CHANGES IN HEMODYNAMICS WITH ADVANCING AGE IN CONSCIOUS SPONTANEOUSLY HYPERTENSIVE RATS

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The changes of hemodynamics were measured in spontaneously hypertensive rats (SHR) of increasing ages. Male SHR and Wistar rats of the Kyoto strain (WKY) at 4, 12, 24 and 48 weeks of age were used. The right jugular vein and the left femoral artery were cannulated and a thermister was placed in the ascending aorta. After 24-hour rest, heart rate (HR), mean arterial pressure (MAP) and cardiac output (CO) were measured. The ratio of left ventricular weight (LVMI) of 4-week-old SHR had already increased significantly when compared to WKY. The HR in 4-week-old SHR was significantly higher than WKY. The increased HR in young SHR indicates the hypersensitivity of the sympathetic nervous system. Increased CO in 4-week-old SHR was due to high HR. The ratio of heart work to left ventricular mass (HW/LVM) of SHR at all age groups was not different from that of WKY, although the ratio of heart work to body weight (HWI) had a tendency to rise in SHR as compared to that in WKY. Our conclusion is that the development of LVM adapts to HW.

In the early stage of human hypertension, heart rate (HR), cardiac output (CO) and left ventricular ejection fraction (LVEF) are increased significantly, which indicates that a hyperdynamic circulation might be one of the pathogenetic mechanisms. For this reason, accentuated central neurogenic drive to the cardiovascular system may be an initiating factor in essential hypertension. However, in essential hypertension, the cardiac index (CI) is reduced to normal levels as total peripheral resistance (TPR) and mean arterial blood pressure (MAP) are elevated. In particular the hemodynamic characteristics during the progressive stages of hypertensive cardiovascular disease in the course of this spontaneous hypertension have not been sufficiently understood. A better understanding of these hemodynamic changes is very important for the follow-up of early hypertensive patients. The spontaneously hypertensive rat (SHR), which is the best model developed to date as an experimental counterpart for essential hypertension in man, has been reported to show similar changes in hemodynamics. To the best of our knowledge, however, most researchers have reported hemodynamics under anesthesia or in a limited age range (for example only young SHR etc.). There has been no report about hemodynamic changes in the conscious state due to aging (from early age to old age). Because anesthesia alters hemodynamics in the rat to various degrees, depending on the anesthetic agents used and it is especially variable in the circulatory system of

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- Spontaneously hypertensive rat
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- Cardiac hypertrophy

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TABLE I  MEAN VALUES ± SD OF BODY WEIGHT (BW: g), LEFT VENTRICULAR MASS WEIGHT (LVM: g), THE RATIO OF LVM TO BW (LVMI; %) AND MEAN ARTERIAL PRESSURE (MAP: mmHg) IN THE EACH GROUPS OF RATS

<table>
<thead>
<tr>
<th></th>
<th>BW</th>
<th>LVM</th>
<th>LVMI</th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 week old</td>
<td>SHR</td>
<td>113 ± 8</td>
<td>0.38 ± 0.02</td>
<td>0.33 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>WKY</td>
<td>94 ± 10</td>
<td>0.27 ± 0.05</td>
<td>0.28 ± 0.03</td>
</tr>
<tr>
<td>12 week old</td>
<td>SHR</td>
<td>288 ± 29</td>
<td>0.91 ± 0.08</td>
<td>0.32 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>WKY</td>
<td>310 ± 26</td>
<td>0.67 ± 0.05</td>
<td>0.24 ± 0.03</td>
</tr>
<tr>
<td>24 week old</td>
<td>SHR</td>
<td>350 ± 6</td>
<td>1.04 ± 0.07</td>
<td>0.30 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>WKY</td>
<td>413 ± 19</td>
<td>0.79 ± 0.02</td>
<td>0.19 ± 0.04</td>
</tr>
<tr>
<td>48 week old</td>
<td>SHR</td>
<td>400 ± 35</td>
<td>1.31 ± 0.12</td>
<td>0.33 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>WKY</td>
<td>338 ± 22</td>
<td>0.91 ± 0.02</td>
<td>0.20 ± 0.01</td>
</tr>
</tbody>
</table>

* = significant difference from WKY (p < 0.05)

hypertensive animals\(^2\),\(^2\) the measurements should preferably be made with animals in the conscious state. In this study, hemodynamic studies were performed on various age groups of normotensive and SHR in the conscious and almost unrestrained state.

MATERIALS AND METHODS

Male SHR and ordinary normotensive Wistar rats of the Kyoto strain (WKY) at the following ages (N for each) were used in the present study: 4 week-old (n = 5), 12 week-old (n = 6), 24 week-old (n = 7) and 48 week-old (n = 5). The animals were anesthetized with pentobarbital sodium (30 mg/kg) and prepared for hemodynamic measurements by a method previously described\(^2\)\(^3\). In brief, the right jugular vein and the left femoral artery were cannulated to pressure transducer (TP-101T, Nihon Koden L.t.d.). The thermistor was placed in the ascending aorta through the right carotid artery. Heparin-filled catheters were placed on the back of the neck. After 24-hours rest, measurements were performed in the plexiglass cage in which the rats had been habituated. After placing the rat in plexiglass cage for 30 minutes, resting MAP, HR and CO were recorded. CO was determined by the thermodilution method described previously\(^2\)\(^3\). Each parameter was determined four times and all data except the first one were averaged. The first measurement was discarded because the saline in the tube passed under the skin had been warmed by body temperature before the first procedure. At the end of experiment, the rat was killed and the wet weight of the left ventricle was determined after blotting on the paper and relative heart weight was expressed as a percentage of total body weight. From the direct measurements, the derived data of cardiac index (CI, ml/min/100g: CO divided by total body weight), stroke volume index (SI, ml/100g: CI divided by HR) and total peripheral resistance (TPR, mmHg/ml/min/100g: MAP divided by CI) were determined. The ratio of left ventricular work to body weight (HWI, mmHg·L/min/100g) was obtained by CI multiplied by the difference between MAP and right atrial pressure. A ratio of heart work to left ventricular mass (HW/LVM, mmHg·L/min/g) and ratio of cardiac output to left ventricular mass (CO/LVM, ml/min/g) were obtained by heart work and cardiac output divided by left ventricular mass respectively. During the entire observation period, the temperature in the ascending aorta was monitored continuously by thermistor probe and, when necessary, maintained between 36\(^\circ\)C and 38\(^\circ\)C with an electric heating lamp. These data were analyzed by the Student's t-test.

RESULTS

Body and left ventricular weights in WKY and SHR are compared in Table I. The ratio of left ventricular weight to total body weight (left ventricular mass index: LVMI, %) of 4 week-old SHR had already increased significantly as compared with WKY, before the MAP of SHR in the group increased.
Hemodynamics

MAP was significantly higher in SHR (except 4 week-old SHR) than in WKY (Table). HR in SHR except in the 48 week-olds tended to be higher than in WKY. This increase was especially significant (477 ± 10 vs 382 ± 56, p < 0.01) in 4 week-old SHR as compared with WKY. SHR had a tendency toward slowing in HR with increasing age. And in 48 week-old SHR, there was no difference between SHR and WKY. CI in 4 week-old SHR was significantly higher than in WKY (87.6 ± 10.9 vs 70.0 ± 16.1, p < 0.05). However, in contrast, CI in 48 week-old SHR decreased significantly when compared to WKY (31.4 ± 1.8 vs 40.0 ± 4.0, p < 0.001) (Fig. 1). CI in SHR and WKY in all ages tended to reduce with increasing age. There was no significant difference at any age in SI. TPR was not significantly different between SHR and WKY in 4 week-old. However, TPR in 12, 24 and 48 week-old SHR increased significantly when compared to WKY (3.46 ± 0.59 vs 2.80 ± 0.54, p < 0.001, 3.84 ± 0.57 vs 2.45 ± 0.24; p < 0.01, 6.34 ± 0.41 vs 3.06 ± 0.25; p < 0.001, respectively) (Fig. 2). The rate of TPR in SHR increased with increasing age, however, that of TPR in WKY was unchanged. HWI was in a tendency to be higher in SHR than in WKY at all ages. However, in all age groups, there was no difference between SHR and WKY in HW/LVM. The ratio of CO to left ventricular mass (CO/LVM) in SHR had a tendency to decrease with increasing age. CO/LVM in SHR except in the 4 week-old was significantly lower than age matched WKY (Fig. 3).

DISCUSSION

In the present study, HR and CI were detected to be raised significantly in 4 week-old SHR as compared with WKY, although MAP was much the same between the groups. Thus these results demonstrate that young SHR have a hyperkinetic circulation, characterized by increased HR and CO. MAP and TPR in 12 week-old SHR were raised significantly when compared to WKY. These results suggest that a gradual structural adaptation of precapillary resistance vessels to intermittent stimuli may gradually increase systemic resistance and vascular reactivity until a state of established

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hypertension is accomplished. Lundin et al. indicated the presence of a hyperkinetic circulatory state in early borderline SHR hypertension especially during awake "resting" conditions. That this state of hyperdynamic circulation seems to be a stage prior to one of normal output and increased resistance is suggested by the work of Eichert et al.24 These studies showed that several "hyperkinetic" labile hypertensive patients, who later developed fixed diastolic hypertension, demonstrated a normal output and increased resistance at that later stage. This increased CI is mainly due to a raised HR, suggesting a hyperkinetic circulatory state, and not a consequence of plasma volume expansion because plasma volume in young SHR is in the lower normal range.25 The initial increase in CI proposed in the total body autoregulatory model could lead to an enhanced sympathetic drive to the heart and is commonly associated with an increased sympathetic discharge to the heart in combination with decreased vagal activity. Howe et al. suggested increased activity of adrenaline neurons terminating in the spinal cord in 4-week-old SHR. McCarthy and Kopin also showed a greater increase in plasma adrenaline and noradrenaline than controls when exposed to electrical foot shock. This autonomic hyperactivity is likely to excite more easily and emphasize cardiovascular response in early life. Such intermittent but accentuated pressure increases may be a potential trigger mechanism for hypertension. In the early stages of hypertension, the increased MAP was associated with an increased CO and normal TPR. Later, in these forms of experimentally induced hypertension, the elevated pressure was sustained by an increased resistance as the CO returned to normal. The mechanism by which the increased CO could produce long-term increases in vascular resistance remains unknown. However, in the pathogenesis of long-term hypertension, the increased resistance may result from adaptive changes because of the increased CO. In our oldest group of SHR with massive hypertrophy there was a gross reduction in the pumping function per gram of left ventricular mass (CO/LVM) when compared to age-matched WKY. Therefore, this oldest SHR demonstrated Mersen's third stage of ventricular hypertrophy in which there is a progressive deterioration of myocardial function leading to eventual deterioration of cardiac function. These hemodynamic and structural changes arising from increasing afterload, lead us to think that the stable phase of adaptive left ventricular function may be overcome by a further increase in left ventricular afterload.

In our studies, LVMl of SHR was significantly larger than that of WKY at all ages. This development of concentric cardiac hypertrophy in arterial hypertension is believed to represent a physiological adaptation of the heart whereby normal CO is maintained in the presence of an increased pressure load. It is useful to note that LVMl was greater in our youngest SHR than in WKY despite similar MAP levels. This could either reflect a structural myocardial adaptation to increased volume load (for example increased CO) in SHR, or a genetically determined cardiomegaly. In our studies, HW/LVM of SHR at all age groups was not different from that of WKY, although HWI had a tendency to rise in SHR when compared to that in WKY. This suggests that the development of LVM adapts to HW. But the true mechanism of the hypertrophy remains unknown. More investigation is needed concerning these mechanisms in young SHR. But when more clearly understood, this hypertrophy may be very useful for discovering a prehypertensive stage of children.

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