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Responses in Portal Venous Flow and Pressure Produced by Cerebral Sympathetic Activation in Rats

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Summary. **Changes in portal venous flow (PVF) and portal venous pressure (PVP) were examined following sympathetic activation with cerebral ischemia in rats. Cerebral ischemia with carotid arterial occlusion (30 s) produced a reduction in PVF concomitant with an increase in PVP, and an inverse relationship between PVF and PVP was detected. Nanomolar quantities of adrenaline injected into the portal vein brought similar responses in PVF and PVP that were seen after cerebral ischemia. The PVF response produced by the ischemia disappeared when the hepatic splanchnic branch or bilateral splanchnic nerve was sectioned. At the same time, the PVP response produced by the ischemia was blocked by sectioning the bilateral splanchnic branches. In contrast, sectioning the hepatic splanchnic branch did not completely abolish the response. In the superior mesenteric vein, blood flow decreased with an increase in pressure after cerebral ischemia; these responses were blocked by sectioning the bilateral splanchnic nerves, but sectioning the hepatic splanchnic branch exerted no influence. Blood flow in the splenic vein was unaffected by the sympathetic activation.**

The results suggest that values of PVF and PVP following stimulation of splanchnic sympathetic nerve are determined by an increase in flow resistance due to the vasoconstriction of the adrenergic vasculature, and that the pressure in the superior mesenteric vein is tonically reflected in the PVP.

INTRODUCTION

Large abdominal splanchnic veins have been shown to participate in blood mobilization of the visceral organs by neurogenic vascular constriction when the sympathetic nerve activity is increased.[1-4] Recently, it was observed that activation of the sympathetic nerve with cerebral ischemia or electrical stimulation of the hepatic splanchnic branch resulted in a decrease in portal venous flow (PVF).[5-7] Moreover, it was evident that the active site of the sympathetic nerve controlling PVF was localized in the hepatic portal vessels.[6] These findings suggest that the sympathetic nerve innervating the portal vein actively contributes to blood mobilization. However, rheologically, there has been no general agreement on the relationship between PVF and portal venous pressure (PVP).[5,8] On the other hand, blood flow in the portal vein is mainly collected from two venous structures[1,9]: the superior mesenteric vein and the splenic vein.

This experiment was designed to investigate whether sympathetic activation influences portal venous flow and pressure in relation to the two structures.

MATERIALS AND METHODS

Animals

Twenty male Wistar rats weighing about 350-400 g were used. They were housed individually (12 : 12 ; light-dark cycle) at room temperatures ranging from 22.0 to 24.0℃, and were fed ad lib on a standard diet with free access to tap water before the experiments. The experiments were carried out in the afternoon (13 : 00-18 : 00 h) to eliminate diurnal changes in sympathetic activity.[10]

Anesthesia and general monitoring

The rats were initially anesthetized with pentobarbital sodium (45 mg/kg, i.p.), and an amount of this agent (10 mg/kg) was injected intramuscularily every

30 min to maintain the depth of the anesthesia.[11] The trachea was intubated to allow adequate ventilation. The aortic and carotid sinus nerves were sectioned bilaterally to eliminate any aortic pressure responses which would affect portal venous flow and portal venous pressure.[12,13]

Systemic arterial pressure was monitored at the right carotid artery. A portion of the portal vein about 0.8 mm long upstream from the cranial pancreaticoduodenal vein was cleared, keeping the nerves intact while separating it from the surrounding connective and fat tissues. Anal temperature was maintained at 37.5±0.5℃ with a heating lamp throughout the experiments.

Estimation of blood flow and pressure

The probe for blood flow estimation was placed around the portal vein, and PVF was measured with an ultrasonic blood flow meter (Transonic T201, Advance, NY). Blood flow in the superior mesenteric vein or in the splenic vein was also estimated with the same probe.[6,14] A small catheter was inserted into the portal vein or into the superior mesenteric vein to measure intravascular pressure.[14] The data were recorded on a pen writing recorder (SR6221, Graphtec, Tokyo).

Sympathetic activation with cerebral ischemia

Cerebral ischemia was obtained by occluding both carotid arteries. Duration of the occlusion was fixed at 30 sec based on a report that carotid arterial occlusion for 30 sec provokes reproducible reduction in PVF through cerebral sympathetic activation in the rat.[6] A heifetz clip (Edward weck, NC) was applied for occlusion.

Sectioning nerve

The abdominal sympathetic pathway was sectioned at the required position by the method described earlier:[15] a loose thread was looped around the nerve, then both ends of the thread were passed through a plastic tube so that the nerve could be cut by closing the loop of the thread.

Adrenaline injection

Adrenaline (Wako, Osaka) dissolved in physiological saline was injected into the portal vein, over a period of 20s, by means of an infusion pump. Physiological saline was used as the control.

Data analysis

The data were ANOVA analyzed, and specific values were evaluated with Duncan's multiple range test: $p<0.05$ was defined as significant. Regression analysis was also utilized.

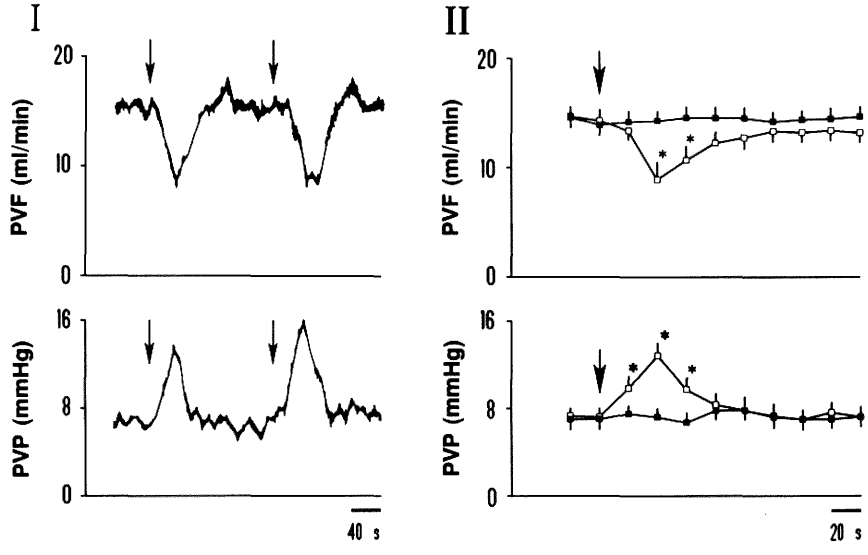

Fig. 1. I. Representative response in PVF and PVP to 30-s carotid arterial occlusion. Arrows indicate the start of occlusion. II. PVF and PVP with (□) or without (■) the occlusion. Arrows show the start of occlusion. Values are the mean ± SEM (n=6). *$p<0.01$ vs ■.

RESULTS

PVF and PVP associated with cerebral ischemia

When carotid arterial occlusion was applied for 30 sec, PVF was transiently reduced. The response reached its nadir about 40 sec after the occlusion, then recovered to the control level within another 2 min (Fig. 1). ANOVA revealed that the differences among groups and times were reliable, with $F_{1,119}=23.053$, $p<0.005$ and, $F_{9,119}=3.168$, $p<0.005$, respectively. PVP was increased following the occlusion, and its peak was seen 40 sec after occlusion, returning to the control level within another 2 min (Fig. 1). The differences among groups and times were significant, with $F_{1,119}=13.075$, $p<0.005$ and $F_{9,119}=3.137$, $p<0.005$, respectively. Nadir PVF and peak PVP values were observed approximately 40 sec after the occlusion. Using these findings, the levels of PVF and PVP 40 sec after the occlusion were compared.

Relationship between PVF and PVP

A significant correlation between PVF and PVP was detected from the values obtained immediately before and 40 sec after cerebral ischemia (Fig. 2). The regression coefficient ($r=-0.893$) was significant, $p<0.01$.

Effects of adrenaline on PVF and PVP

Adrenaline injected into the portal vein brought a reproducible fall in PVF concomitant with an increase in PVP (Fig. 3). The responses in PVF and PVP due to the agent were dose-dependent. The differences in PVF and PVP among groups were ANOVA significant, $F_{3,23}=18.438$, $p<0.01$ and $F_{3,23}=33.541$, $p<0.01$, respectively.

PVF and PVP following splanchnicectomy

A transient fall in PVF with an increase in PVP was seen immediately after the nerve was interrupted. However, such a response disappeared within 10s after treatment. The reduction in PVF caused by cerebral ischemia was not significant when both splanchnic nerves were sectioned. Moreover, it was noted that the PVF response due to the ischemia was substantially inhibited by sectioning the hepatic splanchnic branch (Fig. 4). On the other hand, PVP response due to the ischemia was not reproduced when both splanchnic nerves were sectioned. Furthermore, this response was not completely blocked by sectioning the hepatic splanchnic branch (Fig. 4). The differences in PVF and PVP among groups were ANOVA reliable, $F_{3,23}=30.030$, $p<0.01$, and $F_{3,23}=27.512$, $p<0.01$, respectively.

Mesenteric venous flow and pressure due to cerebral ischemia

Blood flow and its pressure in the superior mesenteric vein were altered in response to cerebral ischemia: the flow decreased and the pressure increased simultaneously (Fig. 5). Although sectioning both splanchnic nerves eliminated the response, no appreciable effect on the mesenteric flow and pressure was seen when the hepatic splanchnic branch was sectioned. The differences in PVF and PVP among groups were ANOVA significant, $F_{3,23}=11.738$, $p<0.01$ and $F_{3,23}=17.379$, $p<0.01$.

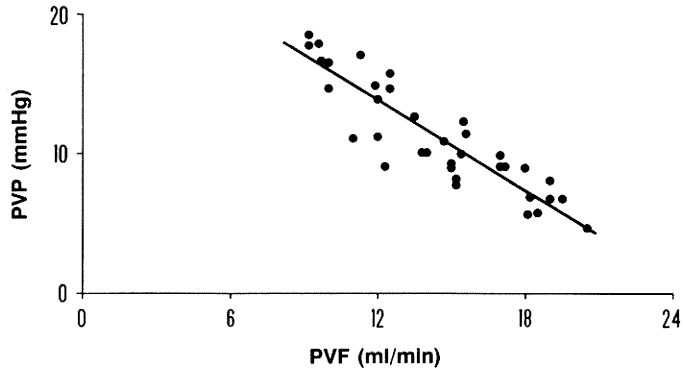

Fig. 2. Relationship between PVF (X) and PVP (Y). Regression line is $Y=-0.94X+23.70$

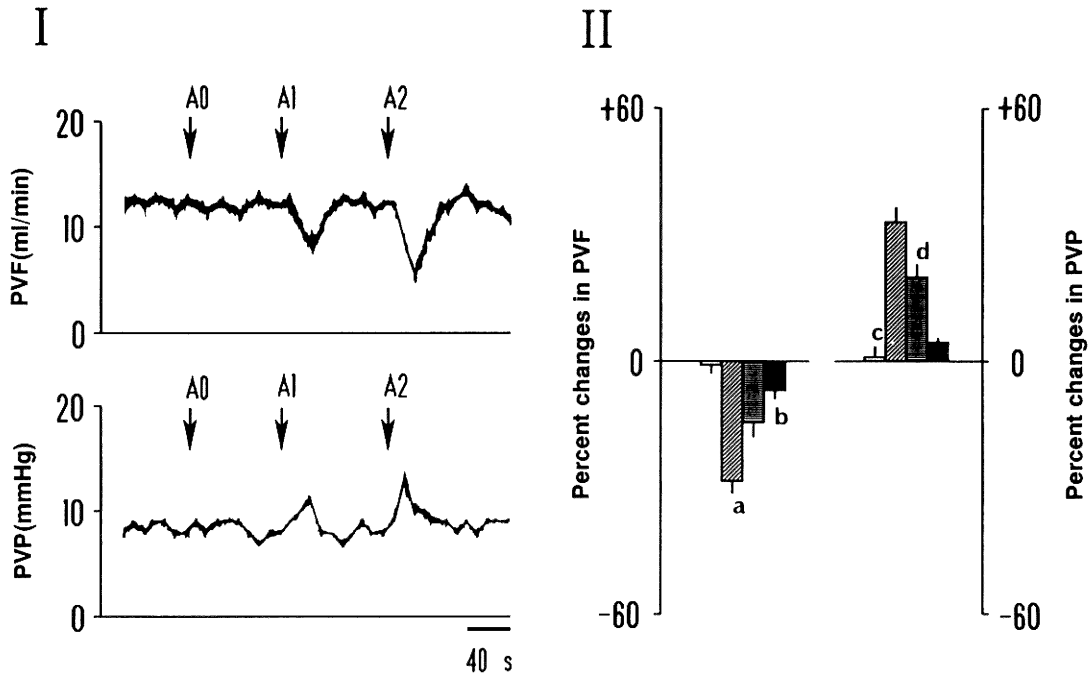

Fig. 3. PVF and PVP in response to adrenaline. I. Adrenaline (Al, 5×10^{-9}; A2, 1×10^{-8} M) or saline (A0) was portally injected. Arrows show the start of injection. II. PVF and PVP 40 s after saline (□) and adrenaline (▨, 1×10^{-8} M; ▤, 5×10^{-9} M; ■, 1×10^{-9} M) were compared. Values are the mean ± SEM (n=6). $^{a}p<0.01$ vs ▤. $^{b}p<0.01$ vs □. $^{c}p<0.01$ vs ▤. $^{d}p<0.01$ vs ▨.

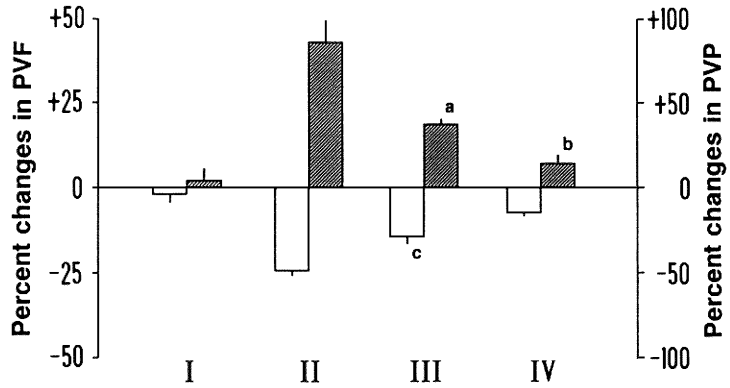

Fig. 4. Effects of splanchnicectomy on PVF (open bar) and PVP (shaded bar). Sectioning of the hepatic splanchnic branch (III) or bilateral splanchnic nerve (IV) was made with cerebral ischemia. Neurally intact rats with (II) or without (I) ischemia are indicated. Values are the mean ± SEM (n=6). $^{a}p<0.01$ vs II. $^{b}p<0.01$ vs II. $^{c}p<0.01$ vs I and II.

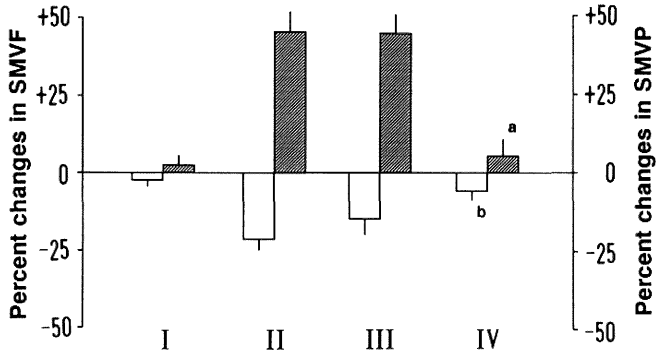

Fig. 5. Effects of splanchnicectomy on SMVF (open bar) and SMVP (shaded bar). Sectioning the hepatic splanchnic branch (III) or bilateral splanchnic nerve (IV) was applied with cerebral ischemia. Neurally intact rats with (I) or without (II) cerebral ischemia are shown. Values are the mean ± SEM (n=6). [a]$p<0.01$ vs II and III. [b]$p<0.01$ vs II.

Table 1. Blood flow in the splenic vein after cerebral ischemia or splanchnicectomy. The carotid artery was closed for 30 sec.

Treatment	Splenic blood flow (ml/min)	
	Before	40 sec after
No treatment	3.8±0.1	3.6±0.2
Cerebral ischemia	3.9±0.3	3.6±0.2
Splanchnicectomy	4.1±0.2	3.8±0.2

Values are the mean ± SEM (n=6).

Splenic venous flow with cerebral ischemia

Blood flow in the splenic vein was unaffected even when cerebral ischemia or bilateral splanchnicectomy or hepatic branch splanchnicectomy was applied (Table 1). The differences among groups were insignificant, $F_{5,35}=0.420$, $p>0.05$.

DISCUSSION

The finding that cerebral ischemia with carotid arterial occlusion resulted in a decrease in the portal venous flow (Fig. 1) is consistent with the previous report that sympathetic activation with cerebral ischemia was effective in reducing portal venous flow.[5,16] This response could play an important role in blood mobilization in the visceral organs, as already suggested by Greeway and Stark,[7] in preventing the fall in portal venous pressure during the pressor response due to cerebral ischemia.[7]

Although PVF has principally been considered to be determined by the two components—portal venous pressure or portal venous resistance or both[13,17,18]—there has been disagreement concerning the relationship between portal venous flow and portal venous pressure.[5,8] In this study, portal venous flow was decreased concomitant with an increase in portal venous pressure, and a reliable relationship between portal venous flow and pressure was obtained (Figs. 1 and 2). Because electrical stimulation has been shown to enhance vascular constriction,[16,19] this could be interpreted as indicating that sympathetic activation contracted the portal vessels, which is reflected in portal venous pressure.

The density of the adrenergic nerve network of the portal vein is comparatively sparse,[20] however, the maximum noradrenaline-induced contraction that can be induced by the maximum neurogenic contraction is 85 to 90%.[21] Moreover, using an isolated portal vein preparation has demonstrated its contracting in response to biologically active catecholamines such as adrenaline and noradrenaline.[4] As shown in Fig. 3, adrenaline directly injected into the portal vein increased PVP. The rise in PVP due to the agent may be ascribed to adrenergic vasoconstriction of the portal and hepatic venules within the liver.[22,23] The injected dosage of adrenaline was a concentration which is released into the circulation in response to electrical stimulation of the nerves innervating the adrenal gland.[24] Considering this finding together with the report that the adrenal gland received innervation from the splanchnic nerve,[9,24] it is possbile that portal circulation is synergistically

controlled by the circulating catecholamine during sympathetic activation. In connection with this, it has been pointed out that adrenal components could elongate the sympathetic effect on portal venous flow.[6]

The splanchnic nerve has been considered to exert a vasoconstrictor influence upon the hepatic vessels, based on the finding that hepatic branch splanchnicectomy substantially increases hepatic blood flow.[17] No observable increase in basal PVF was detected, however, though reaction in PVF and PVP due to neural interruption was transiently seen. It is likely that basal levels of efferent nerve action on the portal vasculature were ineffective, especially under these anesthetic conditions.

The visceral organs have been shown to be innervated with several sympathetic structures[9,25]: the splanchnic nerves, the celiac ganglions and the lumbar sympathetic chain. The response in PVP caused by cerebral ischemia did not entirely disappear when the hepatic splanchnic branch was sectioned (Fig. 4). It is possible that the nervous structure except for the hepatic splanchnic branch also contributes to the portal circulatory regulation.

Circulation in the superior mesenteric vein varied with cerebral sympathetic activation (Fig. 5); blood flow was decreased, but blood pressure was increased, and both parameters changed synchronistically. This may imply that there exists a correlation between blood flow and pressure at the mesenteric level. However, these parameters were unaffected by sectioning the hepatic splanchnic branch. It seems that the sympathetic nerve innervating the superior mesenteric vein directly regulates the vascular tone independent of the nerve controlling the portal venous tone. Support for such speculation comes from recent research showing that electrical stimulation applied to the nerves innervating the mesenteric vasculature produced a reaction in venous flow.[6]

A synchronized interaction between portal and superior mesenteric circulation may exist; peak responses in blood flow and pressure were seen in the same latent periods when cerebral ischemia was introduced (Figs. 1, 3 and 4), and PVP response due to the ischemia was not completely blocked by sectioning the hepatic splanchnic branch (Fig. 4). Since the portal blood stream followed the mesenteric blood stream, these results could mean that venous pressure in the superior mesenteric vein is tonically reflected in PVP because of the vascular canal. This may also explain the disagreement on the relationship between portal venous flow and pressure.[5,8]

The spleen has been shown to be an organ reserving blood volume; constrictor responses of the splenic vein were evoked when the sympathetic nerve was activated,[26–28] and it has been presumed that the nerve takes part in blood mobilization from the spleen to the portal vein. However, as shown in Table 1, blood flow in the splenic vein was entirely uncontrolled by the splanchnic nerve. It is not easy to explain this phenomenon, and it is not possible to exclude a specific difference from animal to animal. One interpretation of this is that under special conditions, the sympathetic nervous system may perform a sort of "reciprocal innervation" of functionally antagonistic autonomic effector systems. We might regard the response as an "adjustment".[29,30]

In view of these observations, it is suggested that sympathetic control of PVF is determined by changing PVP through the adrenergic vasculature, and such a regulatory system in the portal circulation is substantially modulated by pressure in the superior mesenteric vein.

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