Measurement of Cardiac Output by the Thermodilution Method in Conscious Spontaneously Hypertensive Rats

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SUMMARY

The usefulness of the thermodilution method for measuring cardiac output (CO) was evaluated in awake rats by comparison with electromagnetic flowmetry. CO was measured in 3- and 6-month-old conscious spontaneously hypertensive rats (SHR) and normotensive Wistar-Kyoto rats (WKY). The correlation coefficient between CO obtained by the two methods was 0.66 (p<0.01). Although CO values obtained by the thermodilution technique tended to be overestimated in comparison with those determined by electromagnetic flowmetry, this method was shown to be useful for measuring CO in unanesthetized rats because of its technical simplicity. Left ventricular mass (LVM) and the ratio of CO to LVM were significantly greater in SHR than in WKY at both ages and CO/LVM increased with increasing age in SHR. The ratio of heart work (HW) to body weight (HW/BW) was increased only in 3-month-old SHR compared with WKY and there was no difference in HW/LVM in 3- and 6-month-old SHR compared with age-matched WKY. The present results suggest that the development of cardiac hypertrophy in SHR is an adaptation to the increased HW due to high afterload.

Additional Indexing Words:
Cardiac output Thermodilution method Spontaneously hypertensive rat Conscious state

Many studies have been reported dealing with the hemodynamics of the spontaneously hypertensive rat (SHR), which is frequently used as the most suitable animal model for essential hypertension in man. However, most of the work has been done in anesthetized animals and there have

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been few studies using SHR in the awake state because it has been technically
difficult to measure cardiac output (CO) without anesthesia.8)−11) In the
present study CO was measured in awake animals using the thermodilution
method12)−15) which is simpler than other methods such as electromagnetic
flowmetry.

**Materials and Methods**

Study I: Comparison between the electromagnetic flowmetry and
thermodilution methods

Studies were performed on 10 male normotensive Wistar-Kyoto rats
(WKY) aged 3–8 months. All rats were anesthetized with pentobarbital
(30 mg/Kg). One polyethylene catheter (PE 50 connected to a PE 10 intra-
vascular catheter on the tip) was inserted into the left femoral artery and
another catheter into the right atrium (RA) through the right jugular vein.
Each catheter was connected to a pressure transducer (TP-101T, Nihon
Koden Ltd.). The thermister was inserted in the ascending aorta through
the right carotid artery. At the beginning of the operation the sternum was
removed at the intercostal space. After the thymus was divided in the mid-
line, the ascending aorta was exposed without incising the pleura. The
ascending aorta was carefully dissected free from its surrounding tissues and
two ligatures were looped under it. Using these ligatures the aorta was
gently lifted and the electromagnetic flow probe (with an inside diameter of
either 2.0, 2.5 or 3.0 mm) was placed around it (Fig. 1). The probe was
fixed in order to obtain the clearest flow tracing. CO was determined by
thermodilution using a Columbus Cardiotherm 500-R. One hundred micro-
liters of saline at room temperature were injected into the right atrium. CO
was calculated as follows;

![Fig. 1. Position of catheter, thermister and electromagnetic flow probe.](image-url)
The procedure was repeated 5 times at 1 min intervals and the data obtained averaged.

Study II: Hemodynamic studies in conscious animals

Hemodynamic measurements were performed in 3-month-old SHR and WKY (8 each) and in 6-month-old SHR and WKY (5 each). The right carotid artery, the right jugular vein and the left femoral artery were cannulated in the same way as in Study I. These catheters were filled with heparin and their free tips placed on the back of the neck. Twenty-four hours after the operation measurements were performed in the plexiglass cage to which the rats had been habituated. Each catheter was connected to a pressure transducer and arterial blood pressure and RA pressure were continuously recorded using a Nihon Koden Polygraph. CO was determined by the same technique described previously. After placing the rat in a plexiglass cage for 30 min, resting mean arterial pressure (MAP), heart rate (HR) and CO were measured. Each parameter was determined 4 times and all data except the first set were averaged. The first set of measurements was discarded because the saline in the tube passing under the skin had been warmed by body temperature before the first procedure. The temperature in the ascending aorta was monitored continuously by a thermister probe. At the end of the experiment, the rat was sacrificed and the wet weight of the left ventricle was determined and expressed as a percentage to body weight. These were compared using Student’s t-test.

**RESULTS**

Study I: Comparison between the electromagnetic flowmetry and thermodilution methods

CO were 37.5±7.2 (mean±SD, ml/min/100 g) and 29.2±7.3 by the thermodilution and electromagnetic flow methods, respectively. Correlation coefficient between the two methods was 0.66 (Fig. 2).

The regression equation was as follows;

\[ Y = 0.59X + 12.58 \]

X: CO by thermodilution technique
Table I. Mean Values±SD of Body Weight (BW : g) Heart Rate (HR : beat/min), Blood Pressure (mmHg) and the Ratio of Left Ventricular Mass Weight to Body Weight (LVM : %) in Conscious and Resting Condition

<table>
<thead>
<tr>
<th>Age Number</th>
<th>WKY</th>
<th>SHR</th>
<th>WKY</th>
<th>SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3M</td>
<td>3M</td>
<td>6M</td>
<td>6M</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>8</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>310±26</td>
<td>288±29</td>
<td>413±19</td>
<td>350±6</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td>370±26</td>
<td>411±59</td>
<td>347±31</td>
<td>380±30</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>115±6</td>
<td>150±23*</td>
<td>109±8</td>
<td>157±4*</td>
</tr>
<tr>
<td>Left ventricular mass (g)</td>
<td>0.67±0.05</td>
<td>0.91±0.08*</td>
<td>0.80±0.02</td>
<td>1.04±0.07*</td>
</tr>
<tr>
<td>Left ventricular mass per body weight (%)</td>
<td>0.24±0.03</td>
<td>0.32±0.02*</td>
<td>0.19±0.04</td>
<td>0.32±0.02*</td>
</tr>
</tbody>
</table>

* significant differences from WKY (p<0.01).

Y: CO by electromagnetic flowmetry

Study II: Hemodynamic studies in conscious animals

As shown in Table I, there was no difference in body weight between the 2 groups of 3-month-old rats, but body weight of 6-month-old rats was significantly lower in SHR than in WKY (p<0.01). The ratio of left ventricular mass to total body weight (LVM/BW, %) was significantly higher in 3- and 6-month-old SHR than in age-matched WKY (p<0.01 and p<0.01, respectively). No significant difference in HR was observed between SHR and WKY though HR tended to be higher in 3- and 6-month-old SHR. MAP was significantly elevated in 3- and 6-month-old conscious SHR as
Fig. 3. Changes in the ratio of stroke volume to body weight (SV/BW: ml/min/beat/100 g), total peripheral resistance (TPR: mmHg·ml/min/100 g), the ratio of heart work to BW (HW/BW: mmHg·ml/min/100 g), the ratio of HW to left ventricular mass (HW/LVM: mmHg·l/min/g), the ratio of cardiac output to BW (CO/BW: ml/min/100 g) and the ratio of CO to LVM (CO/LVM: ml/min/g) at 3 and 6 months of age. Vertical bars indicate SD.

compared with conscious WKY (p<0.01 and p<0.01, respectively). In conscious 3- and 6-month-old rats, there was no significant difference in the ratio of stroke volume to total body weight (SV/BW, ml/100 g), the ratio of cardiac output to total body weight (CO/BW, ml/min/100 g) and the ratio of heart work to LVM (HW/LVM, mmHg·l/min/g) between SHR and WKY (Fig. 3). Though HW/BW (mmHg·ml/min/100 g) in 3-month-old rats was significantly elevated in SHR as compared with WKY, there was no difference between 6-month-old WKY and SHR. Total peripheral resistance (TPR) was significantly increased in SHR as compared with WKY (p<0.05 in 3-
month-old rats and p<0.01 in 6-month-old rats) and TPR in SHR tended to increase with increasing age as compared with WKY (Fig. 3). The ratio of CO to LVM (CO/LVM, ml/min/g) in 3- and 6-month-old rats was significantly lower in SHR than WKY (p<0.01 in 3-month-old rats and p<0.001 in 6-month-old rats) (Fig. 3).

DISCUSSION

It is critically important to perform hemodynamic studies in conscious animals because the circulatory system is easily influenced by anesthesia. In most of the previous work with SHR,2)-5),10) CO was measured with the electromagnetic probe implanted around the root of the ascending aorta, but this method is always accompanied by technical difficulties in fitting the probe and therefore by the problem of reproducibility. First, it is technically difficult to fit the electromagnetic flow probe consistently at the same portion of the aorta and there is a risk of rupturing the aorta during implantation. The second problem is the physiological alterations that occur during measurement by this method. Thoracotomy was usually, but not in the present study, performed in implanting the probe but it has a considerable influence on the circulatory system.16) For example, thoracotomy and artificial ventilation in the dog produce a 48% decrease in mean carotid artery flow17) as well as shrinkage of the heart.18) And pentobarbital anesthesia and thoracotomy decreased CO in both SHR and WKY rats, as well as decreased aortic pressure in SHR.9) Compared with this method, the thermodilution method is technically simple and it is unnecessary to perform thoracotomy. The cannulations used in the thermodilution method in the present study were not found to influence significantly the circulatory system of rats and the preparation for the thermodilution method is safe compared with the procedures used in implanting a probe as indicated by the few accidents that occurred during insertion of the thermister and catheters in the present study. However, the thermodilution method gives good reproducibility. For these reasons, the thermodilution method was employed to measure CO in conscious rats. Although CO measured by the thermodilution method was higher than that measured by electromagnetic flowmetry, the correlation between the two methods was good (r=0.66). The overestimation by the former method seems to occur because the heat of the saline injected in to the RA is radiated during its passage through the pulmonary capillaries.

In the present study, MAP, TPR and LVM/BW in 3-month-old SHR were higher than age-matched WKY (p<0.01, p<0.05 and p<0.01, respectively). However, there was no significant relationship between HR in SHR
and WKY aged 3- and 6-month-old. These results suggest that in 3- and 6-month-old SHR, high MAP is not due to high HR but mainly due to a raised TPR and normal CO is maintained in spite of the presence of an increased afterload. According to previous reports, the increased resistance may result from neurogenic functional vasoconstriction in the early stage of hypertension and successive adaptive structural changes in the precapillary resistance vessels. The increase in TPR with increasing age in SHR shown in the present study may therefore be due to the structural adaptation of the resistance vessels, although the vessels of the rats were not examined histologically. In 3- and 6-month-old rats there was no significant difference in CO/BW between SHR and WKY at each age. But CO/LVM was significantly decreased as compared with WKY at the ages of 3 and 6 months (p<0.05 and p<0.01, respectively). These results suggest that in SHR CO to BW remained constant irrespective of increased afterload, but the pumping function per gram of left ventricle was reduced in SHR as compared with WKY because of cardiac hypertrophy in SHR. As for heart work (HW), an index of myocardial performance which reflects the ability of the heart to maintain flow in the presence of increased afterload, the ratio of HW to body weight (HW/BW) had a tendency to be higher in 3-month-old SHR as compared with WKY. However, the ratio of HW to LVM (HW/LVM) was not significantly different between SHR and WKY aged 3 and 6 months old. Based on the present results, it is therefore concluded that the cardiac output in SHR may continually adapt to the increased HW due to high afterload.

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References

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