Cardiac Output and Total Peripheral Resistance in Spontaneously Hypertensive Rats

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SUMMARY

By means of an electromagnetic flowmeter, cardiac output was measured simultaneously with arterial pressure in spontaneously hypertensive rats (SHR, Okamoto strain) anesthetized with pentobarbital sodium under positive pressure respiration. The rats were aged 12-23 weeks and in the early stage of hypertension. Cardiac output, arterial pressure, and total peripheral resistance were 12.6±2.7 ml/min/100 Gm, 116±24.6 mmHg, and 9.46±2.74 mmHg/(ml/min/100 Gm) respectively, each being the mean of 9 rats with SD. When compared with normotensive control rats (NCR), cardiac output was not different, while arterial pressure (P<0.005) and total peripheral resistance (P<0.025) were significantly higher in SHR. After ganglion blockade with hexamethonium bromide, there was no difference in the above 3 parameters between SHR and NCR. Heart rate was also significantly higher in SHR before ganglion blockade and not so after blockade.

Additional Indexing Words:
SHR Hypertension Sympathetic activity

Despite extensive studies on spontaneously hypertensive rats, there have been no studies on the cardiac output except a preliminary work by Albrecht et al, which reported a decreasing tendency of cardiac output with age. These authors employed the Stewart-Hamilton principle for the measurement of cardiac output. An attempt was made in this study to measure cardiac output in SHR by applying an electromagnetic flowmeter probe at the ascending aorta under anesthesia and artificial respiration. Arterial pressure was recorded simultaneously and total peripheral resistance was calculated. These parameters were compared with those in normotensive control rats and effects of ganglion blockade were also studied.

METHODS

Experiments were performed on 9 spontaneously hypertensive rats (Okamoto strain, SHR), 12-23 weeks old (mean age with SD, 17.3±3.5 weeks) of either
sex, weighing 219±39 Gm and 9 normal Wistar rats (normotensive control rats, NCR), 12-25 weeks old (17.4±4.5 weeks) of either sex, weighing 294±54 Gm. They were anesthetized by intraperitoneal injection of sodium pentobarbital (50 mg/Kg). A catheter was introduced into the left femoral artery for measurement of arterial pressure. The trachea was cannulated and, after starting positive pressure respiration with a Harvard rodent respirator, the thorax was opened through a median sternotomy. The stroke frequency and volume of the respirator were adjusted just enough to suppress the animal’s own respiratory movement. The pericardium was slit over the ascending aorta. A Statham electromagnetic flow-meter probe (2 or 2.5 mm id) was attached around the ascending aorta to measure aortic flow, which is actually cardiac output since coronary flow occupies only a small portion of cardiac output. Aortic flow and arterial pressure were recorded simultaneously with a pen-writing oscillograph.

RESULTS

One example of the measurements of aortic flow and arterial pressure in an SHR is presented in Fig. 1 and another in an NCR in Fig. 2. Each figure shows tracings shortly before and 10 min after intravenous injection of hexame-

![Fig. 1. Simultaneous recording of aortic flow and arterial pressure in an SHR, aged 18 weeks, weighing 285 Gm. Left: control; right: 10 min after C6, 30 mg/Kg.](image1)

![Fig. 2. Simultaneous recording of aortic flow and arterial pressure in an NCR, aged 18 weeks, weighing 370 Gm. Left: control; right: 10 min after C6, 30 mg/Kg.](image2)
Table I. Comparison of Several Cardiovascular Parameters between SHR and NCR before and after Ganglion Blockade

<table>
<thead>
<tr>
<th>Before Ganglion Blockade</th>
<th>SHR</th>
<th>NCR</th>
<th>Level of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output in ml/min/100 Gm</td>
<td>12.6±2.7</td>
<td>13.2±4.63</td>
<td>N.S.</td>
</tr>
<tr>
<td>Mean arterial pressure in mmHg</td>
<td>116±24.6</td>
<td>80.1±15.3</td>
<td>0.005</td>
</tr>
<tr>
<td>Total peripheral resistance in mmHg/(ml/min/100 Gm)</td>
<td>9.46±2.74</td>
<td>6.48±1.67</td>
<td>0.025</td>
</tr>
<tr>
<td>Heart rate in beats/min</td>
<td>423±30.3</td>
<td>374±38.9</td>
<td>0.025</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>After Ganglion Blockade</th>
<th>SHR</th>
<th>NCR</th>
<th>Level of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output</td>
<td>6.97±2.70</td>
<td>8.34±2.79</td>
<td>N.S.</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>50.1±13.6</td>
<td>47.8±11.1</td>
<td>N.S.</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>8.06±3.38</td>
<td>6.24±2.46</td>
<td>N.S.</td>
</tr>
<tr>
<td>Heart rate</td>
<td>332±44.1</td>
<td>309±44.6</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Each mean with SD from 9 rats

Fig. 3. Changes of arterial pressure (MEAN AP), cardiac output (CO), total peripheral resistance (TPR) and heart rate (HR) on administration of C6 (30 mg/Kg) in SHR (filled circles) and NCR (open circles). Each mean from 9 rats with SD.
thionium bromide (C6), 30 mg/Kg. The results in each group of 9 rats are summarized for comparison in Table I and also in Fig. 3.

Before the ganglion blockade with C6, mean arterial pressure was significantly higher in SHR than in NCR (P<0.005). There was no significant difference in cardiac output per 100 Gm body weight. Therefore, total peripheral resistance, calculated as the ratio of mean arterial pressure and cardiac output per 100 Gm body weight, was significantly larger in SHR than in NCR (P<0.0025).

After the ganglion blockade, cardiac output and arterial pressure were decreased markedly in both groups. However, the decreases in total peripheral resistance were not significant. After the blockade, there was no significant difference in cardiac output, arterial pressure and total peripheral resistance between SHR and NCR.

Heart rate was significantly higher in SHR before the ganglion blockade. However, after the blockade, no significant difference was observed in heart rate between SHR and NCR.

The values presented in Table I, on which the above description was based, were observed after thoracotomy under positive pressure respiration. Before these procedures, when the animals breathed spontaneously, mean arterial pressure with SD was 146±14.6 mmHg in SHR and 102±18.9 mmHg in NCR. This difference between SHR and NCR was significant at P<0.001.

**Discussion**

Arterial pressure, total peripheral resistance, and heart rate were higher in SHR than NCR. The difference disappeared after administration of hexamethonium bromide. This may be ascribed, for the most part, to blocking of impulses in sympathetic vasoconstrictors and cardiac sympathetics at sympathetic ganglia. In other words, in the early hypertensive stage of SHR under pentobarbital anesthesia, increased arterial pressure was maintained by the presence of tonic sympathetic activity.

There are 3 possible ways in which sympathetic activity induces hypertension: 1) increased impulses in sympathetic nerves, 2) an elevated sensitivity of the effector system to a given sympathetic activity, and 3) an increase in transmitter release per impulse. The first mechanism seems to play a major part. By observing action potentials, Okamoto et al3) found an increase in spontaneous impulses in the splanchnic nerve of SHR. Folkow et al4) revealed that immunosympathectomy in new born SHR litters prevented the development of high blood pressure. Shibayama et al5) could observe no increase in cardiovascular reactivity to norepinephrine in SHR. Since total
peripheral resistance and heart rate were both higher in SHR, if they had been induced by increases in the sensitivities, the changes in sensitivity should have occurred in 2 different effector tissues, vascular smooth muscle and cardiac pace-maker, simultaneously. On the other hand, considered from the diffuse nature of the sympathetic activity, an increase in tonic discharges in vasoconstrictors and cardiac sympathetics concurrently seems more likely. No data are at present available whether the quantity of transmitter released per impulse is increased in SHR. However, the observation by Matsumoto\cite{6} that SHR had larger nerve cell bodies in the cervical ganglia might point to this possibility.

Folkow et al\cite{7} observed a raised systemic resistance in SHR in a perfusion experiment when vasculature was maximally dilated with guanethidine. They assumed a structurally based change in the vascular bed to account for this result. Their experiment was done in SHR aged 7 months or more, when the hypertensive state had persisted more than 4 months already. Presumably, this structural change is secondary to the hypertensive state induced by the increase in sympathetic activity. In the early hypertensive state, the secondary change may not be enough to reveal a significant increase in total peripheral resistance after blocking the sympathetic impulses. As seen in Table I and Fig. 3, mean total peripheral resistance was larger in SHR than NCR even after the ganglion blockade. Though this difference was statistically not significant (level of significance: 0.10<P<0.25), it is possible that it betrayed a structurally based increasing tendency of peripheral resistance.

Iriuchijima\cite{8} proposed 2 indices, C_l and C_R, to quantitatively describe the relative importance of change in cardiac output and that in total peripheral resistance in a given change in arterial pressure. The 2 indices calculated for mean values in Table I for the decrease in arterial pressure induced with C6 were: C_l=0.787 and C_R=0.213 for SHR and C_l=0.913 and C_R=0.087 for NCR. The major part of the decrease in arterial pressure was contributed by a decrease in cardiac output in both groups. This suggests that dilatation of capacitance vessels plays an important role in the drastic decrease in arterial pressure on administration of C6. However, it is also to note that CR was larger in SHR than in NCR.

One might think that mean arterial pressure of SHR before ganglion blockade, which was 116±23.6 (SD) mmHg as presented in Table I, was too low to be considered as 'hypertensive'. However, this was significantly higher than the corresponding value for NCR. Before thoracotomy, mean arterial pressure for SHR was really hypertensive (146±14.6 mmHg) despite anesthesia, while that for NCR was not (102±18.9 mmHg). Percent decrease in arterial pressure by thoracotomy was similar for both SHR and NCR.
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REFERENCES

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