Mechanism of Elevation of Hindquarter Vascular Resistance in Spontaneously Hypertensive Rats

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Abstract In spontaneously hypertensive rats and normotensive control rats in the conscious state, hindquarter flow was observed with an electromagnetic flow probe chronically implanted around the terminal aorta. In separate groups of hypertensive and control rats, arterial pressure was observed with an indwelling catheter inserted into the terminal aorta. On ganglion blockade with hexamethonium bromide, hindquarter flow tended to increase in hypertensive rats and to decrease in normal rats. The percent change of hindquarter flow on ganglion blockade was significantly greater in the former than in the latter (p < 0.05). Hindquarter peripheral resistance, estimated from flow and pressure values obtained in separate rat groups, was greater in hypertensive rats than in normal rats before ganglion blockade, but there was no difference between the groups after blockade. Presumably, an elevated sympathetic tone is responsible for the higher hindquarter peripheral resistance in spontaneously hypertensive rats, which plays an important part in the elevation of total peripheral resistance. However, bilateral lumbar sympathectomy did not induce chronic lowering of arterial pressure in hypertensive rats. This was at least partly due to the development of denervation supersensitivity.

Key words: SHR, muscle flow, sympathetic tone, denervation supersensitivity.

Hypertension of spontaneously hypertensive rats (SHR) (Okamoto and Aoki, 1963) is sustained by an elevation of total peripheral resistance with an almost normal cardiac output. The elevation of vascular resistance is not uniformly distributed over the whole body but is especially marked in the hindquarter area supplied by the terminal aorta (Iriuchijima, 1983). In this area the elevation of vascular resistance is about 50% more intense than the average over the whole body. The decrease in vascular conductance, inverse of resistance, in this area accounted for about 40% of the decrease of total conductance. In other words, should the vascular abnormality in this area be eliminated, the hypertension of SHR would be
corrected by about 40%.

The aim of the present study was to clarify the mechanism of the elevation of vascular resistance in the hindquarter area of SHR. Observations of hindquarter flow and arterial pressure in conscious SHR and normotensive control rats before and after ganglion blockade point to an elevated sympathetic tone as the major mechanism.

METHODS

Rats. Male SHR and normotensive control Wistar rats (NCR) 10–20 weeks of age were used in this study. All experiments were performed on conscious rats in their home cage environment, 2–6 days postsurgery.

Flow probe implantation. Rats were anesthetized with thiamylal sodium (50 mg/kg, i.p.) and placed right side down. A longitudinal skin incision was made from the left iliac crista cranially for about 3 cm. The thoracolumbar fascia was cut and the terminal portion of the abdominal aorta was reached retroperitoneally. After separating the aorta from the adjacent vena cava, a Nihon Kohden flow probe with an internal diameter of 1.5 or 2 mm was placed around the aorta. After suturing the fascia around the lead wire from the probe, the wire ending in a plug was tunneled subcutaneously, exteriorized, and fixed in the dorsal neck by suturing to neck muscles so that the plug was placed outside the skin.

Arterial catheter. The catheter for measurement of arterial pressure was prepared by fusing a PE 20 polyethylene tube to a PE 10. The thinner part (PE 10) was inserted into a femoral artery so that the tip was placed in the terminal aorta. The thicker part was tunneled subcutaneously and exteriorized in the dorsal neck. Each rat was implanted with either a flow probe or an arterial catheter.

Venous catheter. The indwelling catheter for intravenous injection was prepared using the same polyethylene tubes as those used for the arterial catheter. The thinner end was inserted into the right external jugular vein and the thicker end was also exteriorized in the dorsal neck. All rats were implanted with a venous catheter.

Lumbar sympathectomy. A midline incision was made in the abdomen, and the viscera were retracted to expose the aorta and vena cava below the left renal vessels. The bilateral lumbar sympathetic chains were found under the abdominal aorta, about 2 mm apart. They were cut at the level of the left renal vein and the chains below the cut were removed down to their confluence.

In some rats this operation was performed simultaneously with implantation of the flow probe or arterial catheter. In others sympathectomy was performed after observations with intact lumbar sympathetic chains were completed. In either, flow and pressure were observed 2–4 days after sympathectomy.

Recording. After surgery each rat was housed individually in a white polyethylene cage measuring approximately 35×30×17 (depth) cm. The floor of the
Cage was covered with wood chips. Water and pellets were given ad libitum. For flow measurement, an external cable from the flowmeter circuit (Nihon Kohden MFV-1100) was connected to the plug of the flow probe. Arterial pressure was measured by connecting a polyethylene tube from a pressure transducer to the arterial catheter. The cable and tube were flexible enough to allow the rat to move almost freely in the cage during recording. Most recording was done in the morning. Both flow and pressure were recorded with a Nihon Kohden RJG-3024 recticorder.

Continuous injection of drugs. For this purpose a Natsume KN-201 micro-injector was employed. This instrument pushed the piston of a 1 ml tuberculin syringe at a speed of 0.76 mm/min and injected the fluid in the syringe at a rate of 0.032 ml/min through a polyethylene tube (PE 20) connected to the venous catheter. Hexamethonium bromide, a ganglion blocker, was routinely injected at a rate of 0.8 mg/min for a total dose of 25 mg/kg. In both SHR and NCR, arterial pressure was lowered to a horizontal level long before the completion of the injection of this drug. The injection rate of catecholamines was adjusted by changing dilution ratios with 0.9% NaCl according to the body weight. Injection was continued for 1–2 min until the flow or pressure reached a new plateau level. After that, flow or pressure was allowed to return to baseline before the next injection was started. Dl-Noradrenaline and l-adrenaline were routinely injected at 0.1, 0.2, 0.5, and 1 µg/(kg·min) and dl-isoproterenol HCl at 0.01, 0.02, 0.05, and 0.1 µg/(kg·min). No expression of discomfort was observed in the rats during injection of any drug at any injection rate employed.

Estimation of hindquarter peripheral resistance. Probe implantation around the terminal aorta and cannulation to the terminal aorta were not performed in the same rat to avoid possible intervention of the latter to the hindquarter flow. The cannulation might also interfere with the arterial pressure itself. However, in no rat in the present study did the hind limb, in which femoral artery had been ligated for cannulation, present obvious signs of circulatory disturbance. Since the hind limb was nearly adequately perfused, the intervention to the systemic pressure was supposed to be slight, if present at all. Some collateral flow to the limb distal to cannulation might be supplied from the aorta at levels higher than the usual site of probe application. Therefore, it seemed adequate to avoid implantation of both probe and catheter in one rat.

Although flow and pressure were observed in separate rat groups, the mean pressure in one rat group under one set of experimental conditions was divided by the mean hindquarter flow in another group measured under the same conditions, to obtain a rough estimation of hindquarter peripheral resistance under the particular conditions.

Estimation of percent change of hindquarter peripheral resistance. The effect of injected catecholamines was expressed as percent change of flow or pressure. Percent change of hindquarter peripheral resistance was estimated by subtracting
the mean percent change of hindquarter flow from the mean percent change of arterial pressure. The justification for this treatment is as follows.

Denoting arterial pressure by $P$, hindquarter flow by $q$, and hindquarter peripheral resistance by $r$,

$$P = rq.$$  

If we denote a small change of each variable by the prefix $\Delta$,

$$P + \Delta P = (r + \Delta r)(q + \Delta q)$$

$$\simeq rq + r\Delta q + q\Delta r.$$  

Dividing both sides by $P = rq$, we obtain

$$\frac{\Delta P}{P} \simeq \frac{\Delta q}{q} + \frac{\Delta r}{r},$$

or

$$\frac{\Delta r}{r} \simeq \frac{\Delta P}{P} - \frac{\Delta q}{q}.$$  

In the present study the above calculation was routinely executed even with percent changes of flow and pressure too large to be called "small" changes. This is permitted because this calculation was performed only to obtain some estimates for resistance changes.

Statistical treatment. Significance was determined by Student’s $t$-test.

RESULTS

Change of hindquarter flow on ganglion blockade

Figure 1 presents one example each of hindquarter flow recording in SHR and NCR when hexamethonium bromide was infused at a constant rate for the underlined period for a total dose of 25 mg/kg. The hindquarter flow was increased by

![Graph showing hindquarter flow changes](image)

Fig. 1. The effect of intravenous infusion of hexamethonium bromide (C6) at a rate of 0.8 mg/min for the underlined period for a total dose of 25 mg/kg on hindquarter flow recorded at the terminal aorta in a spontaneously hypertensive rat (SHR) and a normal control rat (NCR) in the conscious state. Note that the flow increased in the SHR and decreased in the NCR. These were rather extreme examples, but by and large the flow tended to increase in SHRs and to decrease in NCRs.
Ganglion blockade in this particular SHR and decreased in this particular NCR. These examples in Fig. 1 were both rather extreme instances, but, by and large, the flow tended to increase on ganglion blockade in SHR and to decrease in NCR.

The mean values ± S.D. of hindquarter flow from 7 SHR and 9 NCR before and immediately after completion of hexamethonium injection are presented in Fig. 2 at the top left. The percent change of flow on ganglion blockade was significantly greater in SHR than in NCR (p < 0.05).

**Lowering of arterial pressure on ganglion blockade**

The mean arterial pressures ± S.D. from 6 SHR and 6 NCR before and after ganglion blockade with hexamethonium (25 mg/kg, i.v.) are presented in Fig. 2 at the middle left. Although the percent decrease in pressure on ganglion blockade did not differ between the groups (−32.5 ± 6.18 % vs. −23.3 ± 7.70 %, 0.05 < P < 0.1), the absolute decrease in arterial pressure on blockade was greater in SHR than in NCR (−48.8 ± 9.48 mmHg vs. −27.4 ± 10.6 mmHg, P < 0.01).
Fig. 3. Effects of intravenous infusion of noradrenaline for underlined periods at rates as indicated on hindquarter flow in an SHR with intact sympathetic chain (top) and in a lumbar sympathectomized SHR (bottom). Note that the decrease in flow on infusion was more marked in the sympathectomized. Flow is proportional to the deflection from the zero flow baseline.

Fig. 4. Effects of noradrenaline infusion on hindquarter flow (HQF), arterial pressure (AP), and estimated hindquarter resistance (HQR). Filled circles, SHR with intact lumbar sympathetic chain; open circles, NCR with intact lumbar sympathetic chain; filled triangles, lumbar sympathectomized SHR; open triangles, lumbar sympathectomized NCR. For HQR and AP, mean±S.D., n=all 5.
**HINDQUARTER RESISTANCE IN HYPERTENSIVE RATS**

Estimated hindquarter peripheral resistance before and after ganglion blockade

The results are presented in Fig. 2, at the bottom left. From these estimated values, one may assume that hindquarter peripheral resistance was greater in SHR than in NCR before blockade but equalized after blockade. In NCR the estimated hindquarter resistance remained almost unchanged on ganglion blockade.

Hindquarter flow and arterial pressure after lumbar sympathectomy

Since the above findings point to participation of the sympathetic nerves in the elevated hindquarter resistance in SHR, observations of hindquarter flow and arterial pressure were repeated in SHR and NCR after bilateral lumbar sympathectomy.

The results are summarized in Fig. 2, right. The tendency to increase on ganglion blockade of hindquarter flow in SHR was not observed after lumbar sympathectomy. Although the mean hindquarter flows before ganglion blockade were greater in lumbar sympathectomized SHR and NCR than each corresponding values with intact lumbar sympathetic chains, the difference was not significant in either group. Lumbar sympathectomy did not induce chronic lowering of arterial pressure in either SHR or NCR. The decrease in arterial pressure on ganglion blockade did not differ between the groups (−39.8±15.0 mmHg for SHR and −35.6±6.15 mmHg for NCR). The decrease in the estimated hindquarter flow resistance on blockade in SHR was greatly diminished after lumbar sympathectomy. The estimated hindquarter resistance was about 25% larger in SHR than NCR even after blockade.

Effects of catecholamines on hindquarter flow and arterial pressure

This experiment was performed with the original intention of evaluating denervation supersensitivity after lumbar sympathectomy. However, it also furnished information that confirms the presence of elevated sympathetic tone to the hindquarter area in SHR.

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Noradrenaline. As seen in Figs. 3 and 4, without lumbar sympathectomy in both SHR and NCR, noradrenaline at the infusion rates employed in this study induced no appreciable changes of hindquarter flow. However, in sympathectomized SHR, noradrenaline diminished hindquarter flow significantly at the infusion rates of 0.5 ($p<0.05$) and 1 $\mu$g/(kg·min) ($p<0.01$). At these two infusion rates arterial pressure was elevated in sympathectomized SHR as in unsympathectomized SHR (Fig. 4, middle). Estimated peripheral resistance was elevated markedly in sympathectomized SHR and NCR at higher infusion rates (Fig. 4, bottom). These differences observed between sympathectomized and unsympathectomized rats may be ascribed to denervation supersensitivity. It appeared that denervation supersensitivity occurred similarly in both SHR and NCR.

Adrenaline. As shown in Figs. 5 and 6, infusion of adrenaline increased hindquarter flow markedly in unsympathectomized NCR without appreciable change in arterial pressure. In unsympathectomized SHR, the increase in flow was less marked. For example, at the infusion rate of 1 $\mu$g/(kg·min), the percent increase in flow in NCR was significantly greater than that in SHR at $p<0.001$. After lumbar sympathectomy...
Fig. 7. Effects of isoproterenol on hindquarter flow in an SHR (top) and an NCR (bottom). Note that the flow increase was more marked in the latter.

Fig. 8. Summary data of isoproterenol infusion. For details, see the legend for Fig. 4.
sympathectomy, in both SHR and NCR, the increase in hindquarter flow on adrenaline infusion was slight, if present at all.

*Isoproterenol.* Without lumbar sympathectomy, this drug too increased hindquarter flow more markedly in NCR than in SHR (Figs. 7 and 8). For example, at the infusion rate of 0.02 μg/(kg·min), this drug increased hindquarter flow in NCR significantly at $p<0.05$ but not in SHR. Such a difference between NCR and SHR was not observed after lumbar sympathectomy, as was observed for adrenaline.

**DISCUSSION**

The estimated value of hindquarter peripheral resistance in SHR was about 50% greater than that in NCR (Fig. 2, bottom left). This difference between the groups was abolished by ganglion blockade with hexamethonium bromide (25 mg/kg, i.v.). These findings suggest that the high hindquarter vascular resistance in SHR is maintained by an elevated sympathetic tone.

However, lumbar sympathectomy did not increase the hindquarter flow in SHR significantly. Neither did it lower the arterial pressure of SHR.

Injection of noradrenaline induced a marked decrease in hindquarter flow in lumbar sympathectomized SHR and NCR but not in SHR and NCR with intact lumbar sympathetic chains (Figs. 3 and 4). The denervation supersensitivity, at least partly, accounts for the failure of lumbar sympathectomy to alleviate hypertension in SHR.

Injection of adrenaline and isoproterenol induced more marked increase in hindquarter flow in NCR than in SHR (Figs. 6 and 8). This difference between the groups is consistent with the assumed elevated sympathetic tone in the hindquarter area of SHR, its $\alpha$-adrenergic effect counteracting the $\beta$-adrenergic vasodilating effect of both drugs. After lumbar sympathectomy, adrenaline did not increase hindquarter flow appreciably in either SHR or NCR. This may be due to denervation supersensitivity of the $\alpha$-adrenergic vasoconstrictor mechanism in the hindquarter area.

Elevated sympathetic tone as the cause of hypertension in SHR was first proposed by Okamoto et al. (1967) on the basis of observations of blood pressure and splanchnic nerve activity under anesthesia. Also in anesthetized SHR, the increase in efferent discharge in the splanchnic nerve was quantitated by Iriuchijima (1973). That the sympathetic nerves, in the conscious state as well play an important role in hypertension in SHR was shown by Numao et al. (1975), who observed normalization of total peripheral resistance by ganglion blockade with hexamethonium. Increased sympathetic discharge in conscious SHR was observed with the splanchnic nerve by Judy et al. (1976) and with the renal nerve by Lundin and Thoren (1982) and Lundin et al. (1984). From these studies it is almost certain that elevated sympathetic tone to the splanchnic and renal areas.
participates in the increase in total peripheral resistance in hypertension of SHR. Measurement of flow in the superior mesenteric artery and renal artery revealed, in conscious SHR compared with NCR, that the decrease in conductance in the superior mesenteric area and that in the bilateral kidneys each accounted for about 15% of the decrease in total conductance (IRIUCHIJIMA, 1983).

In the present study, it was shown that the decrease in hindquarter conductance, which accounts for as much as 40% of the decrease in total conductance, was corrected by ganglion blockade (Fig. 2, bottom left). Note that the hindquarter resistance in NCR was almost unaffected by ganglion blockade, which suggests that tonic vasoconstrictor discharge to the hindquarter area is almost non-existent in conscious NCR. It is quite understandable that such an area contributes greatly to elevation of total peripheral resistance when constrictor fibers to the area are excited as in SHR. The major part of hindquarter flow is thought to perfuse skeletal muscles in the hind limbs. It is our opinion that the role of the vascular bed in skeletal muscles in SHR hypertension is not at all inferior to that of splanchnic and renal vascular beds.

One might argue against elevated sympathetic tone as the main cause of SHR hypertension by referring to the fact that arterial pressure was still higher in SHR than in normal rats after ganglion blockade (Fig. 2, middle left). However, this is due to a larger cardiac index in SHR than in NCR after ganglion blockade. Total peripheral resistance is somewhat lower in the former than the latter after blockade (NUMAO et al., 1975). The larger cardiac index may be ascribable to left ventricular hypertrophy and some possible change in the capacitance section of the circulatory system of SHR (NILSSON and FOLKOW, 1980; RICKSTEN and THOREN, 1980; RICKSTEN et al., 1980). Since these are structural changes, they are spared by ganglion blockade.

In the conscious state, the hindquarter flow per body weight is smaller in SHR than in NCR at rest, but the increase in the flow in transposition response is greater so that the flow is equalized between SHR and NCR during the response (IRIUCHIJIMA, 1983). The increase in hindquarter flow in transposition response is for the most part ascribable to the \( \beta \)-effect of adrenaline from the adrenal medulla (IRIUCHIJIMA et al., 1982). Among the possible causes for this feature in SHR, therefore, would be the presence of an enhanced \( \beta \)-adrenergic vasodilation in the hindquarters. This was, however, negated by the present study, because injection of adrenaline induced a more marked increase in hindquarter flow in NCR than in SHR (Fig. 6, top). The exaggerated increase in hindquarter flow in transposition response in SHR might be ascribable to inhibition of the vasoconstrictor tone to this area.

The estimated hindquarter resistance after lumbar sympathectomy was still greater in SHR than in NCR after ganglion blockade by about 25% (Fig. 2, bottom right). This suggests that denervation induces some vascular change leading to an increased resistance in SHR alone, besides the denervation supersensitivity which seems to develop similarly in both SHR and NCR.
REFERENCES


