Hindquarter Vascular Resistance as Compensator for Hypotension in Conscious Rats

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The purpose of this study was to test whether hindquarter (terminal aortic) vascular resistance uniquely increases in order to compensate for interventions which result in a lowering of arterial pressure. Changes in hindquarter resistance were compared to changes in superior mesenteric resistance after the administration of the nitrovasodilator drug, molsidomine. Hindquarter blood flow or superior mesenteric flow was measured in conscious rats using an electromagnetic flow probe implanted around the terminal aorta or the superior mesenteric artery, respectively. Twenty minutes after an intravenous bolus injection of molsidomine (1 mg/kg), ganglionic blockade with hexamethonium bromide (25 mg/kg, i.v.) significantly decreased hindquarter resistance, but not superior mesenteric resistance. In the absence of molsidomine, ganglionic blockade has no effect on resistance in either vascular bed. These findings suggest that excitation of sympathetic vasoconstrictor fibers supplying the hindquarters but not those supplying the superior mesenteric area occurred in response to the hypotensive effect of molsidomine. This is consistent with the hypothesis that augmenting-hindquarter resistance is the first line of defense against hypotensive interventions. ——— hindquarter vascular resistance; molsidomine; compensator for hypotension; superior mesenteric flow

In previous studies (Kawaue and Iriuchijima 1984; Teranishi and Iriuchijima 1992), we observed that pentobarbital anesthesia induced a sympathetic vasoconstrictor tone which specifically increased regional vascular resistance in the hindquarter area of the rat. We believe that this was a compensation for the hypotensive effect of the anesthetic since it was almost absent in rats in which the sino-aortic nerves had been severed (Teranishi and Iriuchijima 1992). While the hindquarter resistance was increased following pentobarbital anesthesia, the resistances in the superior mesenteric, carotid, and renal areas were all decreased (Kawaue and Iriuchijima 1984: Iriuchijima and Sakata 1985).

We suspect that this phenomenon is not due to anesthesia per se, but rather
that the hindquarter resistance vessels are available for constriction as a general "compensator" for various kinds of interventions which lead to a lowering of arterial pressure. In the current study, the long acting nitrovasodilator molsidomine was used as the test intervention, and its effect on hindquarter and mesenteric vascular resistance was evaluated.

**Methods**

*Implantation of flow probes and catheters*

Male Wistar rats, (343 ± 35 (mean ± S.D.) g and 13 ± 2 weeks old) were anesthetized with thiamylal sodium (50 mg/kg, i.p.). An electromagnetic flow probe (Nihon Kohden, type FC) with an internal diameter of 1.5 or 2 mm was implanted around the terminal aorta or the superior mesenteric artery (Kawaue and Iriuchijima 1984). Superior mesenteric blood flow was selected for comparison to hindquarter flow because these two flows supply entirely different tissues and because they both are capable of substantially influencing arterial pressure in conscious rats (Iriuchijima et al. 1982). A polyethylene catheter (PE 10 fused to PE 20) for arterial pressure measurement was inserted into the right common carotid artery in rats in which the flow probe was implanted at the terminal aorta, and into the terminal aorta via the right femoral artery in those animals in which the probe was implanted at the superior mesenteric artery. Another catheter was inserted into the right external jugular vein for intravenous injection. The distal ends of the cable from the flow probe and the two catheters were all passed under the skin and exteriorized at the dorsal neck. Arterial pressure and blood flow measurements were obtained two to three days after surgery.

*Recording of blood flow and arterial pressure*

Arterial pressure was measured using a strain gauge transducer and a Nihon Kohden carrier amplifier and blood flow was determined using a Nihon Kohden MFV-1100 electromagnetic flow meter. Flow and pressure were recorded with a rectangular pen-writer, after smoothing the output with an RC low pass filter with a 1 sec time constant. Blood flow was normalized to 100 g of body weight. Peripheral resistance was calculated as arterial pressure divided by blood flow. In a given rat in a given situation, the pressure and flow values noted were the averages when the rat was apparently at rest during the whole length of the situation. All experiments were performed with the rat remaining in the home cage. The baseline values were observed more than 15 min after the start of recording.

*Drugs*

Animals were administered molsidomine (Takeda, Osaka) as a bolus intravenousous dose of 1 mg/kg and the arterial pressure and blood flow responses were recorded. Twenty minutes after molsidomine, a 2.5% (w/v) solution of hex-
amethonium bromide (C6) was infused at a rate of 0.8 mg/min for a total dose of 25 mg/kg. A significant fall of peripheral resistance after ganglionic blockade with C6 was assumed to indicate the presence of regional sympathetic vasoconstrictor tone (Iriuchijima and Sakata 1985).

**Statistical analysis**

Values were expressed as mean±s.d. Two way analysis of variance (ANOVA) was used to test the effect of successive injection of molsidomine and C6 on arterial pressure, regional blood flow, and peripheral resistance. Paired t-test was used for the difference in a variable between two situations.

**Results**

**Hindquarter resistance**

The top part of Fig. 1 shows an example of the effect of ganglionic blockade by infusion of C6 (25 mg/kg) on arterial pressure and hindquarter flow in a rat which had been administered molsidomine (1 mg/kg) about 20 min beforehand. During infusion of C6, arterial pressure was markedly decreased but hindquarter flow remained almost unchanged, hindquarter resistance being decreased.

![Simultaneous recording of arterial pressure (AP) and hindquarter flow (HOF) (top) or superior mesenteric flow (SMF) (bottom) in conscious rats. Twenty min beforehand, rats were administered a bolus i.v. dose of molsidomine (1 mg/kg). For the underlined period hexamethonium bromide (C6) was infused intravenously for a total dose of 25 mg/kg. C6 infusion decreased AP and SMF but not HOF. Near the letters Sc in the HOF recording, the rat was scratching with a hind limb.](image-url)
The successive changes in mean arterial pressure, hindquarter flow, and hindquarter resistance after molsidomine injection and C6 infusion, summarized from 5 rats, are shown in Fig. 2 (left panel). The hypothesis that the variable was unaffected by the two drugs was rejected for the pressure and resistance (both at \( p < 0.01 \)) by ANOVA but not for the flow. The decrease in arterial pressure by molsidomine was insignificant by the paired t-test. Arterial pressure and hindquarter resistance were decreased by C6 significantly at \( p < 0.005 \) for pressure and at \( p < 0.025 \) for resistance.

Superior mesenteric resistance

The parallel experiment was performed observing superior mesenteric flow instead of hindquarter flow. One example of the record is presented in the lower part of Fig. 1 and the summary data from 5 rats in the right part of Fig. 2. This time the hypothesis that the variable was unaffected by the two drugs was rejected.
DISCUSSION

After molsidomine, hindquarter resistance was decreased by ganglionic blockade. Since ganglionic blockade does not decrease hindquarter resistance in normal rats in the absence of molsidomine (Iriuchijima 1988), the data suggest that exciting action of sympathetic vasoconstrictor fibers supplying the hindquarters occurs, presumably as a reflex triggered by the hypotensive effect of molsidomine. Such excitation of regional sympathetic nerves was not observed in the superior mesenteric area after molsidomine. These findings are consistent with the hypothesis that the hindquarter resistance is the "first line of defense" compensator against hypotensive interventions.

One might think that, if C6 given after molsidomine increased vasopression or angiotensin II in the blood and if the superior mesenteric resistance vessels were especially sensitive to either pressor agent, similar results might be obtained despite an excitation of sympathetic vasoconstrictor fibers in the superior mesenteric bed by molsidomine. If this were the case, C6 should decrease superior mesenteric resistance after pretreatment with a vasopressin antagonist and angiotensin converting enzyme inhibitor to follow molsidomine. In two rats, under observation of arterial pressure and superior mesenteric flow, a vasopressin antagonist (Manning compound) and captopril were intravenously injected after injection of molsidomine. Ganglionic blockade with C6 to follow did not decrease superior mesenteric resistance in these two rats either. We consider that these experiments showed that intervention from the vasopressin and angiotensin systems was immaterial.

Primary site of action of molsidomine is thought to be the capacitance vessels and not the resistance vessels (Kikuchi et al. 1970a, b). We thought that a specific effect on capacitance vessels was important for the present study because the constricting capacity of smooth muscle of the resistance vessels must be preserved to allow the hindquarter resistance to act as a compensator for hypotension.

However, since hindquarter resistance was not increased by molsidomine despite the assumed generation of sympathetic tone, it is possible that this drug had some direct dilating effect on the hindquarter resistance vessels. Perhaps this direct effect was compensated for by the constricting effect of the induced sympathetic vasoconstrictor tone in this area to keep hindquarter resistance almost unchanged after molsidomine administration. In one rat the effect of molsidomine on arterial pressure and hindquarter flow was observed after ganglionic blockade with C6. Molsidomine decreased hindquarter resistance by about 20%.
This supports direct dilating effect of molsidomine on the hindquarter resistance vessels. Apparently this effect did not deprive the resistance vessels of their constricting capacity in response to regional sympahtetic vasoconstrictor fiber excitation.

For hypotensive interventions of greater intensity, sympathetic fibers supplying areas other than the hindquarters would also be recruited. However, the anesthetic dose of pentobarbital and the dose of molsidomine used in this study excited sympathetic fibers for the hindquarters but not those for the superior mesenteric area. In other words, of the hindquarter and superior mesenteric resistances, only the hindquarter resistance worked as an effective compensator.

It is unlikely that the carotid and renal resistances would serve as substantial compensators for the following reasons. Firstly, blood flow in these vascular beds is much less than that in the hindquarter and superior mesenteric beds. Secondly, in contrast to the hindquarter and superior mesenteric beds, the carotid and renal beds have considerable resting sympathetic vasoconstrictor tone, which should lessen the responsive constricting capacity of their resistance vessels (Iriuchijima and Sakata 1985). Thirdly, after pentobarbital anesthesia, both carotid and renal resistances decreased (Iriuchijima and Sakata 1985). Since there are no other sizable vascular beds in the rat, the hindquarter resistance may be said to be the unique compensator.

The major role of the hindquarter compensator is presumably played by the resistance vessels of the skeletal muscle in this region. In the cat under chloralose anesthesia, resistance vessels in skeletal muscle are known to have the lowest threshold to be recruited for constriction following baroreceptor inhibition (Folkow 1962). In the conscious rat, whether skeletal muscles in areas other than the hindquarter region also have the same compensator function is not known. In humans, a similar role seems to be played by forearm muscles, since lower body negative pressure increases forearm vascular resistance (Lundvall and Edfeldt 1991).

Vatner et al. (1970, 1974) have observed that, in both dogs and primates in the conscious state, iliac flow decreases postprandially, concomitantly with increased mesenteric flow. It is possible that this phenomenon is an example of the hindquarter compensator at work.

In summary, we have obtained results suggesting that sympathetic vasoconstrictor fibers supplying hindquarter resistance vessels are specifically excited after administration of molsidomine in such a way as to justify calling the hindquarter resistance the “first line of defense” compensator for hypotension.

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References


