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Regional Haemodynamic Differences Between Normotensive and Spontaneously Hypertensive Rats – A Microsphere Study

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Summary

The objective of the present study was to compare systemic and regional haemodynamics in a large series of spontaneously hypertensive rats (SHR, n=32) with normotensive Wistar-Kyoto rats (WKY, n=26) at the age of 12–16 weeks. All rats were anaesthetized with thiobutabarbital and the radioactively labelled microsphere method was used to evaluate regional blood flow with special emphasis on different cerebral areas. The high blood pressure in the SHR was mainly due to elevated total peripheral resistance, which was 90 % higher in the SHR compared to the WKY. Furthermore, heart rate was 25 % ($p<0.001$) higher, but the cardiac index was lower by 20 % ($p<0.01$) in the SHR. Blood flow was significantly lower and vascular resistance higher in several organs such as the kidneys, other visceral organs, skeletal muscle and skin of the SHR compared to the WKY. On the contrary, blood flow in the myocardium was augmented by 40 % ($p<0.01$) in the SHR. Blood flow was 20–50 % higher in the cerebral cortex, thalamus and caudatus ($p<0.05$–0.001), but attenuated in the hypophysis of the SHR. In the pons, medulla and cerebellum, blood flow was similar in the two strains. In this large microsphere study, the basal cardiac index was lower in the SHR already at this relatively early stage of established hypertension. Despite this, increased blood flow in the above mentioned cerebral regions was found in the SHR compared to the WKY.

Key words
Regional blood flow – Haemodynamics – Microsphere method – SHR rats – Hypertension.

Introduction

The spontaneously hypertensive rat (SHR) is one of the most widely studied animal models for hypertension. Several similarities between human essential hypertension and hypertension seen in the SHR have been pointed out both in the pathophysiology and the clinical course of the hypertensive disease (Yamori 1977, Folkow 1982, Rettig and Schmitt 1994).

It has been suggested that increased sympathetic tone and enhanced mental alertness are involved in the early stages of the development of hypertension in the SHR (Yamori 1977, Judy and Farrell 1979, Folkow 1982). The involvement of the heart in the development of hypertension has also been considered since left ventricular hypertrophy already develops at about 4 weeks of age (Morton *et al.* 1990, Kondo *et al.* 1990, Yamori 1994) and a hyperdynamic circulation has been shown at this early stage before hypertension is established (Smith and Hutchins 1979, Folkow 1982). Left ventricular weight has been demonstrated to be significantly increased by 6 to 35% at the age of 13–14 weeks (Pfeffer *et al.* 1979, Yamori 1983).

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The kidney has been shown to be of importance in establishing hypertension in the SHR, since hypertension developed in F1 hybrids of WKY and SHR rats which received kidney from SHR rats (Kawabe *et al.* 1979, Rettig *et al.* 1989, Rettig and Schmitt 1994). Both media hypertrophy of blood vessels and diffuse arteriosclerosis develop in the SHR from about 12 weeks of age, when hypertension is established in this strain (Lundgren 1974, Folkow 1982, Yamori 1994). This has generally not been regarded as the cause of hypertension in the SHR, but rather as a consequence of high blood pressure. Once vascular hypertrophy has been established, it contributes to the maintenance of hypertension throughout life (Yamori 1994).

The haemodynamic and structural arterial changes in the SHR result in an increase of total peripheral resistance (Albrecht 1974, Folkow 1982, Reed and Tuma 1986, Thomas *et al.* 1990). However, it has been observed that the rise in vascular resistance is not uniform in various organs (Reed and Tuma 1986, Thomas *et al.* 1990). There are surprisingly few comparisons between the SHR and the WKY about haemodynamic differences in various vascular beds (Albrecht 1974, Nishiyama *et al.* 1976, Natsume *et al.* 1985, Reed and Tuma 1986, Thomas *et al.* 1990) and most of these studies include only a small number of observations. Furthermore, although cerebral involvement has been suggested as a pathogenetic mechanism in the development of hypertension in the SHR and the brain might be greatly damaged by raised blood pressure in terms of stroke, differences in cerebral blood flow between hypertensive and normotensive rats have not been thoroughly evaluated. In the present study, a comparison of regional and systemic haemodynamics in the SHR and WKY was performed in a large number of rats with special emphasis on regional cerebral blood flow.

Methods

Male Wistar-Kyoto (WKY) and spontaneously hypertensive rats (SHR) were obtained from Möllegaard, Denmark. The study was approved by the Animal Ethics Committee of the University of Uppsala. The animals were housed at the hospital research center in air conditioned rooms with controlled lighting (12 hours light and 12 hours dark per day), temperature (21 °C) and humidity (55 %) for at least one week before the studies. The animals had free access to water and food (rat pellets R 36, Lactamin Co., Sweden). Cages were of standardized size (model 4, Makrolon) and contained maximally 5 animals in each cage. Twenty-six normotensive Wistar-Kyoto rats (WKY) and 32 spontaneously hypertensive rats (SHR) were included. The rats were of the same age (12–16 weeks), an age at which hypertension has been established and irreversible hypertrophy of arterioles has been shown in the SHR (Folkow 1982, Yamori 1994). Their body weight varied from 260 to 370 g. Acid-base analysis was performed before and after the experiments (ABL 300 and Osm 3, Radiometer, Copenhagen, Denmark). The values of pO_2 and pCO_2 after the experiments are shown in Table 1. Regional blood flow (Q) and central haemodynamics were determined by the radioactively labelled microsphere method. The mean arterial blood pressure (MAP) and heart rate were recorded continuously (Transducer: p50 Gould Statham, England; Amplifier: Siemens, Germany; Recorder: Mingocard 7, Siemens Elema, Sweden).

Anaesthesia and operative procedures

All animals were anaesthetized intraperitoneally with thiobutabarbital (120 mg/kg). Body temperature was maintained at about 37 °C by a thermistor-controlled heating pad (Atew, Sweden) and a lamp.

The animals were tracheotomized and breathed spontaneously. Both femoral arteries were cannulated with polyethylene tubing of 0.58 mm inner diameter (i.d.) for continuous blood pressure and heart rate recordings and collection of blood samples. One femoral vein was cannulated for slow infusion of saline (rate 1–1.5 ml/h). The right common carotid artery was cannulated with straight narrow tubing (i.d. 0.40 mm) to make heart catheterization possible. Position in the left ventricle was assessed by pressure registration and controlled during dissection at the end of the experiment. The microspheres were given in the left heart ventricle during the experiments. At the end of operative procedures, heparin (500 U/kg) was given i.v. to prevent clogging of catheters.

Microsphere procedure

Regional blood flow was determined with 15 μm radioactive microspheres (Hillerdal 1987, Koskinen 1989). Spheres labelled with ^{141}Ce were used for the determination of blood flow. Approximately 500 000 spheres were diluted in saline to a total volume of approximately 0.3 ml. A small amount of blood was aspirated prior to the injection from the left heart ventricle and care was taken to ensure a homogeneous solution. The injection was performed over 15–20 s and sampling of reference blood in one femoral artery started simultaneously and continued for 1 min. The sample was obtained by constant suction of blood from the artery tubing connected to a peristaltic pump at a rate of approximately 0.6 ml/min (P-1, Pharmacia Fine Chem., Sweden). Tubing length was minimized to about 25 cm (i.d. 0.58 mm in the artery and i.d. 1.0 mm in the pump). After the sphere injection a small amount of blood (0.1 ml) was aspirated. The exact amount of radioactivity injected could be calculated by

taking small aliquots (10 μl) of the initial sphere volume before and of the diluted aspirated volume after the sphere injection for gamma counting. Cardiac output (CO) was then calculated by multiplying the total amount of administered radioactivity with the reference flow, divided by the radioactivity in the reference blood sample. Cardiac index (CI) was defined as CO/body weight, bw (kg). The index of total peripheral vascular resistance (TPRI) was obtained by dividing the average of mean arterial pressure (MAP) during the sphere injection by the CI.

The animals were then given a lethal dose of anaesthesia i.v., followed by a KCl injection causing immediate cardiac arrest. Several tissue samples from both sides of the brain, (frontal cortex, thalamus, caudatus, medulla, pons and cerebellum) and the hypophysis (whole organ), both kidneys (whole organs), skeletal muscles (biceps and triceps brachii), skin (from the left foreleg), heart (apical area of left ventricle), stomach (antral section), duodenum (2 cm distal of the pylorus), thyroid gland (left lobe), left adrenal gland (whole organ) and the pancreas were dissected for measurement of CPM (counts per minute) in a gamma spectrometer (Nuclear Chicago, USA). In order to obtain the correct activity, background activity was taken into consideration for the sphere measurements. Both the tissue samples and the reference flow samples were weighed and local blood flow (Q) and peripheral vascular resistance (R) were related to tissue weight (g). Q was calculated by multiplying tissue CPM with the reference flow and dividing by reference CPM. Blood flow values are given as g/min/g (tissue weight, tw). With a blood density of approximately 1.05 g/ml a flow value of 1 g/min/g (tw) corresponds to 0.95 ml/min/g (tw). R was calculated by dividing the average MAP during the sphere injection with Q and presented as mm Hg/g/min/g (tw). The average MAP during sphere injections was used to avoid the influence of small MAP fluctuations during sphere injection on the calculations of TPRI and peripheral vascular resistance.

Drugs

Heparin was diluted to 500 U/ml from a stock solution of 5000 U/ml (Lövens, Denmark). Inactin (Sodium thiobutabarbital) was purchased from RBI Co (Natick, MA, USA) and potassium chloride from Sigma (St Louis, MO, USA). Radioactively labelled microspheres (^{141}Ce) were obtained from Dupont in normal saline with 0.01 % Tween (Wilmington, USA).

Statistical analysis

Statistical analysis was carried out with unpaired Student's t-test. A parametric test was used since evaluation revealed normal distributions for the variables. All values were given as the mean ± S.E.M. and $p<0.05$ was regarded as significant.

Table 1. Resting levels of systemic haemodynamics, pO_2, pCO_2 and body weight in the WKY (n=26) and the SHR (n=32)

	WKY	SHR	WKY vs SHR
MAP (mm Hg)	94±2	165±3	$p<0.001$
TPRI (mm Hg/g/min/kg)	0.55±0.08	1.05±0.06	$p<0.001$
Heart rate (beats/min)	266±6	330±6	$p<0.001$
CI (g/min/kg)	210±15	166±7	$p<0.01$
pO_2 (kPa)	10.6±0.3	13.3±0.3	$p<0.001$
pCO_2 (kPa)	6.0±0.2	5.4±0.2	$p<0.05$
Body weight (kg)	0.312±0.001	0.317±0.002	

Data are means ± S.E.M., MAP = mean arterial blood pressure, TPRI = total peripheral vascular resistance index, CI = cardiac index

Results

The most pronounced differences between the strains in systemic haemodynamics were observed in the MAP and the TPRI, which were 75 % and 90 % higher in the SHR compared to the WKY, respectively (Table 1). However, the heart rate was also significantly increased by 25 %, whereas CI was significantly lower (−20 %) in the SHR compared to the WKY (Table 1).

In both strains, the highest blood flow, when related to tissue weight, was found in the heart, thyroid gland, kidneys and some of the other visceral organs (Table 2). During anaesthesia, very low blood flow was

seen in skeletal muscles and the skin. The distribution of blood flow was different in most organs of the SHR compared to the WKY (Figs 1 and 2) with lower blood flow in the kidneys, skeletal muscle, skin, spleen, stomach, duodenum, pancreas and the hypophysis (Tables 2 and 3). In some tissues, such as the heart, and most cerebral areas, except for the brainstem, significantly higher blood flow was found in the SHR (Tables 2 and 3). The fraction of the cardiac index that supplied each kidney was significantly higher in the WKY than in the SHR (9.8±0.6 % versus 6.5±0.3 % for each kidney, $p<0.001$). Both the renal fraction of cardiac index and the absolute values for blood flow were very similar in the left and the right kidney in both strains, indicating reliable handling with homogeneous sphere solutions.

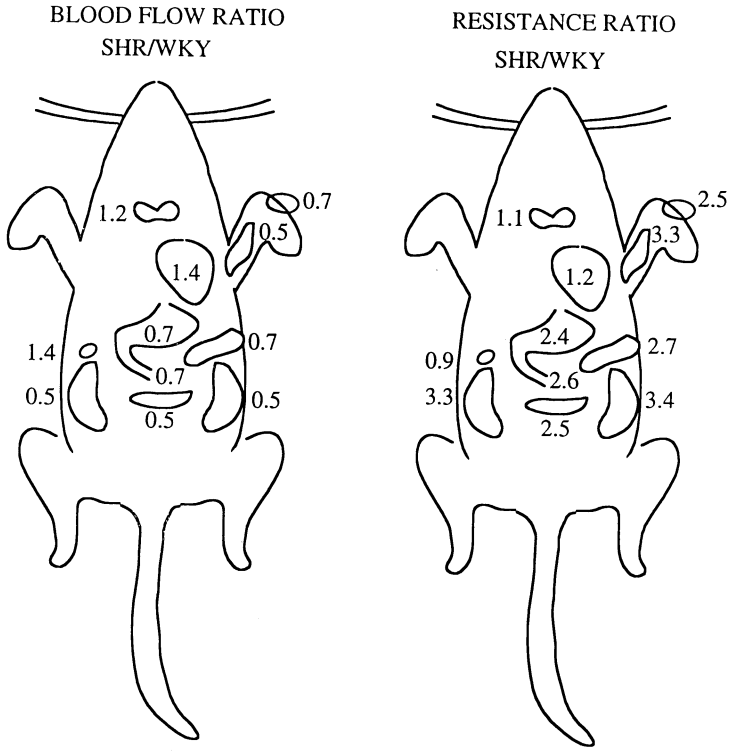

Fig. 1. *Left section indicates blood flow ratio between SHR and WKY and right section indicates vascular resistance ratio between SHR and WKY. Ratios are calculated by dividing the mean value for blood flow in the SHR with the mean value for WKY. The ratios for vascular resistance were calculated similarly.*

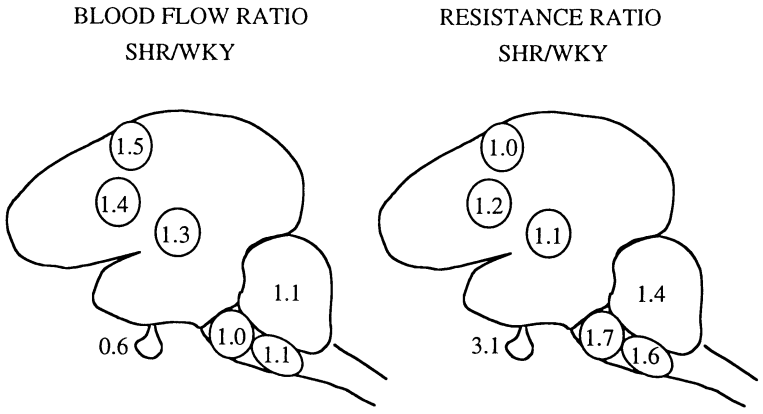

Fig. 2. *Left section indicates cerebral blood flow ratio between SHR and WKY and right section indicates cerebral vascular resistance ratio between SHR and WKY. Ratios are calculated by dividing the mean value for blood flow in the SHR with the mean value for WKY. The ratios for vascular resistance were calculated similarly.*

Most of the examined tissues showed a significantly higher vascular resistance in the SHR than in the WKY (Figs 1 and 2). This was most pronounced in the kidneys, skeletal muscle, skin, spleen, stomach, duodenum and the hypophysis (Figs 1 and 2, Tables 2 and 3). The only tissues examined which had similar vascular resistance in the two strains were the heart, adrenal gland, thyroid gland and some cerebral areas, such as the cerebral cortex.

The operative procedure involved ligation of the right carotid artery. Blood flow was measured in both the left and right hemisphere. Similar levels of blood flow and vascular resistance in both hemispheres were obtained from all parts of the brain in both strains. Only data from the left hemisphere are presented in detail (Table 3).

Table 2. Regional blood flow and peripheral vascular resistance in WKY and the SHR in different organs

Organ	Blood flow g/min/g (tw)		Vascular resistance mm Hg/g/min/g (tw)	
	WKY	SHR	WKY	SHR
Left kidney	5.89±0.35	2.97±0.15***	18±2	62±6***
Right kidney	5.93±0.35	3.07±0.15***	18±2	60±6***
Heart	4.94±0.49	6.91±0.44**	23±2	27±2
Biceps	0.14±0.01	0.07±0.01***	866±99	2827±257***
Triceps	0.12±0.01	0.07±0.01***	948±112	2998±217***
Skin	0.17±0.02	0.12±0.01**	659±58	1645±111***
Spleen	1.06±0.06	0.73±0.04***	95 ±5	256±20***
Stomach	1.88±0.19	1.27±0.11**	67±8	158±12***
Duodenum	5.24±0.42	3.71±0.24**	20±1	51±4***
Adrenal gland	2.17±0.36	3.12 0.36	100±21	91±19
Thyroid gland	8.11±1.31	9.98±1.42	23±5	25±3
Pancreas	1.30±0.22	0.61±0.10**	241±79	595±108*

*Data are means ± S.E.M., *p<0.05, **p<0.01 and ***p<0.001, unpaired Student's t-test WKY vs SHR.*

Table 3. Regional blood flow and peripheral vascular resistance in the WKY and the SHR from the left side of the brain

Organ	Blood flow g/min/g (tw)		Vascular resistance mm Hg/g/min/g (tw)	
	WKY	SHR	WKY	SHR
Thalamus	0.63±0.06	0.84±0.06*	207±32	236±22
Caudatus	0.56±0.06	0.80±0.06**	213±27	253±27
Cortex	0.49±0.04	0.73±0.04***	241±27	249±15
Medulla	0.71±0.06	0.76±0.08	152±12	249±15***
Pons	0.81±0.05	0.82±0.04	128±9	214±10***
Cerebellum	0.80±0.06	0.90±0.05	135±11	196±10***
Hypophysis	1.60±0.18	0.92±0.10**	80±11	249±32***

Data are means ± S.E.M., *p<0.05, **p<0.01 and ***p<0.001, unpaired Student's t-test WKY vs SHR.

Discussion

In this large microsphere study, reduced blood flow was found in the main organs regulating total vascular resistance in the SHR compared with the WKY. However, despite the lower cardiac index, blood flow was significantly elevated in the SHR in some tissues, such as the heart and in some cerebral areas.

In several studies, including the present one, TPRI has been shown to be increased in the SHR compared to the normotensive rat (Albrecht 1974, Folkow 1982, Yamori 1983, Natsume *et al.* 1985, Thomas *et al.* 1990). An increase in TPRI has already been demonstrated at 8 weeks of age (Albrecht 1974). Before hypertension had been established in the SHR, a hyperdynamic stage with increased cardiac output has

been shown (Albrecht 1974, Smith and Hutchins 1979, Folkow 1982). At the age of 12–18 weeks, several authors found no difference in cardiac output between SHR and normotensive rats (Albrecht 1974, Reed and Tuma 1986, Natsume *et al.* 1985, Thomas *et al.* 1990). However, using a large number of rats in each group, we found a significantly lower cardiac index in the hypertensive rats despite a higher heart rate. A reduced basal cardiac index in the SHR has previously been reported to occur only in elderly SHR (Pfeffer *et al.* 1979), but in our study it was also present at this early phase of established hypertension. In this study, blood flow was lower in the SHR in the main organs regulating TPRI, such as the kidneys, other visceral organs, skeletal muscles and the skin in accordance with a previous study (Kimura *et al.* 1988). However, some previous studies reported attenuated blood flow in only a few organs such as the kidneys (Reed and Tuma 1986, Thomas *et al.* 1990), skeletal muscles (Thomas *et al.* 1990) or the skin (Natsume *et al.* 1985), while one study reported no impairment of regional blood flow in the SHR (Nishiyama *et al.* 1976). It is possible that the lower blood flow in several organs of the SHR could partly be due to a reduced cardiac index. However, the reduced blood flow in the kidneys, other visceral organs and skeletal muscles of the SHR was much lower than could be explained by the difference in cardiac index. The total fraction of cardiac output to the kidneys was previously shown to be 20 % in both SHR and WKY (Nishiyama *et al.* 1976). However, in the present study the kidneys together received about 20 % of cardiac output in the WKY compared to 13 % in the SHR, in agreement with Thomas *et al.* (1990).

Both in the present and in previous studies, higher vascular resistance was found mainly in the kidneys, skeletal muscle, skin and the gastrointestinal tract in the SHR compared to the WKY (Natsume *et al.* 1985, Reed and Tuma 1986, Thomas *et al.* 1990).

A higher myocardial blood flow in the hypertensive rat compared to the normotensive rat was observed in the present investigation in accordance with previous studies (Albrecht 1974, Nishiyama *et al.* 1976, Natsume *et al.* 1985, Thomas *et al.* 1990). The increase in myocardial blood flow might be a consequence of the increased myocardial oxygen consumption generated by the hypertrophied left ventricle in the hypertensive rat. However, at this stage of hypertension no increase in myocardial vascular resistance was found in the SHR, in agreement with otherts (Natsume *et al.* 1985, Thomas *et al.* 1990).

Although it has previously been reported that the cerebral blood flow is increased in the SHR (Thomas *et al.* 1990), no detailed analysis of differences in the haemodynamics in different cerebral regions study has been performed. In the present experiments, cerebral overperfusion was found in higher cerebral areas, such as the thalamus, caudatus and cortex, while the blood flow in the cerebellum and brainstem was not altered in the SHR. These findings could be interpreted in two ways. First, the autoregulation in the higher parts of the brain is not as sufficient as in the brainstem of the SHR. Secondly, the metabolic demand is increased in the higher cerebral areas of the SHR, and indeed an increased mental alertness has been advocated as a possible pathogenetic factor in the SHR (Yamori 1977, Folkow 1982). It remains to be investigated if these alterations in cerebral perfusion are involved in the early structural changes in cerebral arterioles and in the pathogenesis of stroke so commonly seen in elderly SHR. The Circle of Willis is known to be very efficient in the rat. However, in a previous report on normotensive rats, a 20% decrease in cerebral blood flow occurred on the side of surgical carotid artery occlusion (Tuma *et al.* 1986). In contrast, in the present study, ligation of the right carotid artery did not affect cerebral blood flow either in normotensive or hypertensive rats, suggesting a well preserved Circle of Willis at this age also in hypertensive animals.

The breathing of the WKY rats seemed to be somewhat more sensitive to the depressing effect of barbiturate anaesthesia compared to the SHR rats. In both strains, much care was taken to achieve an adequate anaesthetic level before the operation started. The lower pO_2 and slightly higher pCO_2 in the WKY seemed to mainly reflect a different breathing pattern during the anaesthesia, since no signs of inadequate anaesthetic level such as pain sensitivity, unstable blood pressure or unstable heart rate were observed.

In conclusion, the SHR showed a raised blood pressure due to an elevated vascular resistance in the main organs regulating blood pressure. Cardiac output was reduced and differently distributed in the SHR compared to the WKY with an increased blood flow in the heart and higher cerebral regions in the SHR.

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Reprint requests

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