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Cardiac Output in Conscious and Almost Unrestrained Spontaneously Hypertensive Rats*)

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ABSTRACT

Cardiac output and arterial pressure in the conscious state were measured in spontaneously hypertensive rats and normal control rats with chronically implanted electromagnetic flow probe and arterial indwelling cannula. Cardiac index at rest was greater in hypertensive rats than in controls. However, the mean arterial pressure in probe implanted hypertensive rats was significantly lower than that in those without probe. Even in probe implanted hypertensive rats, those with relatively higher arterial pressures showed elevated total periperal resistance and normal cardiac output. These findings suggest that the hypertensive state is maintained by elevated total peripheral resistance with normal cardiac output and that aortic probe implantation induces a decrease in total peripheral resistance, which, being a decrease in afterload, brings rise to an increase in cardiac output. The increase in cardiac output in transposition response induced by transposing the rat from the home cage to a new cage was greater in hypertensive rats than in controls. The decrease in cardiac output in grasp response induced by grasping the rat by the human hand was insignificant in hypertensive rats.

INTRODUCTION

For a better understading of the hemodynamic state of a hypertensive animal, measurement of cardiac output in addition to arterial pressure is highly desirable. Since anesthetics have a considerable influence on the circulatory system of hypertensive animals[6,9], the measurement should preferably be made with animals in the conscious state. The electromagnetic flow probe chronically implantable around the root of the aorta is suitable for this purpose. In the present study this method was applied to spontaneously hypertensive rats (SHR)[8] and normotensive control rats (NCR) to compare cardiac output in natural living conditions as well as in response to two kinds of stimulus, that is, grasping with the human hand and transposition to a new habitat. The probe implantation might have interfered with the hypertensive mechanism, the arterial pressure in probe implanted SHR being lower than that in those without probe implantation. Nevertheless, the results obtained seem to provide some clues on the hemodynamic characteristics of this hypertensive model.

METHODS

SHR and NCR used in this study were 10–20 weeks of age. The method employed in measuring cardiac output and arterial pressure in consious rats has been described previously[7]. Briefly, under thiamylal anesthesia, a 2–3 mm Biotronex electromagnetic flow probe was implanted around the ascending aorta after median sternotomy or horizontal thoracotomy at the third intercostal space. A polyethylene arterial cannula was inserted into the left femoral artery so that the tip was positioned in the abdominal aorta beyond the iliac bifurcation. The wire from the flow probe and the arterial cannula were passed under the skin to the dorsal neck so that the plug at the end of the wire and the external end of the arterial cannula were exteri-

*) 入内島十郎，寺西泰弘：無麻酔無拘束の高血圧自然発症ラットの心拍出量

orized there. After recovery from the operation, aortic flow and pressure were observed in conscious rats by connecting the cable from the flowmeter circuit to the plug of the flow probe and the polyethylene tube from a pressure transducer to the arterial cannula.

Each implanted rat was kept in isolation in a polyethylene box cage containing wood chips and recordings were usually made with the rat remaining in the cage. The cable and tube were both made long enough to allow the rat to move almost freely in the cage during measurement.

For statistical analysis the student's t-test for group or paired data was used throughout. P values of <0.05 were considered to indicate statistical significance.

RESULTS

Cardiac index and other parameters at rest

An example of recording of aortic flow and blood pressure in an SHR at rest is presented in Fig. 1. In the home cage the rat was apparently immobile and appeared relaxed despite the external wire and tube connected to the dorsal neck. In such a recording the number of cardiac cycles in 1 sec was counted down to the second decimal place and multiplied by 60 to obtain the heart rate in beats/min. The stroke volume was calculated from the area under the aortic ejection curve. The minute volume was obtained by multiplying the mean stroke volume over several beats by the heart rate. For comparison, the minute volume was normalized to 100 g of body weight to obtain the cardiac index. The total peripheral resistance index was calculated by dividing the mean arterial pressure by the cardiac index. For the cardiac work index, the mean arterial pressure was multiplied by the cardiac index.

The mean values ± SD for the above cardiovascular parameters from 26 recordings in 11 SHR's at rest are presented in Table 1. The corresponding values from 44 recordings in 25

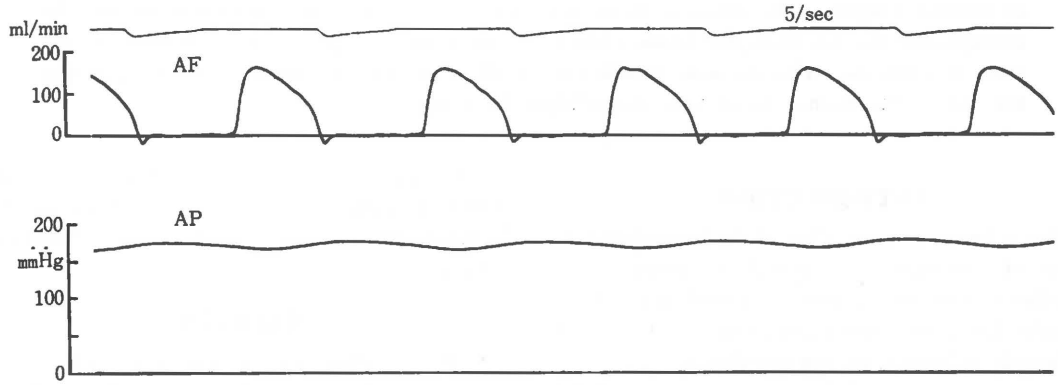

Fig. 1. Simultaneous recording of aortic flow (AF) and arterial pressure (AP) in a conscious SHR at rest

Table 1. Comparison of several cardiovascular parameters at rest between SHR and NCR. mean±SD.

	SHR	NCR	p<
Arterial pressure (mmHg)	139±15.9	111±12.0	0.001
Heart rate (beats/min)	372±61.7	405±46.0	0.01
Cardiac index (ml/min/100 g)	28.8±7.75	23.9±5.80	0.01
Total peripheral resistance index (mmHg/ml/min/100 g)	5.19±1.61	4.91±1.14	0.25
Cardiac work index (mmHg·ml/min/100 g)	3930±1020	2650±660	0.001
n	26 (11 rats)	44 (25 rats)	
male/female ratio	8/3	16/9	
body weight (g)	219±47.1	293±65.8	
age (w. o.)	14.5±3.42	15.2±3.80	
days after implantation	7.85±4.15	5.11±2.14	

NCR's are also presented for comparison. Arterial pressure, cardiac index and cardiac work index were significantly greater in SHR than NCR. Heart rate was lower in SHR and total peripheral resistance index was not different between the two rat groups. These findings appear to indicate that the hypertension in SHR is maintained largely by a greater cardiac index rather than an elevated vascular resistance in comparison to controls. However, the arterial pressure in SHR implanted with aortic probe presented in Table 1 was lower than in SHR without probe. The mean arterial pressure ± SD from 7 male SHR's in which only arterial cannulation had been performed without aortic probe implantation was 161±21.7 mmHg[11], while the corresponding value from 8 male SHR's with aortic probe, the male part of the rat group from which the values in Table 1 were obtained, was 140±15.8 mmHg. These two pressure values were significantly different at $p<0.05$. In NCR arterial pressure was not signifcantly different depending on the presence or absence of the implanted probe.

If the all 26 sets of SHR data used to calculate the figures presented in Table 1 are divided into two equal parts, that is, the part with higher arterial pressures and that with lower arterial pressures, the mean values ± SD for the group with higher pressures are: arterial pressure, 152±9.97 mmHg; heart rate, 331±39.4 beats/min; cardiac index, 25.2±4.94 ml/min/100 g; total peripheral resistance index, 6.26±1.31 mmHg/ml/min/100 g; and cardiac work index, 3820±870 mmHg·ml/min/100 g. If these values are compared with those of NCR in Table 1, the total peripheral resistance index was significantly higher ($p<0.005$), while the cardiac index was not. Therefore, in SHR implanted with aortic probe, the hypertension tended to be dominated by an increase in cardiac output when arterial pressure was relatively low and by an increase in total peripheral resistance when arterial pressure was high. With lapsed days after implantation a tendency was observed arterial pressure to be elevated, cardiac output to be decreased, and total peripheral resistance to be increased.

Transposition response in SHR

Transposition response is a cardiovascular response complex induced when a rat is transposed from its home cage to a new cage[7]. It consists of increases in heart rate and cardiac output and a decrease in total peripheral resistance. In NCR it is an isopressor response and arterial pressure remains almost unchanged. Thus this response is sharply contrasted with the denfense reaction in which arterial pressure is elevated[1,3].

However, when the same transposition stimulus was given to SHR, the arterial pressure was increased[11]. In other words, this response is not an isopressor but a pressor response in SHR.

The change in cardiac output in transposition response was studied in SHR implanted with the aortic probe. One example of the recording of aortic flow and pressure in an SHR before and during transposition response is presented in Fig. 2. After taking a control run at a fast recording paper speed (left), the paper speed was reduced and the rat was grasped by hand, lifted from its home cage and then transposed to and released in a new cage (middle). The marked

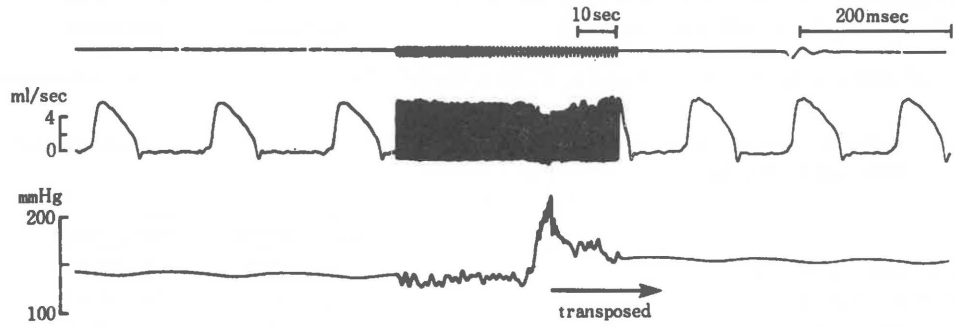

Fig. 2. Changes in aortic flow (top) and arterial pressure (bottom) in an SHR in transposition response. The marked rise in arterial pressure near the center was induced while the rat was being grasped for transposition.

elevation in arterial pressure in the middle of the recording was induced while the rat was being grasped. Elevation of arterial pressure was ascribable in part (about 20 mmHg) to the hydrostatic effect of raising the rat in relation to the pressure transducer, but largely to the cardiovascular response induced in the rat by grasping. This response to grasping may be in the category of defense reaction but here it is noncommittally designated 'grasp responce'. Grasp response will be dealt with in more detail below. Transposition response is a phenomenon separate from grasp response and develops after the rat has been released to a new environment, presumably as the rat recognized the change of habitat. The second fast recording to the right in Fig. 2 was made when transposition response was thought to have been completed. An elevation of the arterial pressure compared to the pretransposition control level is evident together with elevated heart rate.

The mean cardiovascular parameters ± SD before and during transposition response from 7 male SHR's tabulated in Table 2. Arterial pressure, heart rate, cardiac index, and cardiac work index were all increased significantly in transposition resposne, but the decrease in total peripheral resistance index was insignificant ($p<0.1$). In the same rat group transposition response was repeated after beta adrenoceptor blockade with propranolol (1 mg/kg, i. p.). The results are summarized in Table 3. It is noteworthy that the arterial pressure was elevated in the response more markedly than before the blockade and that cardiac output was still increased unlike NCR whose cardiac output was no longer increased in transposition response after beta blockade[7].

Grasp response

Grasp response, which the rat presented while being grasped preceding each transposition, was also a response of considerable physiological interest. Changes in cardiovascular parameters in this response were studied in 7 male SHR's and 6 male NCR's. One example of the recording of aortic flow and blood pressure in an SHR before and during grasp response is presented in Fig. 3. The means ± SD of cardiovascular parameters before and during grasp response in SHR and NCR are tabulated in Table 4. A transitory arrhythmia presumably due to vagal excitation was frequently observed in both SHR and NCR in grasp response. However, calculation of the parameters for Table 4 was made only on the recording when the cardiac rhythm was regular and arterial pressure was at its peak in each response. From each arterial pressure value in grasp response, 20 mmHg which corresponded to the hydrostatic effect was subtracted.

Table 2. Changes in cardiovascular parameters in transposition response in SHR

	before transposition	after transposition	$p<$
Arterial pressure (mmHg)	132±13.3	149±17.5	0.025
Heart rate (beats/min)	387±75.8	437±53.9	0.05
Cardiac index (ml/min/100 g)	28.6±5.89	37.4±10.6	0.01
Total peripheral resistance index (mmHg/ml/min/100 g)	4.79±1.03	4.21±0.896	0.10
Cardiac work index (mmHg·ml/min/100 g)	3780±1010	5690±2250	0.025

n=7 (all male); body weight: 218±23.2 g; 13.3±3.54 week-old; 4.43±2.44 days after implantation

Table 3. Changes in cardiovascular parameters in transposition response 30 minutes after propranolol (lmg/kg, i. p.)

	before transposition	after transposition	$p<$
Arterial pressure (mmHg)	130±20.1	161±24.8	0.005
Heart rate (beats/min)	356±46.2	370±26.9	NS
Cardiac index (ml/min/100 g)	24.3±8.55	28.7±10.1	0.01
Total peripheral resistance index (mmHg/ml/min/100 g)	5.82±1.88	6.08±1.53	NS
Cardiac work index (mmHg·ml/min/100 g)	3200±1430	4780±2250	0.01

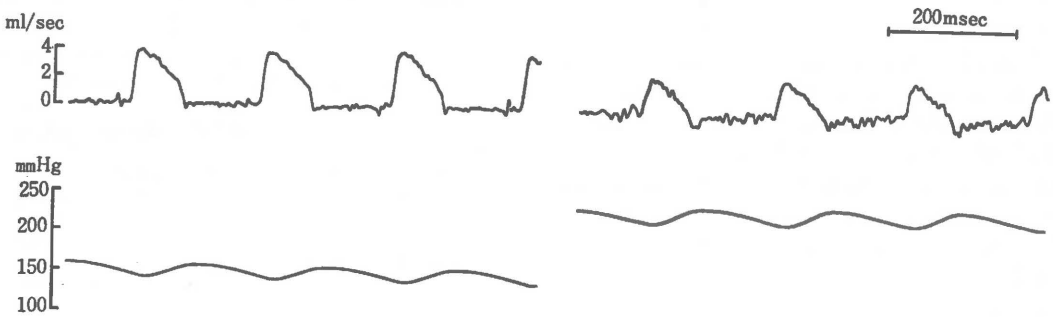

Fig. 3. Changes in aortic flow (top) and arterial pressure (bottom) in an SHR in grasp response. Left: at rest; Right: while being grasped.

Table 4. Changes in cardiovascular parameters in SHR and NCR in grasp response

	SHR		NCR	
	before	during	before	during
Arterial pressure	130±15.7	175±19.5	108±11.6	171±47.1
Heart rate	414±76.9	435±59.6	434±34.1	451±34.3
Cardiac index	25.9±5.22	22.7±4.42	25.7±5.28	19.2±3.70
Total peripheral res. index	5.20±1.12	8.00±1.55	4.51±1.32	9.63±4.12
Cardiac work index	3360±635	4020±980	2760±531	3160±602
n (all male)	7		6	
body weight (g)	221±32.7		341±56.7	
age (w. o.)	12.4±2.19		15.8±7.65	
days after implantation	3.43±2.06		3.00±1.53	

In both SHR and NCR, arterial pressure was elevated markedly in grasp response. The elevation of pressure was greater in NCR than in SHR and arterial pressure during grasp response was not significantly different between the groups. In both groups the elevation of arterial pressure in the response was caused by a marked rise in total peripheral resistance, which indicated a considerable vasoconstriction. Cardiac output was significantly decreased in NCR ($p<0.01$). In SHR the decrease in cardiac output in grasp response was statistically insignificant.

DISCUSSION

Whether the hypertension in SHR is maintained by an increase in cardiac output or vascular resistance is one of the fundamental questions about the hemodynamic state in this hypertensive animal. Under anesthesia most authors have observed an elevation of vascular resistance with almost normal cardiac output[2,4,12]. In the present study in which cardiac output was measured in the conscious and almost unrestrained state, when the rats were apparently at rest, the mean cardiac index in SHR was significantly greater than that in NCR. The difference in total peripheral resistance index between the groups was insignificant. However, arterial pressure in probe implanted SHR in general was unusually low and the increased cardiac output in such SHR might have been secondary to this decrease in afterload.

Smith and Hutchins[10], using a method supposedly similar to ours, observed almost no difference in cardiac index between adult SHR and Wistar Kyoto rats. In our own work[5] the sum of carotid, superior mesenteric, renal and terminal aortic flows was not different between SHR and NCR. Also in the present study, cardiac index in probe implanted SHR with higher arterial pressures was similar to that in NCR. These are the reasons why the elevated cardiac index in probe implanted SHR is con-

sidered unusual. It is possible that probe implantation at the ascending aorta but not at peripheral arteries in some way interferes with the hypertensive mechanism and induces a vasodilation, which first works as a decrease in afterload and secondarily increases cardiac output. In some animals the vascular tone seems to be restored with time after implantation, since the arterial pressure is elevated to the usual hypertensive level and the cardiac output is reduced to the normal value. This speculation presupposes that SHR possesses a powerful heart which has a normal cardiac output against the elevated vascular resistance but has a supranormal one when the vascular resistance is diminished.

The elevation of arterial pressure in transposition response in SHR was found to be ascribable to a greater increase in cardiac output as well as a smaller decrease in total peripheral resistance compared with NCR. Although this was an observation in SHR with aortic probe in which hypertension was supposed to be somewhat restricted, it was consistent with the finding in SHR with probe implanted around peripheral arteries[5]. In SHR the cardiac output was still increased in transposition response after beta adrenoceptor blockade. In NCR this parameter remained almost unchanged in response after this procedure[7].

Since arterial pressure is the product of cardiac output and total peripheral resistance, a percent change of arterial pressure is approximately equal to the sum of the percent change of cardiac output and that of total peripheral resistance:

$$\Delta P/P \simeq \Delta Q/Q + \Delta R/R,$$

where P is arterial pressure, Q cardiac output and R total peripheral resistqnce. Δ refers to the change in reflex or response. The percent changes in the foregoing three variables in SHR in transposition response before and after propranolol calculated from the mean values in Table 2 are tabulated in Table 5. Also included are the corresponding values in NCR calculated from the data in a previous paper[7]. The values before blockade are largely consistent with the results of a similar treatment made on the sum of flows in four peripheral arteries[5]. This table suggests that SHR has a mechanism of increasing cardiac output in transposition response which is not blocked by beta adrenoceptor blockade and that the greater increase in cardiac output in SHR than in NCR in the response is ascribable to this mechanism. A greater mobilization of blood from capacitance vessels than NCR would be a candidate for such mechanism. It is also suggested by this table that the vasodilation in transposition response caused by mechanisms other than beta effect is more marked in SHR.

Table 5. Percent changes in arterial pressure (P), cardiac output (Q), and total peripheral resistance (R) in transposition response before and after beta blockade with propranolol

		$\Delta P/P$	$\Delta Q/Q$	$\Delta R/R$
before blockade	SHR	12.9	30.8	−12.1
	NCR	−1.82	14.5	−16.3
after blockade	SHR	23.9	18.1	4.47
	NCR	19.6	2.11	15.0

In contrast to transposition response in which cardiac output is increased, grasp response was found to be characterized by a decrease in cardiac output in NCR. Presumably the marked elevation of arterial pressure due to vasoconstriction worked as an increase in afterload to interfere with cardiac ejection. However, the decrease in cardiac output in grasp response was insignificant in SHR. This may be ascribable to the fact that the heart in SHR was accustomed to eject against an arterial pressure higher than the level before grasping.

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