by 3. In some instances heart rate was also measured. Measurements were made between 0900 and 1500 hours. Blood pressures were measured first at the age of 7 weeks, and thereafter at regular intervals (Figure 1).

Dissection
Two days before the experiments, the final blood pressure measurement was made. Treated rats were therefore also given ordinary tap water to clear the plasma and vasculature of hydralazine. On the day of the experiment, rats were killed using CO2 and part of the proximal jejunum was rapidly excised, together with its associated vessels. As described previously, a segment (length, 1.9 ± 0.2 mm) was isolated from this portion and mounted as a ring preparation on an isometric myograph. 11,12 A double myograph was used, 17 permitting two vessels to be tested and exposed simultaneously to the same solutions. The dissection and mounting were performed in standard saline (see Protocol) at room temperature.

Immediately after killing the animal, the heart was also dissected out. After removal of extraneous tissue, coagulated blood, and the atra, the heart was lightly blotted and weighed.

Solutions
Vessels were normally held relaxed in standard saline solution consisting of (mM): NaCl, 119; KCl, 4.7; NaHCO3, 25; CaCl2, 2.5; KH2PO4, 1.18; MgSO4, 1.17; ethylenediaminetetraacetic acid, 0.026; and glucose, 5.5. The potassium-saline solution was a standard saline solution in which NaCl was exchanged for KCl on an equimolar basis. The control activating solution was potassium-saline solution containing 10 μM L-norepinephrine-HCl (Sigma Chemical Co., St. Louis, MO, USA), which gives a near maximal response. 12 All solutions were bubbled with 95% O2, 5% CO2 to give pH 7.4. Solutions were held at 37 °C.

![Figure 1. Development of mean (± SE) blood pressure (MBP) measured in hydralazine-treated SHR (filled circles), untreated SHR (open circles), and untreated WKY (open squares). All points for each group refer to the same animals (n = 10, treated SHR; n = 10, control SHR; n = 11, control WKY). Points for treated WKY (filled squares) are taken from Table 1.](image-url)
Protocol

After the samples had been mounted, the temperature of the chamber was raised to 37 °C and the vessels were allowed to equilibrate for about 30 minutes with the vessel internal circumference set to give a wall tension of 0.2 N/m. At this internal circumference, the internal circumference and media thickness were measured as described previously, except that a light microscope at 340 power and bright field illumination were used. The resting tension–internal circumference characteristic was then determined, and from this the internal circumference (L_internal) corresponding to a transmural pressure of 100 mm Hg was determined. The vessels were then set to the normalized internal circumference, which equals 0.9 L_internal. The corresponding media thickness (m media) was calculated from the previously determined values of internal circumference and media thickness on the assumption that the media volume remained constant. Normalized internal lumen diameter was equal to the normalized internal circumference divided by π.

Table 1: Characteristics of Rat Study Population

<table>
<thead>
<tr>
<th>Age</th>
<th>Young adult</th>
<th>Mature</th>
<th>p_age</th>
<th>p_m</th>
<th>p_m</th>
<th>p_m</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SHR</td>
<td>13.6 ± 0.1 (15)</td>
<td>13.6 ± 0.1 (15)</td>
<td>26.7 ± 0.3 (12)</td>
<td>26.7 ± 0.3 (11)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>WKY</td>
<td>13.7 ± 0.2 (6)</td>
<td>13.7 ± 0.2 (6)</td>
<td>22.7 ± 0.11 (5)</td>
<td>26.3 ± 0.6 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>MBP</td>
<td>SHR</td>
<td>88.2 ± 4.9* (15)</td>
<td>138.7 ± 5.6 (15)</td>
<td>94.5 ± 7.0* (12)</td>
<td>136.2 ± 6.3 (11)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>WKY</td>
<td>96.9 ± 4.9 (13)</td>
<td>97.9 ± 5.8 (11)</td>
<td>81.0 ± 3.3* (7)</td>
<td>110.1 ± 3.1 (6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>SHR</td>
<td>291 ± 4 (15)</td>
<td>293 ± 3 (15)</td>
<td>357 ± 9 (12)</td>
<td>375 ± 5 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>WKY</td>
<td>322 ± 7 (6)</td>
<td>327 ± 3 (6)</td>
<td>363 ± 5§ (5)</td>
<td>396 ± 8 (7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>SHR</td>
<td>434 ± 17 (10)</td>
<td>381 ± 12 (10)</td>
<td>382 ± 17§ (6)</td>
<td>358 ± 16 (6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>WKY</td>
<td>381 ± 9 (11)</td>
<td>385 ± 16 (8)</td>
<td>376 ± 5 (6)</td>
<td>378 ± 12 (5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE. Number of rats is in parentheses.

Two-way analysis of variance was used to determine significance of effects of treatment (p_treatment), age (p_age), and treatment-age interaction (p_m). NS = not significant; MBP = mean blood pressure.

Table 2: Summary of Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SHR</th>
<th>WKY</th>
<th>p_m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine + Cocaine</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Gradient was then repeated in the presence of cocaine (3 μM) to inhibit neuronal uptake of norepinephrine. Responses have been normalized in three ways: 1) as active wall tension (i.e., the increase in wall force above resting wall force divided by twice the segment length, ΔT), 2) as active media stress (i.e., the active wall force per media cross-sectional area, equal to active wall tension divided by media thickness), and 3) as contractility or effective active pressure (i.e., as an estimate of the pressure against which the vessels would have been able to contract calculated from Δp = ΔT/(normalized internal lumen diameter/2). Norepinephrine and calcium sensitivities are expressed in terms of pD2 values (i.e., the negative logarithm of the dose in mol/L required to give a half-maximal response).

Statistics

The data were analyzed by using two-way analysis of variance to compare effects of treatment and age in each strain. Three-way analysis of variance to allow analysis of strain differences was also performed, but the analysis is not presented herein because, although treatment clearly was affecting the two strains of animals differently, the measurement variance of some parameters was too great to be able to demonstrate strain-treatment interaction; in such cases it was found that the analysis tended to conceal obvious effects of the treatment, particularly as regards the SHR. The analysis was performed with the generalized linear interactive modeling program GLIM, designed by a Royal Statistical Society group. Probability levels less than 0.05 were considered significant.

Results

As indicated in Figure 1 and Table 1, treatment of SHR with hydralazine prevented the blood pressure
rise seen in the untreated SHR and kept it at or below the
blood pressure level seen in the control WKY throughout the treatment period. Treatment of WKY
caused a reduction of pressure only in the mature rats. The growth rate of SHR was unaffected by treatment,
while it was slightly reduced (8%) in the mature WKY
(see Table 1).

Effects of Treatment
Heart weight was reduced 12% in the treated mature
SHR, while it was reduced 8% in the WKY at both
ages (Table 2). Heart to body weight ratio was affected
only in the mature SHR (a reduction of 7%; see Figure
2). Treatment caused a 10% increase in the heart rate
of the SHR but did not affect the heart rate of the
WKY.
The structural and contractile properties of the mes-
enteric resistance vessels are shown in Table 3. Al-
though the media thickness of the vessels was unaffected
ed by treatment in either SHR or WKY, treatment
caused an 8% increase in normalized lumen diameter
in the SHR. Thus, the media to lumen ratio of the
evessels of the SHR was decreased 11% by treatment
(Figure 2). The response of vessels to control activat-
ing solution was unaffected by treatment, but because
of the greater lumen in the vessels of the treated SHR,
the contractility (effective active pressure) of vessels in
the treated SHR was reduced by 10% (see Figure 2).
Treatment did not affect the media stress.
The sensitivity of the mesenteric resistance vessels
to norepinephrine and calcium is shown in Table 4.
Under control conditions, treatment had no effect on
norepinephrine sensitivity. If cocaine was included in
the bathing solutions to reveal the norepinephrine sen-
sitivity of the smooth muscle cells (see Methods),
however, it was found that treatment did cause a small
increase in norepinephrine sensitivity of the vessels of
the SHR (approximately 0.15 log unit increase in
pD2). Treatment did not affect the norepinephrine sen-
sitivity of the vessels of the WKY or the calcium sen-
sitivity of the norepinephrine response in vessels from
either SHR or WKY.

Age Effects
In addition to the age-dependent effects of treatment
already noted, and apart from increases in body weight
and heart weight, the only age effects seen were a 9%
decrease in the heart rate of the SHR, a 10% decrease
in heart to body weight ratio in the WKY, and a small
increase (approximately 0.09 log unit) in the calcium
sensitivity of the resistance vessels of the WKY.

Strain Differences
Our statistical analysis did not allow direct compari-
sion of the parameters of SHR and WKY (see Meth-
ods); however, an inspection of the tables shows that
the results are fully consistent with our previous find-
ings12-15, showing that compared with the WKY,
SHR have a greater heart to body weight ratio while
their mesenteric resistance vessels have a smaller lu-
men, a larger media, a greater active response, a great-
er contractility, an increased norepinephrine sensi-
tivity (in the presence of cocaine) and an increased

### Table 2. Heart Weight and Heart to Body Weight Ratio in Hydralazine-Treated and Untreated SHR and WKY

<table>
<thead>
<tr>
<th>Weight</th>
<th>Young adult</th>
<th>Control</th>
<th>Mature</th>
<th>Treated</th>
<th>Control</th>
<th>p_\text{age}</th>
<th>p_\text{strain}</th>
<th>p_\text{interaction}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>1.003 ± 0.018 (15)</td>
<td>1.023 ± 0.016 (15)</td>
<td>1.207 ± 0.033* (12)</td>
<td>1.364 ± 0.012 (11)</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>0.949 ± 0.033+ (6)</td>
<td>1.008 ± 0.023 (6)</td>
<td>1.031 ± 0.023+ (5)</td>
<td>1.116 ± 0.037 (7)</td>
<td>&lt;0.01 &lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart/body (mg/g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>3.44 ± 0.042 (15)</td>
<td>3.489 ± 0.046 (15)</td>
<td>3.377 ± 0.048* (12)</td>
<td>3.646 ± 0.052 (11)</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>2.94 ± 0.062 (6)</td>
<td>3.083 ± 0.057 (6)</td>
<td>2.837 ± 0.029 (5)</td>
<td>2.821 ± 0.11 (7)</td>
<td>&lt;0.05 NS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. Number of rats is in parentheses.
Two-way analysis of variance was used to determine significance of effects of treatment (p_\text{strain}), age (p_\text{age}), and treatment-age interaction (p_\text{interaction}).
*p < 0.001 (significant effects of treatment where p_\text{age} < 0.05), parameters of treated rats compared by two-tailed t test with age- and strain-matched controls. t_p_\text{strain} < 0.05 (significant effects of treatment where p_\text{strain} is not significant).

### Figure 2

(A) heart to body weight ratio (mg/g). (B) resistance vessel media to lumen ratio (% media thickness-normalized lumen diameter); (C) pressure against which resistance vessels would be able to contract when activated (effective active pressure, kPa; see Methods) for hydralazine-treated SHR (filled circles), untreated SHR (open circles), hydralazine-treated WKY (filled squares), and untreated WKY (open squares). Data obtained from Tables 2 and 3.
TABLE 3. Morphological and Contractile Properties of Mesenteric Resistance Vessels in Hydralazine-Treated and Untreated SHR and WKY

<table>
<thead>
<tr>
<th></th>
<th>Young adult</th>
<th>Mature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>l, ((\mu m))</td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>195.8 ± 6.2* (15)</td>
<td>175.8 ± 5.2 (15)</td>
</tr>
<tr>
<td>WKY</td>
<td>207.2 ± 9.9 (12)</td>
<td>207.3 ± 11.3 (12)</td>
</tr>
<tr>
<td></td>
<td>(m_1 (\mu m))</td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>13.53 ± 0.41 (15)</td>
<td>13.39 ± 0.69 (15)</td>
</tr>
<tr>
<td>WKY</td>
<td>8.61 ± 0.61 (12)</td>
<td>9.69 ± 0.81 (12)</td>
</tr>
<tr>
<td></td>
<td>(m_1/l_1)</td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>0.069 ± 0.002* (15)</td>
<td>0.076 ± 0.004 (15)</td>
</tr>
<tr>
<td>WKY</td>
<td>0.042 ± 0.003 (12)</td>
<td>0.049 ± 0.006 (12)</td>
</tr>
<tr>
<td></td>
<td>(\Delta T_1 (N/m))</td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>3.38 ± 0.21 (15)</td>
<td>3.39 ± 0.17 (15)</td>
</tr>
<tr>
<td>WKY</td>
<td>2.42 ± 0.14 (12)</td>
<td>2.63 ± 0.19 (12)</td>
</tr>
<tr>
<td></td>
<td>(\Delta \sigma (kPa))</td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>252 ± 15 (15)</td>
<td>260 ± 15 (15)</td>
</tr>
<tr>
<td>WKY</td>
<td>288 ± 16 (12)</td>
<td>291 ± 26 (12)</td>
</tr>
<tr>
<td></td>
<td>(\Delta P (kPa))</td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>34.6 ± 1.9* (15)</td>
<td>38.5 ± 1.2 (15)</td>
</tr>
<tr>
<td>WKY</td>
<td>23.5 ± 1.4 (12)</td>
<td>25.1 ± 0.8 (12)</td>
</tr>
</tbody>
</table>

Values are means ± se. Number of vessels is in parentheses (1 or 2 vessels per rat). \(l_1\) = normalized lumen diameter; \(m_1\) = corresponding media thickness; \(\Delta T_1\) = active wall tension response; \(\Delta \sigma\) = active media stress (\(\Delta T_1/m_1\)); \(\Delta P\) = effective active pressure (\(\Delta T_1/(l_1/2)\)).

Two-way analysis of variance was used to determine significance of effects of treatment (\(P_{\text{real}}\)), age (\(P_{\text{age}}\)), and treatment-age interaction (\(P_{\text{int}}\)).

NS = not significant.

*\(P_{\text{real}} < 0.05\) (significant effects of treatment where \(P_{\text{real}}\) is not significant).

calcium sensitivity. More important, it should be noted that, apart from blood pressure, in no case did treatment of SHR cause the cardiac and vascular parameters investigated to regress to the levels seen in untreated or treated WKY.

**Discussion**

Treatment of SHR with hydralazine was completely effective in preventing the blood pressure rise normally seen in these animals up to the age of 12 to 14 weeks and maintained the blood pressure at a low level thereafter. Up to the age of 12 to 14 weeks, treatment of SHR had no effect on heart weight, although after a further 12 weeks of treatment, heart weight did not increase as much as normal. With respect to vascular structure, treatment was found to have an effect at both ages. In no instance, however, did the treatment cause regression of these cardiovascular parameters to the levels seen in WKY.

**Hypotensive Action of Hydralazine**

Although the hypotensive effect of hydralazine is well established,23,24 its mechanism of action is not known. Since the hemodynamic effect of hydralazine is to reduce the peripheral resistance,25 its action may be due to direct vasodilative properties. In a number of isolated preparations direct actions of hydralazine have only been demonstrated at unphysiologically high concentrations (e.g., 10⁻⁴ M),26 but in other preparations, such as rat tail artery,27 human digit artery,28 and rabbit renal artery,29 hydralazine caused relaxation at concentrations of about 1 µM. The vasodilative effect may therefore be due to direct actions on the vascular smooth muscle,30 although the postsynaptic effects of hydralazine appear to be modulated both by neural mechanisms31 and through the endothelium.32

**Structural Effects of Hypotensive Treatment**

Smooth and cardiac muscle, like skeletal muscle, will respond to an increased load by an increase in the quantity of muscle.3 Thus, in essential hypertension, as for perhaps less complex forms of hypertension (e.g., aortic coarctation33), an increased quantity of cardiac muscle and smooth muscle may be expected in the structures exposed to the increased pressure. The cardiac hypertrophy and increased arterial wall to lumen ratio of hypertensive persons are therefore likely to be at least partly due to the increased blood pressure, and hypotensive treatment may therefore be expected to cause regression of these abnormalities. However, experimental findings indicate that even though pressure reduction may be rapid, the degree and speed of regression depend on the method employed to decrease the pressure. In persons with essential hypertension, treatment with methyldopa causes regression of cardiac hypertrophy while treatment with diuretics does not appear to do so.34 Similarly, long-term treatment with pindolol, but not metoprolol, was
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Table 4. Sensitivity of Mesenteric Resistance Vessels of SHR and WKY to Norepinephrine (NE), Norepinephrine in the Presence of 3 μM Cocaine and Calcium (when activated with 10 μM NE)

<table>
<thead>
<tr>
<th></th>
<th>Young adult</th>
<th>Mature</th>
<th>p&lt;sub&gt;age&lt;/sub&gt;</th>
<th>p&lt;sub&gt;max&lt;/sub&gt;</th>
<th>p&lt;sub&gt;tot&lt;/sub&gt;</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>NE</td>
<td></td>
<td></td>
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<tr>
<td>SHR</td>
<td>5.861 ± 0.043</td>
<td>5.714 ± 0.066</td>
<td>5.832 ± 0.087</td>
<td>5.692 ± 0.045</td>
<td>NS</td>
</tr>
<tr>
<td>WKY</td>
<td>5.984 ± 0.052</td>
<td>(11)</td>
<td>5.887 ± 0.061</td>
<td>(8)</td>
<td>5.903 ± 0.069</td>
</tr>
<tr>
<td>Cocaine-NE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>6.820 ± 0.062*</td>
<td>(5)</td>
<td>6.617 ± 0.056</td>
<td>(6)</td>
<td>6.750 ± 0.094*</td>
</tr>
<tr>
<td>WKY</td>
<td>6.647 ± 0.030</td>
<td>(11)</td>
<td>6.551 ± 0.041</td>
<td>(11)</td>
<td>6.534 ± 0.089</td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>4.174 ± 0.070</td>
<td>(5)</td>
<td>4.110 ± 0.037</td>
<td>(6)</td>
<td>4.063 ± 0.045</td>
</tr>
<tr>
<td>WKY</td>
<td>3.827 ± 0.012</td>
<td>(12)</td>
<td>3.774 ± 0.034</td>
<td>(12)</td>
<td>3.895 ± 0.036</td>
</tr>
</tbody>
</table>

Values are means ± se. Number of vessels is in parentheses (1 or 2 vessels per rat). Sensitivity expressed as pD<sub>2</sub> (negative logarithm of concentration, in M), giving half-maximal response.

See Table 3 for key to significance symbols.

found to cause regression of vascular structural abnormalities. Thus, factors other than blood pressure must also play a role in the determination of cardiovascular structure.

The response of cardiovascular structures in SHR to antihypertensive treatment shows a similar heterogeneity depending on the treatment used. Treating 4-week-old SHR for 24 weeks with a cocktail of chlorothiazide, hydralazine, and reserpine causes regression of cardiac hypertrophy and the media to lumen ratio of mesenteric resistance vessels. Conversely, vasodilators, which cause reflex action of sympathetic activity (e.g., minoxidil), do not appear to cause regression of cardiac hypertrophy. Likewise, although treating 14-week-old SHR for 10 weeks with felodipine causes regression of vascular resistance, treatment of younger SHR with this drug does not cause regression of resistance vessel structure. It is also of interest that even when drugs are effective in causing regression of cardiovascular structure the regression takes several weeks, while regression of these structures in renal hypertensive rats that have been unclipped proceeds rapidly and is complete within a few weeks. Thus, these animal studies indicate that although blood pressure influences cardiovascular structure, it is not the only factor of importance.

The results of the present investigation also suggest that the stress of the control WKY, the cardiovascular structure of the treated SHR was still abnormal, even though the animals were normotensive or even hypotensive for most of the treatment period. On the other hand, the cardiovascular structure of the treated SHR was slightly regressed with respect to the control SHR. Thus, although the heart to body weight and resistance vessel media to lumen ratios of the SHR appeared to be largely independent of the ensuing blood pressure changes, the antihypertensive treatment was associated with small alterations in these parameters. Indeed, the small regression seen could be of hemodynamic importance, particularly as regards the resistance vessels where, according to Poiseuille’s law, the 8% increase in lumen represents a 28% decrease in resistance.

There are several possible explanations for the pressure-independent alteration in cardiovascular structure that we noted. First, heart to body weight and resistance vessel media to lumen ratios are already increased in 4-week-old SHR, as well as at an even younger age. Whether these structural alterations are associated with increased pressure is still debated, but it seems likely that even in 4-week-old SHR, the blood pressure is slightly raised. In any event, the abnormal structure seen in older SHR might therefore be attributed to a failure to cause regression rather than a failure to prevent the development of structural abnormalities. However, such an interpretation would discount the fact that between the age of 4 weeks and maturity, there is a large increase in the total mass of the myocardium and the vasculature. Thus, to a great extent, the abnormal cardiovascular structure of the treated SHR is not directly due to pressure.

A second possible explanation of the pressure-independent alteration of cardiovascular structure is that the hydralazine treatment has a trophic effect. Any such trophic effect is unlikely to be a direct effect on the myocardium or vascular smooth muscle, since cardiovascular structural abnormalities were not seen in the treated WKY. A trophic effect could be mediated by a reflex sympathetic activity or plasma factors. The possibility of increased sympathetic activity in the treated SHR is supported by our finding of an increased heart rate in these animals. Furthermore, since increased heart rate was not seen in the hydrala-
zine-treated WKY, the lack of altered cardiovascular structure in the treated WKY could be related to their lack of altered sympathetic activity.

A third possibility, which cannot be discounted entirely, is that part of the abnormal structure developed during the 2-day period for which the hydralazine treatment was discontinued to permit measurements of tirely, is that part of the abnormal structure developed lack of altered sympathetic activity. Structure in the treated WKY could be related to their hydralazine-treated WKY, the lack of altered cardiovascular structure is not an overriding determinant. SHR replicate more rapidly than do those from WKY.48 If this is true, it would imply that the cardiovascular structure of the SHR is programmed from birth to prepare for the increased pressure that usually develops in these animals, even if the pressure does not in fact increase.

Cardiovascular Structure and Hypertension

The results of this investigation raise the question of the importance of the role of cardiovascular structure in blood pressure determination. The results show that cardiovascular structure is not an overriding determinant of blood pressure, which in the face of the large concentration of the vasodilating drug is hardly to be expected. A similar result is obtained following unclipping of two-kidney, one clip hypertensive rats, in which blood pressure is rapidly normalized despite the abnormal cardiovascular structure. Presumably there must here be a high concentration of an endogenous vasodilator present.49 However, as pointed out by Folkow’s group,1,2 if all else is equal, an increased cardiovascular structure will contribute to an increased peripheral resistance and, hence, probably to increased blood pressure. Although this is undoubtedly true, it does beg the question as to whether all else is equal.8 Since vascular structure is only a part, albeit an important part, of the system controlling peripheral resistance, increased structure does not necessarily result in increased peripheral resistance — as indeed demonstrated by the present experiments. Therefore, it may be more correct to view the altered cardiovascular structure of the SHR as a substrate on which other abnormalities may cause the hypertension normally seen in these animals.

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