Cardiovascular Responses to Acute Stress in Young-to-Old Spontaneously Hypertensive Rats

JIN YAMAMOTO, MASATSUGU NAKAI, AND TAKASHI NATSUME

SUMMARY Age-related changes in circulatory responses to short-term shaker stress were investigated in conscious spontaneously hypertensive rats (SHR) and Wistar-Kyoto rats (WKY). Hemodynamics (microspheres) were measured at 8, 24, 48, and 96 weeks of age, and plasma catecholamines were measured at 8 and 96 weeks. At rest, elevated mean arterial pressure was associated with unaltered cardiac index and heart rate in SHR compared with WKY at all ages. Regional blood flow was largely similar in both strains, except for a reduced renal flow in 96-week-old SHR. Cardiac index and most regional blood flow tended to or did decline in both strains between 8 and 96 weeks. Plasma catecholamines were similar in both strains at 8 and 96 weeks. Shaker stress evoked responses similar to defense reactions in both strains. The incremental responses in mean arterial pressure, heart rate, cardiac index, and cerebral, skeletal muscle, and myocardial flow and the decremental responses in splanchnic, renal, and skin flow were greater in SHR than in WKY, particularly at 8 weeks. Most of these responses tended to or did decline between 8 and 96 weeks in both strains. The plasma catecholamine responses were also greater in SHR at 8 and 96 weeks, and they did not differ in either strain between these ages. Thus, circulatory and sympathoadrenal reactivity to acute stress were enhanced in SHR compared with WKY, independently of age. Yet circulatory reactivity declined more or less with age in both strains, despite the absence of age differences in sympathoadrenal reactivity. This dissociation may suggest altered cardiovascular response to acute stress-evoked sympathoadrenal stimulation, particularly in old SHR. (Hypertension 9: 362-370, 1987)

KEY WORDS • shaker stress • systemic and regional hemodynamics • plasma catecholamines • spontaneously hypertensive rats • Wistar-Kyoto rats • age

Both systemic and regional hemodynamics are altered in the presence of hypertension1, 2 and with age.1-4 Spontaneously hypertensive rats (SHR) and humans with essential hypertension have various features in common,1, 5, 6 including resting hemodynamics,1, 2, 6-11 and cardiovascular and sympathoadrenal hyperreactivity to stressful stimuli, 1, 2, 6, 11-23 Stress hyperreactivity seems to vary with advancing age in rats and humans,1-4, 12-14, 19-23 and findings on the effects of aging remain controversial, 3, 4, 12-14, 19, 23-29 In addition, data on aged SHR and its normotensive progenitor strain, Wistar-Kyoto rats (WKY), are generally scanty.

The present investigation was conducted to characterize changes in hemodynamics and stress responses occurring in conscious SHR and WKY as a function of age. Changes in the level of circulating catecholamines as a function of age and stress were also evaluated.

Materials and Methods

Specific-pathogen-free male SHR and WKY, aged 6 weeks, were purchased from Charles River Japan (Atsugi, Japan). All these rats were maintained thereafter in scrupulously clean animal facilities with temperature, humidity, and lighting controlled. Ordinary chow food and tap water were available ad libitum. The rats were subjected to hemodynamic study (n = 102) when they were 8, 24, 48, and 96 weeks of age, and to plasma catecholamine study (n = 36) when they were 8 and 96 weeks of age. These ages—8 (young), 24 (young adult), 48 (mature), and 96 (old) weeks—were considered to represent the evolutionary, established, intermediate, and advanced stages, respectively, of hypertension in SHR. On the evening before the experiment, the rats were lightly anesthe-
tized with ether. Tip-tapered PE-50 catheters (Clay Adams, Parsippany, NJ, USA) were introduced into the femoral artery and vein, respectively, and into the left ventricle through the right carotid artery. All catheters were brought out through subcutaneous tunnels in the dorsal cervical region. The wounds were treated with 1% lidocaine and sutured. A pair of SHR and WKY were prepared. In addition, normal male Wistar rats were prepared with femoral arterial and venous catheters and used as donors for blood transfusion. The next morning, after a 15- to 17-hour recovery period, the conscious rats were placed in a small but unconfining cage. This cage was mounted and fixed on the top board of a shaker (Model 77A; Yuyama, Osaka, Japan) with spring coils. Heparin (100 U) was injected through the femoral venous catheter. All catheters were connected to Statham transducers (Oxnard, CA, USA). Mean arterial pressure (MAP), left ventricular pressure, and heart rate were recorded directly on a polygraph (Model 360; San-er, Tokyo, Japan).

Hemodynamic Study at Rest and During Acute Stress

Cardiac output and regional blood flow were determined in conscious animals using the radioactive microsphere reference sample method, as previously described. In brief, 15 ± 3 μm radioactive microspheres labeled with 143Ce or 46Sc (New England Nuclear, Boston, MA, USA) were suspended in 0.9% saline with 0.01% polysorbate 80 (Tween 80). After vigorous agitation, 0.05 ml of this suspension, containing 40,000 to 100,000 microspheres, was flushed over a 20-second period into the left ventricle with 0.4 ml of fresh blood obtained from donor rats. Starting 10 seconds before this injection, reference blood was withdrawn using a Harvard 901 pump (Millis, MA, USA) from the femoral arterial catheter at a rate of 0.93 ml/min over a 50-second period. Blood loss was immediately restored by donor blood. During this procedure, the rat was usually quiescent.

After the first hemodynamic measurement, the rat was left alone for at least 30 minutes and then was exposed to acute stress, which consisted of shaking at a rate of 90 oscillations per minute (horizontal displacement of about 4 cm) for 5 minutes. This shaker stress evoked responses that combined emotional arousal with consequent behavioral and, hence, skeletal muscle excitation. Since circulatory variables were most stable between 2 and 3 minutes, the second hemodynamic measurement was made during this period, using a different set of radioactive microspheres, as already described.

At the end of the experiment, an overdose of pentobarbital was given, tissue and organs were removed, and gross visual inspections were made. More than 20 g of skin and skeletal muscles was taken from the limbs, neck, dorsum, and abdominal areas. The skeletal muscles collected were a mixture of muscles (e.g., abdominal wall) to markedly (e.g., thigh) activated during the period of shaker stress. Therefore, skeletal muscle blood flow described here represents an average of various degrees of muscular activity. The same muscles were grouped in SHR and WKY, so that muscle blood flow comparisons between these strains were deemed valid. The samples were weighed and counted in a computerized gamma counter (Model 1282; LKB, Stockholm, Sweden); the reference blood sample was also counted. Cardiac and peripheral hemodynamic variables were calculated using the reference and tissue sample radioactivity, based on standard equations. Cardiac output and regional blood flow were reported as ml/min/100 g of body or tissue weight; cardiac output was referred to as cardiac index. Total peripheral and regional vascular resistances were expressed as mm Hg/ml/min/100 g of body or tissue weight. Measurements showing more than 20% differences (left vs right) in blood flow between brain hemispheres and between bilateral kidneys were omitted. Histopathological examinations were not made.

Plasma Catecholamine Study at Rest and During Stress

The 8- and 96-week-old SHR and WKY were prepared with catheters and, after a similar recovery period, were subjected to the experimental protocol already described. Arterial blood samples were withdrawn using the cross-circulation technique at rest and during stress. At rest, the femoral arterial catheter of the donor rat was connected to the femoral venous catheter of the experimental rat by way of a pump (Gilson, Villiers Le Bel, France). The tip of the femoral arterial catheter from the experimental rat was inserted into a tube placed in ice. In such a manner, 1.5 ml of blood was taken from the arterial line of the experimental rat and collected into the tube.

After recovery and restabilization, short-term shaker stress was imposed. Between 2 and 3 minutes after the institution of stress, 1.5 ml of blood was drawn into an ice-chilled syringe, while simultaneous blood transfusion was performed manually, using another syringe containing fresh blood. The plasma was immediately separated at 4°C and stored at −80°C. Within 2 weeks, plasma epinephrine and norepinephrine concentrations were determined by high performance liquid chromatography combined with the trihydroxyindole method. The plasma samples were deproteinized, treated with alumina, and applied to a Zipax SCX column connected with a continuous flow system and a spectrophotometer (autoanalyzing system; Shimadzu Seisakusho, Kyoto, Japan).

Data Analysis

Data were processed using a PDP 11/44 computer (Digital Equipment, Maynard, MA, USA). The variables measured at rest and their responses to stress (assessed as percentage of change from baseline resting values or as stress to resting value ratios) were evaluated separately by two-way analysis of variance; factor 1 was strain, and factor 2 was age. When F was greater than 0.05, the Bonferroni method was used for multiple group comparisons. To assess the effect of age,
comparisons of data for 24- to 96-week-old rats with those for 8-week-old rats were made. Statistical significance was defined as a \( p \) value of less than 0.05. All values are presented as means ± SE.

**Results**

Postmortem examination revealed no signs of heart failure, such as pleural effusion and pulmonary congestion, even in the oldest group of SHR.

**Body, Heart, and Adrenal Weights**

As shown in Table 1, body weight was similar in SHR and WKY at 8 weeks of age but was significantly \((p<0.05)\) less in SHR at 24 to 96 weeks. The left ventricular to body weight ratio, an index of left ventricular mass, was significantly \((p<0.05)\) greater in SHR at all ages studied. This ratio increased between 8 weeks and all subsequent ages; in contrast, it remained unaltered in WKY. The right ventricular to body weight ratio did not differ between SHR and WKY. This ratio decreased in both strains between 8 weeks and all subsequent ages. The adrenal to body weight ratio was significantly \((p<0.05)\) greater in SHR only at 96 weeks of age. This ratio decreased in both strains between 8 weeks and all subsequent ages.

**Resting Systemic Hemodynamics**

Resting systemic hemodynamic data (Figure 1) showed that, compared with WKY, SHR had a significant elevation in MAP resulting from a significant increase in total peripheral resistance while cardiac index remained unchanged at 8 through 96 weeks of age. There was no significant difference in heart rate between groups. MAP in SHR was 142 ± 3 mm Hg at 8 weeks and reached a near-plateau level of 158 ± 3 mm Hg at 24 weeks; MAP of 24- to 96-week-old SHR was higher than that of 8-week-old SHR. In WKY, MAP remained unaltered with age. Cardiac index decreased significantly \((p<0.05)\) in both SHR and WKY between 8 weeks and all subsequent ages. In SHR, heart rate decreased significantly at 96 weeks compared with the level at 8 weeks \((336 ± 9 \text{ vs } 384 ± 9 \text{ beats/min}; p<0.05)\). In both strains, total peripheral resistance increased significantly \((p<0.05)\) between 8 weeks and all subsequent ages.

**Resting Regional Hemodynamics**

Resting blood flow data are shown in Figure 2. Splanchnic (gastrointestinal tract + spleen + pancreas) blood flow was significantly \((p<0.05)\) less in SHR than in WKY as a whole, although no significant difference was obtained at any individual age. Splanchnic blood flow tended to decrease with age, and it decreased significantly \((p<0.05)\) in both SHR and WKY between 8 and 96 weeks of age. Renal blood flow in SHR compared with WKY tended to be less at 8 to 48 weeks and was significantly less at 96 weeks of age \((499 ± 31 \text{ vs } 664 ± 48 \text{ ml/min/100 g}; p<0.05)\). Renal blood flow decreased significantly \((p<0.05)\) in SHR between 8 and 96 weeks of age. Myocardial (i.e., left ventricular) blood flow was not different between the two strains. Myocardial blood flow decreased in SHR between 8 and 96 weeks \((685 ± 39 \text{ vs } 502 ± 25 \text{ ml/min/100 g}; p<0.05)\). Cerebral blood flow was not different with respect to strain or to age. Skeletal muscle blood flow decreased in both strains between 8 weeks and all subsequent ages. No significant difference was evident in cutaneous blood flow with regard to strain or age.

As illustrated in Figure 3, splanchnic vascular resis-

### Table 1. Body, Heart, and Adrenal Weights of SHR and WKY at Various Ages

<table>
<thead>
<tr>
<th>Weight</th>
<th>8 wk</th>
<th>24 wk</th>
<th>48 wk</th>
<th>96 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BW (g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>196 ± 4</td>
<td>358 ± 3*</td>
<td>370 ± 4*</td>
<td>393 ± 10*</td>
</tr>
<tr>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 10)</td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>203 ± 3</td>
<td>378 ± 4†</td>
<td>417 ± 8†</td>
<td>450 ± 5†</td>
</tr>
<tr>
<td>(n = 13)</td>
<td>(n = 14)</td>
<td>(n = 13)</td>
<td>(n = 10)</td>
<td></td>
</tr>
<tr>
<td><strong>LV/BW (g/kg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>2.98 ± 0.06*</td>
<td>2.96 ± 0.04*</td>
<td>3.02 ± 0.05*</td>
<td>3.39 ± 0.10*</td>
</tr>
<tr>
<td>WKY</td>
<td>2.55 ± 0.05</td>
<td>2.48 ± 0.04</td>
<td>2.45 ± 0.05</td>
<td>2.51 ± 0.04</td>
</tr>
<tr>
<td><strong>RV/BW (g/kg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>0.712 ± 0.015</td>
<td>0.547 ± 0.012†</td>
<td>0.587 ± 0.015†</td>
<td>0.619 ± 0.048†</td>
</tr>
<tr>
<td>WKY</td>
<td>0.754 ± 0.026</td>
<td>0.592 ± 0.017†</td>
<td>0.548 ± 0.015†</td>
<td>0.553 ± 0.026†</td>
</tr>
<tr>
<td><strong>Adrenal/BW (g/kg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>0.242 ± 0.006</td>
<td>0.122 ± 0.004†</td>
<td>0.116 ± 0.006†</td>
<td>0.152 ± 0.013*†</td>
</tr>
<tr>
<td>WKY</td>
<td>0.245 ± 0.011</td>
<td>0.114 ± 0.004†</td>
<td>0.099 ± 0.005†</td>
<td>0.093 ± 0.007†</td>
</tr>
</tbody>
</table>

Values are means ± SE. LV/BW = left ventricular to body weight ratio; RV/BW = right ventricular to body weight ratio; adrenal/BW = adrenal to body weight ratio.

*\( p < 0.05 \), compared with age-matched WKY (Bonferroni method).
†\( p < 0.05 \), compared with 8-week-old rats for each strain (Bonferroni method).
FIGURE 1. Resting systemic hemodynamic data in 8-, 24-, 48-, and 96-week-old SHR and WKY. MAP = mean arterial pressure; HR = heart rate; Cl = cardiac index; TPR = total peripheral resistance. Hatched columns represent SHR, and open columns represent WKY. Data are means ± SE. Numbers of rats for each age group are given in Table 1. Asterisks on the shoulders of columns indicate significant strain differences (p<0.05) at each age level, and those with brackets indicate significant age differences (p<0.05) between 8 weeks and subsequent weeks within each strain.

FIGURE 2. Resting regional blood flow (BF) data in 8-, 24-, 48-, and 96-week-old SHR and WKY. Data are means ± SE. Hatched columns represent SHR, and open columns represent WKY. Asterisks on the shoulders of columns indicate significant strain differences (p<0.05) at each age level, and those with brackets indicate significant age differences (p<0.05) between 8 weeks and subsequent weeks within each strain.

FIGURE 3. Resting regional vascular resistance (VR) data in 8-, 24-, 48-, and 96-week-old SHR and WKY. Data are means ± SE. Hatched columns represent SHR, and open columns represent WKY. Asterisks on the shoulders of columns indicate significant strain differences (p<0.05) at each age level, and those with brackets indicate significant within-strain age differences (p<0.05) between 8 weeks and subsequent weeks.

Resistance was significantly (p<0.05) greater in SHR than in WKY at 24 to 96 weeks. This vascular resistance increased significantly (p<0.05) in SHR between 8 weeks and all subsequent ages and in WKY between 8 and 96 weeks. Renal vascular resistance was significantly (p<0.05) greater in SHR than in WKY at 24 to 96 weeks. This resistance increased significantly (p<0.05) in SHR between 8 and 96 weeks. Myocardial vascular resistance was significantly higher in SHR than in WKY at 24 and 96 weeks of age (e.g., 96-week-old SHR and WKY: 0.337 ± 0.022 vs 0.252 ± 0.023 mm Hg/ml/min/100 g; p<0.05). This vascular resistance increased in SHR at 48 and 96 weeks as compared with values obtained at 8 weeks. Cerebrovascular resistance in SHR as compared with WKY was elevated insignificantly at 8 and 24 weeks and significantly at 48 and 96 weeks (e.g., 96-week-old SHR vs WKY: 1.86 ± 0.14 vs 1.39 ± 0.07 mm Hg/ml/min/100 g; p<0.05). Cerebrovascular resistance exhibited minimum or minor changes with age in both strains. Skeletal muscle vascular resistance was significantly higher in SHR than in WKY at 48 and 96 weeks of age. This vascular resistance increased in SHR at 24 through 96 weeks and increased similarly in WKY at 96 weeks, as compared with values at 8 weeks. Cutaneous vascular resistance was significantly higher in SHR at 24 through 96 weeks. Cutaneous vascular resistance increased in SHR at 48 and 96 weeks as compared with values at 8 weeks.
Systemic Hemodynamic Responses to Stress

Systemic hemodynamic responses to short-term shaker stress, assessed as percentage of change from resting values, are shown in Figure 4. The overall response pattern was one of increases in all circulatory variables measured. SHR had a significantly \((p < 0.05)\) greater MAP response than WKY at all ages examined. The MAP response tended to decrease with age and did decrease between 8 and 96 weeks in both SHR \((26.4 \pm 2.3\) vs \(17.1 \pm 1.7\); \(p < 0.05)\) and WKY \((18.8 \pm 1.5\) vs \(11.7 \pm 2.0\); \(p < 0.05)\). The heart rate response was elevated significantly in 8- and 24-week-old SHR, and insignificantly in 48- and 96-week-old SHR, compared with age-matched WKY. This response tended to decline in WKY and did decline \((p < 0.05)\) in SHR between 8 and 96 weeks. The cardiac index response was augmented in SHR as a whole \((p < 0.05)\), although no significant strain difference was noted at any age level. This response appeared to decline with age in both strains and did decline in SHR between 8 and 96 weeks \((18.0 \pm 1.9\) vs \(7.8 \pm 2.3\); \(p < 0.05)\). There was no significant difference in the total peripheral resistance response regarding strain and age; however, this resistance response appeared to be substantially greater in SHR than in WKY at 24 weeks.

Regional Hemodynamic Responses to Stress

As shown in Figure 5, the most remarkable features of the regional hemodynamic responses to stress were increases in blood flow of cerebral (most marked), skeletal muscle (second marked), and myocardial vascular beds, which were associated with decreases in blood flow of splanchnic, renal, and cutaneous vascular beds. Decremental responses of splanchnic blood flow were significantly larger in SHR than in WKY at 24 and 48 weeks. The response decreased significantly \((p < 0.05)\) with age as a whole, although no significant age difference was noted in either strain. Renal blood flow responses in SHR were greater as a whole \((p < 0.01)\) and at 8 weeks \((SHR\ versus \ WKY: -19.1 \pm 3.7\) vs \(-10.4 \pm 2.5\); \(p < 0.05)\). No significant effect of age was noted. Compared with responses in WKY, myocardial blood flow responses in SHR were augmented significantly \((p < 0.05)\) at 8 to 48 weeks and insignificantly at 96 weeks. Myocardial blood flow responses tended to decrease with age and decreased in SHR between 8 and 96 weeks \((34.5 \pm 4.7\) vs \(18.5 \pm 3.2\); \(p < 0.05)\). Incremental responses in cerebral blood flow were enhanced in SHR as compared with WKY significantly at 8 and 24 weeks and insignificantly at 48 and 96 weeks. These responses decreased in SHR between 8 and 48 weeks and between 8 and 96 weeks \((62.8 \pm 6.9\) vs \(24.6 \pm 2.8\); \(p < 0.05)\); a similar decrease was found in WKY between 8 and 96 weeks \((41.4 \pm 6.2\) vs \(14.4 \pm 2.7\); \(p < 0.05)\). Incremental responses in skeletal muscle blood flow were enhanced significantly in SHR at 8 to 48 weeks and insignificantly at 96 weeks. These responses showed an age-related decrease in both strains.
as a whole \((p<0.05)\), with no significant age difference in either strain. Decremental responses in cutaneous blood flow were enhanced significantly in SHR as compared with WKY at 8 to 48 weeks and insignificantly at 96 weeks. These responses declined with age as a whole \((p<0.05)\), with no significant age difference in either strain.

As shown in Figure 6, incremental responses in splanchnic vascular resistance were augmented in SHR at 8 to 48 weeks \((p<0.05)\). These responses decreased with age in both strains as a whole \((p<0.05)\) and in SHR between 8 and 96 weeks \((-54.5 \pm 4.8 \text{ vs } -29.0 \pm 4.0\% ; p<0.05)\). Compared with responses in WKY, renal vascular resistance responses in SHR were augmented significantly at 8 to 48 weeks and insignificantly at 96 weeks. These responses decreased with age as a whole \((p<0.05)\), although no statistically significant age difference was noted in either strain. Myocardial vascular resistance responses were minimal and were not influenced by strain or by age. Decremental responses in cerebrovascular resistance were greater in SHR as a whole \((p<0.01)\), with no significant strain difference at any age. These responses tended to decrease with age in both strains and did decrease in SHR between 8 and 96 weeks \((-20.4 \pm 3.5 \text{ vs } -6.6 \pm 2.4\% ; p<0.05)\). Responses in skeletal muscle vascular resistance were greater in SHR as a whole \((p<0.01)\), but age-matched comparisons yielded no significant difference between strains. There was no overall effect of age. Incremental responses in cutaneous vascular resistance were enhanced in SHR significantly at 8 to 48 weeks and insignificantly at 96 weeks. There were age-related declines in these responses in both strains between 8 and 96 weeks.

**Plasma Catecholamines**

As shown in Table 2, there were no significant differences regarding strain and age with respect to resting plasma concentrations of epinephrine and norepinephrine. Since plasma catecholamine levels during stress increased many times above the resting values, the stress to resting value ratio was used to assess the response (see Table 2). Plasma epinephrine showed a more pronounced response than did plasma norepinephrine in both SHR and WKY. The stress to resting value ratio for plasma epinephrine was significantly greater in SHR as compared with WKY at 8 and 96 weeks, and this ratio was not affected by age. The stress to resting value ratio for plasma norepinephrine was significantly greater in SHR as compared with WKY at 8 and 96 weeks. The stress to resting value ratio showed no statistically significant age difference in either strain, although this ratio at 96 weeks appeared to be somewhat lower than that at 8 weeks.

**Discussion**

We demonstrated that, under conditions of rest and a conscious state, elevated MAP was accompanied by increased total peripheral resistance and no changes in

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**TABLE 2. Plasma Epinephrine and Norepinephrine Concentrations at Rest and Stress to Resting Value Ratio in 8- and 96-Week-Old SHR and WKY**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting EPI (pg/ml)</td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>92±14</td>
</tr>
<tr>
<td>(n=10)</td>
<td>80±15</td>
</tr>
<tr>
<td>WKY</td>
<td>62±9</td>
</tr>
<tr>
<td>(n=10)</td>
<td>58±11</td>
</tr>
<tr>
<td>Stress to resting EPI ratio</td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>12.4±1.6*</td>
</tr>
<tr>
<td>WKY</td>
<td>7.73±1.6</td>
</tr>
<tr>
<td>Resting NE (pg/ml)</td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>298±55</td>
</tr>
<tr>
<td>WKY</td>
<td>242±48</td>
</tr>
<tr>
<td>Stress to resting NE ratio</td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>3.07±0.27*</td>
</tr>
<tr>
<td>WKY</td>
<td>2.19±0.17</td>
</tr>
</tbody>
</table>

Values are means ± SE. EPI = epinephrine; NE = norepinephrine. Two-way analysis of variance was performed separately with respect to the resting plasma catecholamine levels and the stress to resting value ratio for each catecholamine.

*\(p < 0.05\), compared with age-matched WKY (Bonferroni method).
cardiac index and heart rate in 8- through 96-week-old SHR as compared with age-matched WKY. This hemodynamic profile was associated with an increase in the left ventricular to body weight ratio in SHR, thereby reflecting pressure-induced hypertrophy. Our finding is consistent with some6-9 but not all10, 11 reported evidence. This inconsistency may be due to differences in the age and sex of the rats studied, the use or nonuse of anesthetics, and the technique used to measure cardiac output. Our observations are meaningful in that awake animals were evaluated over a wide range of age. It should be emphasized that hypertension was stable and well compensated despite the attainment of old age in SHR.

We also demonstrated that regional blood flow at rest was unaltered for the most part; therefore, regional vascular resistance was increased almost uniformly in SHR at 8 to 48 weeks of age as compared with WKY. This finding corroborates earlier data,6-9 including our own.22 When viewed closely, however, some nonuniformity did exist: there was a tendency toward decreased renal and splanchnic blood flow in SHR, and a significantly decreased renal blood flow was evident in the 96-week-old SHR. A reduction in renal blood flow frequently occurs in patients with clinical essential hypertension, particularly in the late phases.1-2 These strain-specific changes may be due principally to the progression of hypertensive vascular disease. The age-associated decreases we found in blood flow through the skeletal muscle vasculature in both strains were not strain-specific; therefore, the aging process probably was involved.

The age-related decreases we observed in the resting cardiac index between young and old rats from both strains have been noted repeatedly.1 5 6 8 11 In general, the body surface area to which metabolic rate and heat loss seem to be proportionate diminishes with growth; therefore, a relatively decreased cardiac output may be required in the grown animal to meet metabolic demand and maintain constant body temperature.34 Changes in blood volume may play some role in these adjustments. The cardiac sympathetic and parasympathetic interactions may also be contributory. These considerations serve to explain to some extent the observed flow difference between young and old rats.

There is no complete agreement as to circulating catecholamine levels in SHR.35 Our finding of no difference in resting plasma catecholamine levels in 8- and 96-week-old SHR as compared with WKY, despite the increased adrenal to body weight ratio in 96-week-old SHR, is in accord with some data.13 15 Yet this finding is at variance with the hyperadrenergic state often noted in aged humans.33 34 Although plasma catecholamine levels may be normal at rest, they may be excessively heightened in SHR in response to even slight stimuli.

The overall response characteristics of hemodynamics and plasma catecholamines elicited in SHR and WKY with shaker stress replicated those of the defense reaction,1 18 as we noted previously.22 The incremental responses in MAP, heart rate, and cardiac index were greater on average in SHR at all ages tested. Likewise, the regional hemodynamic responses, which in the simplest terms consisted of blood flow redistribution from splanchnic, renal, and cutaneous circulations to cerebral (most marked), skeletal muscle (second marked), and myocardial circulations, were greater on average in SHR at all ages. Plasma catecholamine responses also were heightened in young and old SHR. Accordingly, in comparison to WKY, the SHR had an age-independent cardiovascular hyperreactivity to short-term shaker stress. The hyperreactivity of the sympathoadrenal system to this stress was probably age-independent, considering both present and previous13, 14, 22 findings.

Many investigators insist on a close association between hemodynamic, sympathoadrenal, and behavioral hyperreactivity in SHR13, 14, 22; however, the notion of behavioral hyperreactivity has been challenged recently.36 The proposed mechanisms of such stress hyperreactivity in SHR include genetically determined central hyperresponsiveness,1-18 20, 37 reduced sensitivity of baroreceptor reflexes,38 and peripheral factors such as increased vascular smooth muscle sensitivity and structural hypertrophy.1, 39 In view of the nature of shaker stress33 and the response patterns of blood flow and catecholamines, alterations in the central nervous system, presumably the limbic and hypothalamic areas participating in the defense reaction, are deemed to be most important.

In this study, the stress hemodynamic responses generally were pronounced in both strains at 8 weeks of age, and the majority of these responses tended to or did decline between 8 and 96 weeks. In contrast, there was no statistically significant age difference in the plasma catecholamine responses in either strain, though there was a subtle tendency toward a decrease. If a larger number of rats in each age group had been studied, age-associated decreases might have reached statistical significance.

The manner in which circulatory responses to stress are altered with age remains a matter of debate.1, 4-23, 25-29 Abundant evidence indicates that the heart rate response declines with age but the blood pressure response is variable.1, 2, 23-26, 29 Clinically, many types of stress lead to greater blood pressure changes and at least equivalent or greater catecholamine secretion in elderly as compared with young persons.2, 22, 24 Experimentally, a study showed that blood pressure responses to short-term immobilization stress were diminished in awake, aged Fischer-344 rats (no catecholamine levels were reported).36 Studies of direct sympathetic responses of isolated cardiovascular preparations from aged rats have provided controversial results: some investigators have described blunted contractile responses,25, 27 but others have not.38 Because an age-related decline in adrenergic receptor density in cardiovascular tissues apparently did not occur,24, 25, 28, 40 some researchers attributed the reduced sympathetic responses to impaired postreceptor mechanisms.34, 35

Although altered central mechanisms for the age-
related stress response changes cannot be excluded, our finding of dissociation of cardiovascular from sympathoadrenergic responses might point to peripheral mechanisms. We are inclined to assume that the effectiveness of acute stress-induced sympathoadrenal excitation in the cardiovascular system may be more or less altered in conscious, old rats, tested under the present experimental conditions. We do not know if the use of other types of stress will yield similar results. In addition, the possibility remains that the degree of parasympathetic withdrawal during stress might change with age.12

The mechanisms of the reduced hemodynamic responses observed in old SHR are complicated by the prolongation of hypertension. Marked vascular structural hypertrophy and baroreceptor reflex dysfunction (no data on aged SHR available) may augment stress responses.1,39 On the other hand, decreased β-adrenergic receptor numbers,24,40 changes in postreceptor sites,24,25,40 in cardiovascular tissues, and diminished cardiac pumping reserve24 may become substantial, and the stress responses would be blunted. The balance among these and other events would contribute to the overall responses.

In conclusion, hypertension was maintained by elevated total peripheral resistance and unaltered cardiac output associated with largely unaltered regional blood flow in young through old SHR as compared with WKY. Cardiovascular and sympathoadrenal responses to acute shaker stress, which resembled the defense reaction, were exaggerated in SHR independently of age. Nonetheless, most cardiovascular responses tended to or did decline in SHR and WKY between young and old ages, despite the lack of influence of age on the sympathoadrenal responses. These findings imply that the effectiveness of acute stress-evoked, centrally mediated sympathoadrenal stimulation in the circulatory system is altered in old rats, particularly old SHR.

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